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The Triple Crown: NO, CO, and H_2S in cancer cell biology

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ABSTRACT

Nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S) are three endogenously produced gases with important functions in the vasculature, immune defense, and inflammation. It is increasingly apparent that, far from working in isolation, these three exert many effects by modulating each other's activity. Each gas is produced by three enzymes, which have some tissue specificities and can also be non-enzymatically produced by redox reactions of various substrates. Both NO and CO share similar properties, such as activating soluble guanylate cyclase (sGC) to increase cyclic guanosine monophosphate (cGMP) levels. At the same time, H_2S both inhibits phosphodiesterase 5A (PDE5A), an enzyme that metabolizes sGC and exerts redox regulation on sGC. The role of NO, CO, and H_2S in the setting of cancer has been quite perplexing, as there is evidence for both tumor-promoting and pro-inflammatory effects and anti-tumor and anti-inflammatory activities. Each gasotransmitter has been found to have dual effects on different aspects of cancer biology, including cancer cell proliferation and apoptosis, invasion and metastasis, angiogenesis, and immunomodulation. These seemingly contradictory actions may relate to each gas having a dual effect dependent on its local flux. In this review, we discuss the major roles of NO, CO, and H_2S in the context of cancer, with an effort to highlight the dual nature of each gas in different events occurring during cancer progression.

Abbreviations: 3-MP, 3-mercaptopyruvate; 3-MST, 3-mercaptopyruvate sulfurtransferase; AP-1, activator protein; Apaf-1, apoptosis protease activating factor 1; ARDS, acute respiratory distress syndrome; Bak, Bcl-2 homologous antagonist/killer; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; Ca^{2+}, calcium ions; CAT, cysteine aminotransferase; CBS, cystathionine β-synthase; CDK, cyclin-dependent kinase; cGMP, cyclic guanosine monophosphate; cIAP1, cellular inhibitor of apoptosis protein 1; c-Myc, cellular myelocytomatosis; CO, carbon monoxide; CORM, carbon monoxide-releasing molecule; COX, cyclooxygenase; CSE, cystathionine γ-lyase; CTLA4, cytotoxic T-lymphocyte–associated antigen; DADS, diallyl disulfide; DAO, D-amino acid oxidase; DATS, diallyl trisulfide; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; ERα, estrogen receptor alpha; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; FasL, Fas-ligand; Fox, Forkhead box; GSK3β, glycogen synthase kinase-3 beta; GSNO, S-nitrosoglutathione; H_2S, hydrogen sulfide; H_2S_n, polysulfide; Hb, hemoglobin; HIF, hypoxia-inducible factor; HNO, nitroxyl; HO, heme oxygenase; HSNO, thionitrous acid; Hsp, heat-shock protein; hTERT, human telomerase reverse transcriptase; HUVEC, human umbilical vein endothelial cell; IAP, inhibitor of apoptosis protein; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; IP3, inositol triphosphate; JNK, c-Jun N-terminal kinase; K^+, potassium ion; K_{ATP}, ATP-dependent potassium channel; L-NAME, L-N^G-Nitro arginine methyl ester; LPS, lipopolysaccharide; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; MDSC, myeloid-derived suppressor cells; MEK, mitogen-activated protein kinase kinase; MHC, major histocompatibility complex; miR, micro-RNA; MMP, matrix metalloproteinase; MPO, myeloperoxidase; MRSA, methicillin-resistant *Staphylococcus aureus*; mTOR, mammalian target of rapamycin; NADPH, nicotinamide adenine dinucleotide phosphate; NaHS, sodium hydrosulfide; NDRG-1, N-Myc-downstream-regulated gene 1; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; nm23, non-metastatic protein 23; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase; *Notch-1*, neurogenic locus notch homolog protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; $ONSS^-$, nitropersulfide; NSAID, non-steroidal anti-inflammatory drugs; PBMC, peripheral blood mononuclear cells; PCNA, proliferating cell nuclear antigen; PDE5A, phosphodiesterase 5A; PDL1, programmed cell death ligand 1; PEITC, β-phenylethyl isothiocyanate; PERK, protein kinase R-like endoplasmic reticulum kinase; PGE2, prostaglandin E2; PI3-K, phosphoinositide 3-kinase; PK, protein kinase; PLP, pyridoxal 5′-phosphate; PP2A, protein phosphatase 2A; PPAR, peroxisome proliferator-activated receptor; PTT, photothermal therapy; Rb, retinoblastoma; RKIP, Raf-1 kinase inhibitor protein; RNS, reactive nitrogen species; ROS, reactive oxygen species; RSNO, nitrosothiol; sGC, soluble guanylate cyclase; shRNA, short hairpin RNA; SNAP, S-nitroso-*N*-acetylpenicillamine; SNP, sodium nitroprusside; SPRC, S-propargyl-cysteine; Src, steroid receptor coactivator; STAT, signal transducer and activator of transcription; Tcf, T-cell factor; TCR, T cell receptor; TGF, transforming growth factor; TME, tumor microenvironment; TNF-α, tumor necrosis factor-α; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; TSP-1, thrombospondin-1; UV, ultraviolet; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor 2; Wnt, Wingless/Integrated; XIAP, X-linked inhibitor of apoptosis protein; ZEB-1, zinc finger E-box binding homeobox 1.

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Contents

1. Introduction

Nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S) are gases that have been present in the Earth's atmosphere from the beginning of time. Historically, these three gases have been considered pollutants from industrial activity, such as oil refineries, paper mills, and tanneries (Li et al., 2009). However, it is now understood that these gases are endogenously produced and have important biological roles in most mammalian tissues. The term gasotransmitter was introduced in 2002 to describe NO, CO, and H_2S (Wang, 2002), particularly in relation to their regulatory functions within the nervous system (Nowaczyk et al., 2021, Siracusa et al., 2021).

Jan Baptista van Helmont first observed the formation of a red gas when *aqua fortis* (nitric acid) reacted with silver. This red gas is of course nitrogen dioxide, which is formed when NO reacts with oxygen; thus, van Helmont is credited for discovering NO (Butler & Nicholson, 2003). However, it was Joseph Priestly who, in 1772, published a paper in the *Philosophical Transactions* (Priestley, 1772) where he recognized NO as a distinct entity and gave it the name 'nitrous air' (Brennan et al., 2003, McEvoy, 2015, Lancaster Jr., 2020a). The important role of NO in human biology was first recognized in 1992 when the journal *Science* introduced NO as the "Molecule of the Year" (Culotta & Koshland Jr., 1992), followed by the awarding of the Nobel Prize in Physiology and Medicine in 1998 to Robert F. Furchgott, Louis J. Ignarro, and Ferid Murad for the major discoveries surrounding NO and establishing its role as a messenger molecule. In the same year as his discovery of NO, Joesph Priestly produced CO via heating chalk to produce CO_2 and reduced it to CO over a hot iron; thus, he is also credited with the formal discovery of CO (Hopper et al., 2021; Schofield, 1967). The endogenous formation of CO was demonstrated in the early 1950s (Sjostrand, 1951); but it was not until the mid-1990s that it was acknowledged as the second gasotransmitter (Verma et al., 1993). The discovery of the last gasotransmitter, H_2S, was made in 1775, credited to the Swedish-German chemist Carl Wilhelm who produced this gas by heating sulfur in hydrogen gas (Nicholls & Kim, 1981). French chemist Claude Louis Bethollet then determined the chemical composition of H_2S in 1789 (Mitchell & Davenport, 1924). In a landmark study in 1996, Abe and Kimura demonstrated the physiological importance of H_2S as a neuromodulator (Abe & Kimura, 1996), followed by Rui Wang's proposal in 2002 that this was the third gasotransmitter to be added to the list alongside NO and CO (Wang, 2002). For detailed historical perspectives on NO, CO, and H_2S, please see (Lancaster Jr., 2020b, Ghasemi & Kashfi, 2022; Kashfi & Patel, 2022; Szabo, 2018) respectively.

Although these gasotransmitters can be toxic, they are now recognized as having multiple roles in normal physiology. NO is important in the vasculature for vasorelaxation (Ignarro et al., 1987) and modulation of platelet and leukocyte activation, adhesion, and aggregation (Wallace et al., 2009), in controlling inflammation through modulation of NF-κB activity (Katsuyama et al., 1998a; Hattori et al., 2004), and suppressing the expression of pro-inflammatory mediators in mast cells, macrophages, and vascular smooth muscle (Hogaboam et al., 1993; Huang et al., 1998; Naseem, 2005), and in the nervous system through functions in non-adrenergic non-cholinergic (NANC) signaling (Król & Kepinska, 2020) The second gasotransmitter, CO, has earned itself a reputation as a 'silent killer' because as a colorless, odorless gas, it is hard to detect and its intoxication can be fatal. Despite its known toxic effects, however, CO is an important endogenous signaling molecule with many physiological roles, including smooth muscle relaxation at low concentrations through ATP-dependent potassium (K_{ATP}) channel activation, which lowers blood pressure (Motterlini & Otterbein, 2010), as well as effects on mitogen-activated protein kinase (MAPK) signaling pathways (Szabo, 2016). As for H_2S, functions include vasorelaxation through K_{ATP} channel activation through S-sulfhydration (Meng et al., 2018), and maintenance of antioxidant defense (Xie et al., 2016). The biological half-lives of these gasotransmitters are variable; for NO, it is quite short, in the order of a few seconds; for CO, it is relatively long, in the order of minutes; and for H_2S, it is somewhere in between, seconds to minutes (Szabo, 2016).

The previously mentioned actions of the gasotransmitters have important implications in their effects in the context of cancer. NO, CO, and H_2S have a dichotomous role in cancer, with some studies suggesting anti-inflammatory, anti-cancer effects of these gasotransmitters, while others suggest these gasotransmitters as players contributing to immune-mediated tissue injury and tumor promotion (Bhatia et al., 2005; Bhatia et al., 2008; Kashfi & Duvalsaint, 2017; Li, Bhatia, & Moore, 2006; Szabo, 2018; Tamizhselvi et al., 2007; Wallace, 2007). These controversies may relate to each having a dual effect dependent on the local flux of each gas (Kashfi & Esmaili, 2017; Ridnour et al., 2006; Szabo, 2016; Szabo, 2018). In this review, we present the current evidence surrounding the potential role of NO, CO, and H_2S in the cancer setting, highlighting the paradoxical effects of each seen in cancer cell proliferation and apoptosis, invasion and metastasis, angiogenesis, immunomodulation, as well as consideration of the potential of these gases in the prevention/management of cancer immunosuppression-related infectious complications.

2. NO, CO, and H_2S biosynthesis, metabolism, and signaling

NO is produced from the metabolism of L-arginine by the enzyme nitric oxide synthase (NOS) (Ignarro, 1989; Moncada & Higgs, 1993), which exists as three different isoforms with some differences in tissue specificity (Fig. 1). Neuronal (nNOS or NOS1) and endothelial (eNOS or NOS3) are both constitutive, calcium-dependent forms of the enzyme that undergo negative feedback regulation (Stuehr, 1997), in addition to regulatory phosphorylation (Dimmeler et al., 1999), and interaction with other regulatory molecules (Sessa, 2004). These isoforms produce nanomolar concentrations of NO for seconds or minutes to regulate neural and vascular function, respectively (Geller and Billiar 1998, Alderton et al., 2001). The last NOS isoform, inducible NOS (iNOS or NOS2), is calcium-independent and transcriptionally regulated, induced by the presence of oxidative stress, inflammatory cytokines, hypoxia, and endotoxins (Kleinert et al., 2003; Nathan & Xie, 1994). iNOS produces micromolar to low millimolar levels of NO, which may continue

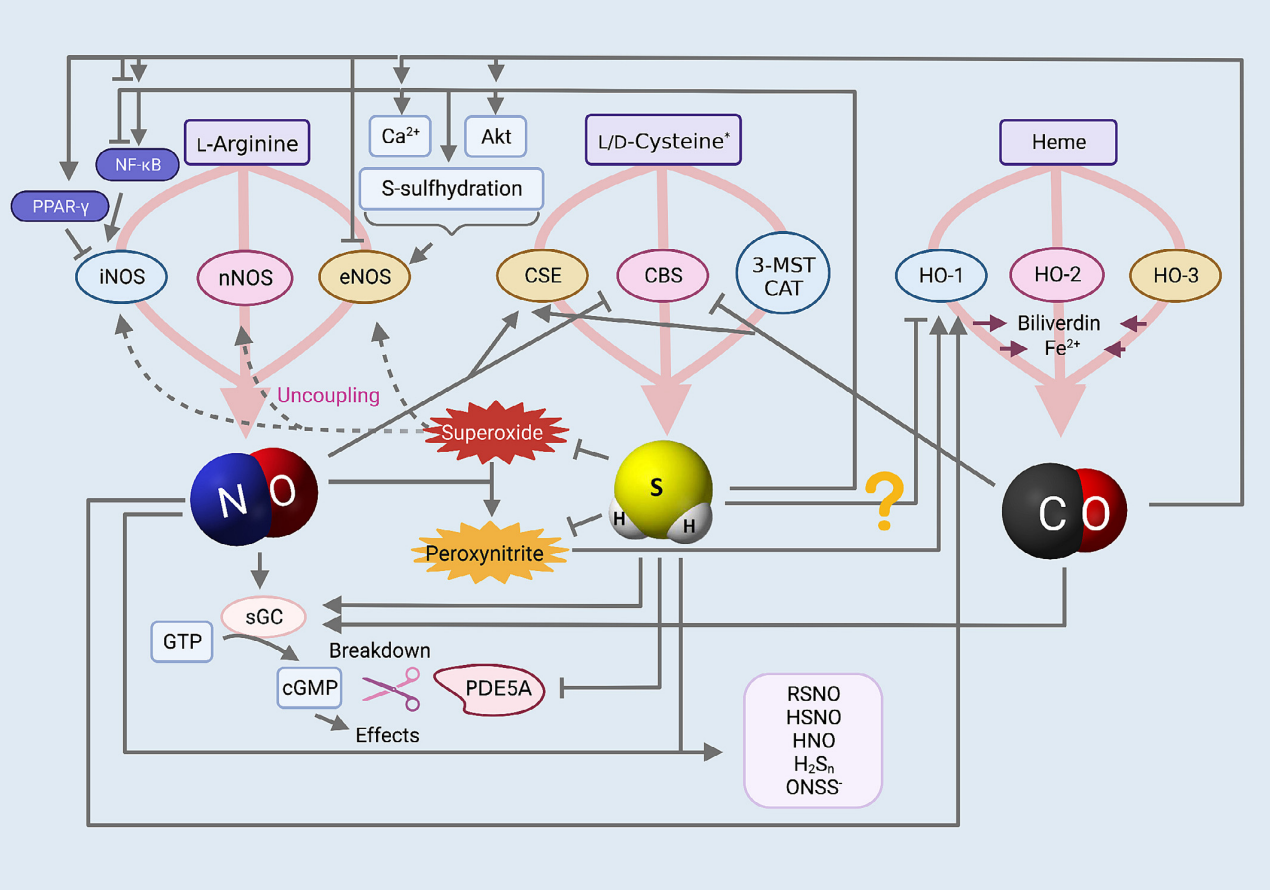

Fig. 1. NO, H_2S, CO biosynthesis and crosstalk. There is an extensive level of crosstalk between the gasotransmitters. NO is enzymatically produced from L-arginine by nNOS, eNOS, and iNOS, mediates many effects through the sGC-cGMP pathway, and this signaling is terminated by the degradation of cGMP by PDE5A. Superoxide anions can reduce NO bioavailability by causing NOS uncoupling and by reacting with NO to form peroxynitrite. H_2S is enzymatically produced from L-cysteine by CBS, CSE, and 3-MST in conjunction with CAT. CO is enzymatically produced from the heme breakdown by the enzymes HO-1, HO-2, and HO-3, which additionally produce biliverdin and Fe^{2+}. *NO and H_2S crosstalk:* NO upregulates CSE expression while it inhibits the activity of CBS. H_2S can upregulate eNOS expression and activity through intracellular Ca^{2+} release, Akt-mediated activating phosphorylation of eNOS, and eNOS S-sulfhydration, which inhibits the negative feedback regulation of NO on eNOS activity and maintains the active dimerized state. H_2S has a dual effect on iNOS activity, and is capable of both increasing and decreasing its activity through similar dual effects on activating or inhibiting the iNOS transcription factor NF-κB. H_2S reduces oxidative stress which increases NO bioavailability, and is a scavenger of peroxynitrite. H_2S augments downstream NO signaling by inhibiting PDE5A activity to allow increased cGMP accumulation, and exerting redox regulation rendering sGC more responsive to NO. NO and H_2S may also react with each other to form new chemical species such as nitrosothiols, nitroxyl, and others. *NO and CO crosstalk:* CO may have a dual effect on eNOS activity, both inhibiting it and augmenting it, the latter through Ca^{2+} release, Akt-mediated activating phosphorylation of eNOS, and protection of the enzyme from downregulation in inflammatory conditions. CO has dual effects on iNOS activity as well by either increasing or decreasing NF-κB transcription factor activity; additionally, CO has been found to activate PPAR-γ to downregulate iNOS as well. NO and peroxynitrite have both been seen to upregulate HO-1 expression. *CO and H_2S crosstalk:* CO may inhibit CBS activity but upregulate CSE expression, while H_2S may inhibit CO-1, although more investigation into these relationships is necessary.

for hours or days (Goligorsky et al., 2004; Kolios et al., 2004; Michel & Feron, 1997) and plays a role involved in immune defense and inflammation. Aligning with its pro-inflammatory role, this isoform is highly expressed in many cancers, including glioma, breast, gastric, colon, leukemia, melanoma, ovarian, prostate, renal, and squamous carcinoma (Granados-Principal et al., 2015; Heinecke et al., 2014; Jahani-Asl & Bonni, 2013; Jenkins et al., 1995; Radomski et al., 1991; Szabo, 2016; Thomsen & Miles, 1998; Vannini, Kashfi, & Nath, 2015). Interestingly, the other two isoforms have also been documented to be upregulated in certain cancers; for instance, nNOS is induced in glioma, melanoma, and myeloma, and eNOS was found induced in pancreatic cancer, sarcoma, and renal cell carcinoma (Szabo, 2016; Thomsen & Miles, 1998; Vannini, Kashfi, & Nath, 2015). In addition to its enzymatic production, NO can also be produced through the reduction of nitrate/nitrite, the so-called 'nitrate-nitrite-NO pathway,' or the non-enzymatic pathway under low oxygen conditions, as reviewed in (Kashfi, 2018). NO signaling involves diffusion of the gasotransmitter across the plasma membrane into the cytoplasm, where it binds to the heme group of soluble guanylate cyclase (sGC) to produce cyclic guanosine monophosphate (cGMP). The downstream effects of this signaling are mediated through cGMP-dependent Protein Kinase (PK) G (Friebe & Koesling, 2003). Most of the actions of NO are a result of this signaling pathway, including, for instance, its inhibitory effects on leukocyte and platelet adhesion and aggregation and vasorelaxation (Dangel et al., 2010; Lincoln et al., 1996). NO also participates in signaling independent of the sGC-cGMP pathway through direct protein modifications, including S-nitrosylation and tyrosine nitration, as well as effects mediated by peroxynitrite, a radical produced by the reaction of NO with superoxide (Chiesa et al., 2018; Martínez-Ruiz et al., 2011). Increased activity of iNOS during periods of inflammation as well as eNOS uncoupling arising from endothelial damage, can lead to increased formation of peroxynitrite (Guzik et al., 2002; Li, Witte, et al., 2006; Münzel et al., 2005; Santhanam et al., 2012), which further promotes inflammation and is important in the defense against pathogens.

The breakdown of heme is the major endogenous source of CO (Fig. 1). Physiological degradation of heme is tightly controlled and

involves the enzyme heme oxygenase (HO) (Tenhunen et al., 1969); the CO-producing reaction also releases free Fe^{2+} and biliverdin, the latter of which is then reduced to yield bilirubin. The enzyme HO has three isoforms, similar to the NOS enzymes. HO-1, also known as heat-shock protein 32 (Hsp32), is an inducible isoform that responds to oxidative stress, hypoxia, hyperoxia, UV irradiation, heat shock, ischemia, hyperthermia, and NO (Applegate et al., 1991; Foresti & Motterlini, 1999; Liu et al., 2020; Otterbein & Choi, 2000). HO-2 is constitutively expressed in the brain, kidney, liver, and sleep; its function is closely associated with neurotransmission and regulation of vascular tone (Foresti & Motterlini, 1999; Maines, 1997). The third isoform, HO-3, is also a constitutive isoform of the enzyme, but cannot degrade heme, and thus its function remains to be elucidated (Mann & Motterlini, 2007; Wu & Wang, 2005). The enzymatic activity of heme oxygenase depends on nicotinamide adenine dinucleotide phosphate (NADPH) and molecular oxygen. Like NO, CO signaling involves the activation of guanylyl cyclase to produce cGMP, but it is approximately only 1/80th as effective in doing so as NO (Mann & Motterlini, 2007). Low concentrations of CO also activate K_{ATP} channels and affect MAPK signaling pathways (Szabo, 2016). The toxicity of CO that is seen with higher concentrations, earning it the name 'silent killer,' arises from its relatively high affinity for hemoglobin (Hb), which is 250 times greater than that of oxygen, resulting in the displacement of oxygen from Hb and preventing sufficient delivery to tissues. Furthermore, CO can also inhibit mitochondrial electron transport by irreversibly inhibiting cytochrome *c* oxidase (complex IV), contributing to CO inhalation poisoning (Motterlini & Otterbein, 2010).With regards to the last of the known gasotransmitters, most of the biosynthesis of H_2S has been attributed to three enzymes (Kashfi & Olson, 2012): cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE) and the tandem enzymes cysteine aminotransferase (CAT) and 3-mercaptopyruvate sulfurtransferase (3-MST) (Fig. 1). CBS, CSE, and CAT metabolize L-cysteine in an enzymatic reaction requiring pyridoxal 5´-phosphate (PLP) as a cofactor (Bukovska et al., 1994; Erickson et al., 1990). 3-MST produces H_2S using 3-mercaptopyruvate (3-MP), a metabolite of L-cysteine produced by CAT (Shibuya et al., 2009), (reviewed in (Kashfi, 2018)). CBS, CSE, and MST are regarded as constitutive enzymes (Szabo, 2016), although there is some evidence suggesting that CBS and CSE may be inducible (Czikora et al., 2022; Paul & Snyder, 2015; Phillips et al., 2017). The expression of CSE can be modulated by tumor necrosis factor-α (TNF-α), lipopolysaccharides (LPS), glucocorticoids, glucose, as well as endoplasmic reticulum (ER) stress (Zhu et al., 2010a, Krishnan et al., 2011, Sen, Paul, et al., 2012a, Hine et al., 2015, Paul & Snyder, 2015). CBS expression has been found to be upregulated in myeloma, breast, colon, prostate, biliary tract, renal, and ovarian cancers compared to adjacent normal tissue or non-cancerous cells (De Vos et al., 2002, Guo et al., 2012, Bhattacharyya et al., 2013, Szabo, Coletta, Chao, Modis, et al., 2013, Sen et al., 2015, Szabo, 2016, Vellecco et al., 2016). CSE has also been reported to have a high expression in colon, melanoma, lung, and prostate cancers (Hellmich et al., 2015, Hellmich & Szabo, 2015, Panza et al., 2015a), while MST is reported to be high in glioma and melanoma (Hellmich & Szabo, 2015; Jurkowska et al., 2011; Szabo, 2016). In addition to the well-known CBS, CSE, 3-MST/CAT enzymes, which metabolize L-amino acids, H_2S can also be synthesized from D-cysteine (Shibuya et al., 2013; Shibuya & Kimura, 2013) by the peroxisomal enzyme D-amino acid oxidase (DAO) (Gould et al., 1988) to 3-MP, the substrate for the mitochondrial enzyme 3-MST (Shibuya et al., 2009). However, as DAO is only localized to the brain and kidneys, the DAO/3-MST pathway is exclusively active in these two organs. Interestingly, D-cysteine is preferentially used by the kidney to produce H_2S (Kimura, 2015). H_2S can also be endogenously produced through nonenzymatic pathways involving the reduction of cysteine (Yang et al., 2019) and elemental sulfur in the blood (Westley & Westley, 1991) using reducing equivalents from glycolysis (Searcy & Lee, 1998), and from sulfur storage forms including thiosulfate, thiocysteine and sulfite (Kolluru et al., 2013), reviewed in (Kashfi & Olson, 2012; Olson, 2018). Furthermore, H_2S levels can be indirectly increased through the activity of cysteinyl t-RNA synthetase (CARS) enzymes, which have been shown to produce cysteine persulfide that can then be metabolized to H_2S and other sulfur species (Akaike et al., 2017). There are two known CARS enzymes, cytosolic CARS1 and mitochondrial CARS2; cysteine persulfide produced by the latter is important as an electron acceptor in the mitochondrial electron transport chain, a process during which H_2S is created (Sawa et al., 2022).

H_2S signaling involves S-sulfhydration of its protein targets, which is responsible for some of its physiological effects, including vasorelaxation (Zhao et al., 2001a) eNOS activity upregulation (Altaany et al., 2014), as well as activation of several signaling pathways including Keap1-Nrf2 (Yang et al., 2012) and NF-κB (Sen, Paul, et al., 2012a). Recent studies have highlighted that a wide range of biological activity attributed to H2S results from other sulfur species, such as hydropersulfides and related polysulfides (Bianco et al., 2019). For instance, cysteine persulfide, which can be produced by the CARS enzymes as previously mentioned (Akaike et al., 2017), and to a lesser extent, by CBS and CSE from serine (Bianco et al., 2019): such hydropersulfides can exist in equilibrium with H_2S in the presence of an oxidized thiol, and can serve to liberate H_2S. There is also evidence to suggest that these sulfur species are responsible for the S-sulfhydration and thiol reduction thus far credited to H2S (Kolluru et al., 2020). Therefore, it is unclear whether H2S or these separate sulfur species are genuinely responsible for the actions attributed thus far to H2S. This is a point to consider when interpreting studies that assess the actions of H_2S on various physiological and pathological models, as it is unclear whether H_2S is always the bioactive molecule behind the effects observed. For more information on the biological roles of additional related sulfur species, please see (Fukuto et al., 2018; Ono et al., 2014).

2.1. NO, CO, and H_2S interactions and crosstalk

There is a vast level of interaction between the three gasotransmitters, which includes modulation of each other's synthesis, downstream signaling, and direct chemical reactions producing intermediates with either enhanced or entirely different actions compared to the individual gasotransmitters (Fig. 1). For instance, NO, CO, and H_2S all bind avidly to hemoglobin. NO and hemoglobin interact to form nitrosyl hemoglobin, H_2S and hemoglobin together form green sulfhemoglobin, and CO combines with hemoglobin to form scarlet carboxyhemoglobin (Arp et al., 1987; Wang, 1998; Wang, 2002). The competition between the three gasotransmitters for binding to hemoglobin is one manner in which each of the gasotransmitters can influence the activity of the others. Understanding of these interactions can be implemented to tailor combination therapies with either two or all three of these gasotransmitters in order to enhance their individual activities while curtailing unwanted effects of any one gasotransmitter. The specifics of these interactions are discussed in the following sections.

2.1.1. Nitric oxide and hydrogen sulfide interactions

Several studies report the modulation of H_2S bioavailability by NO. Increasing NO levels using NO donors and the administration of the NOS substrate L-arginine has been found to increase H_2S production from vascular tissue (Zhao et al., 2001a, Monti et al., 2018) and upregulate CSE expression (Lucetti et al., 2017; Yanfei et al., 2006), whereas inhibiting NOS using non-specific NOS inhibitor L-N^G-Nitro arginine methyl ester (L-NAME) yields the opposite results (Zhong et al., 2003). Thus, exogenous NO administration may serve to both increase NO, as well as increase CS*E*-derived H_2S. On the other hand, NO has been reported to bind and inhibit CBS (Taoka & Banerjee, 2001), and reduce H_2S formation in the liver and kidneys in a murine

lipopolysaccharide (LPS) endotoxic shock model (Anuar et al., 2006), suggesting that the effects of NO on H_2S production may be enzyme- and context-specific. When considering exogenous NO administration, carefully taking advantage of these interactions can allow efficient modulation of two of these gasotransmitters simultaneously.

Increasing H_2S levels has also been found to augment NO bioavailability in mice with CSE knockout (King et al., 2014) and angiotensin II-induced hypertension (Al-Magableh et al., 2015). This effect arises at least partly from H_2S increasing eNOS expression and activity (King et al., 2014; Lucetti et al., 2017), which involves mechanisms including intracellular Ca^{2+} release (Kida et al., 2013), Akt-mediated activating phosphorylation of eNOS (Cardounel et al., 2011), and S-sulfhydration of eNOS, which prevents the negative feedback regulation of NO (Altaany et al., 2014). H_2S may also downregulate iNOS-derived NO in inflammatory conditions by inhibiting its transcription factor, nuclear factor kappa light chain enhancer of activated B cells (NF-κB), as seen in LPS-stimulated macrophages; interestingly, this effect also involved the HO-1/CO pathway, demonstrating the intertwined nature of all three gasotransmitters (Oh et al., 2006). A similar finding was also reported in another study, in which CSE inhibition allowed for increased LPS-induced macrophage production of NO, whereas overexpression of this enzyme curtailed NO release (Zhu et al., 2010b). This effect may depend on the specifics of the experimental model, as highlighted by one study in which H_2S was seen to enhance interleukin (IL)-1β-induced NO production, iNOS expression, and NF-κB activation but had no effect in the absence of IL-1β stimulation (Jeong et al., 2006). Furthermore, the effects of H_2S differ depending on its concentration and the release kinetics of the donor molecules used; for instance, the slow release of H_2S using GYY4137 suppresses LPS-induced NO release, whereas fast-releasing donor NaHS was only inhibitory at lower concentrations (200 μM) (Whiteman et al., 2009). In addition to affecting the production of NO, H_2S also increases the effects of NO signaling through redox regulation of sGC, which enhances the response of sGC to NO (Zhou et al., 2016), inhibition of PDE5A, which allows prolonged effects of NO (Bucci et al., 2010), and antioxidant activity, which decreases oxidative and nitrosative stress, thus protecting against NOS uncoupling (Drachuk et al., 2015).

In addition to modulating one another's synthesis and downstream signaling, the direct reaction of NO and H_2S and their derivatives can produce compounds such as nitrosothiols (RSNO), thionitrous acid (HSNO), polysulfides (H_2S_n), nitroxyl (HNO), and nitropersulfide ($ONSS^-$) (Cortese-Krott et al., 2014; Cortese-Krott et al., 2015; Miyamoto et al., 2017), and these reaction products have been found to have either different, enhanced, or diminished effects compared to the gasotransmitters in isolation (Berenyiova et al., 2015; Whiteman et al., 2006; Yong et al., 2010). These reaction products are reviewed in detail (Kevil et al., 2017). Several NO- and H_2S- co-releasing therapies, such as NOSH-nonsteroidal anti-inflammatory drugs (NSAIDs), have already been designed, taking advantage of the extensive crosstalk between these two gasotransmitters (Kashfi et al., 2015).

2.1.2. Carbon monoxide and nitric oxide interactions

Similar to the level of interaction between H_2S and NO, extensive crosstalk also exists between CO and NO. The vasodilator effects of CO are largely suppressed by NOS inhibition (Foresti et al., 2004), and CO has been found to increase steady-state NO levels in vitro by competing for endothelial intracellular binding sites (Thom et al., 1997). Taken together, these findings suggest the possibility that the vasodilator effects of CO rely at least partly on NOS-dependent NO production. Evidence suggests that the NO-upregulating effects of CO may be concentration-dependent, as in one study, low levels of CO induced NO release from intracellular storage pools. In contrast, higher concentrations reduced NO release due to eNOS inhibition in vitro (Thorup et al., 1999). In contrast to the eNOS inhibition seen in this study, CO has elsewhere been found to induce eNOS activation both in vitro (Choi et al., 2017; Yang et al., 2016) and in vivo (Fujimoto et al., 2004). Mechanistically, this effect was attributed to the stimulation of intracellular Ca^{2+} release through inositol triphosphate (IP3) signaling, activating phosphorylation of Akt, and eNOS phosphorylation and dimerization (Yang et al., 2016). In addition to stimulating eNOS activity, CO has also been seen to inhibit pro-inflammatory TNF-α-mediated eNOS downregulation by inhibiting NF-κB and thus its downstream microRNA (miR)-155-5p (Choi et al., 2017). Therefore, in inflammatory states, CO may be protective toward eNOS. CO can also inhibit iNOS in states of inflammation, as seen in LPS-activated macrophages; mechanistically, this effect has been found to involve peroxisome proliferator-activated receptor (PPAR)-γ activation (Tsoyi et al., 2009) and NF-κB inhibition (Oh et al., 2006). Interestingly, there is evidence that these effects may be tissue-dependent, as in one study, CO prevented LPS-induced lung iNOS upregulation while supporting liver iNOS upregulation, both in vitro and in vivo (Sarady et al., 2004). The effects of CO on iNOS are less well described. In the neuronal system, CO was seen to block NO-mediated increases in cGMP, suggesting the possibility that CO can inhibit nNOS-derived NO. However, no specific enzyme isoform was identified in this study (Ingi et al., 1996).

The effects of NO on CO are less extensively characterized. However, there is evidence that exogenous NO administration can upregulate HO-1 expression and that this enzyme is responsible for the cytoprotective actions of NO in the endothelium (Polte et al., 2000). Additionally, the NO derivative peroxynitrite has also demonstrated the ability to upregulate HO-1, indicating this upregulation as a defense mechanism against NO-mediated oxidative and nitrosative stress (Foresti et al., 1999). Mechanistically, these effects are through the stabilization of HO-1 mRNA (Bouton & Demple, 2000). Further study with the specific effects of NO on CO rather than its enzymatic source would be beneficial to inform future possibilities of combined use of these gasotransmitters, as a combined exogenous administration of the two has already demonstrated promising synergistic effects in the context of infection (Gao et al., 2022).

2.1.3. Carbon monoxide and hydrogen sulfide interactions

Like with CO and NO, the interactions between CO and H_2S are not as well characterized as those between NO and H_2S. With the heme-binding activity of CO and the heme-containing structure of CBS, CO has been found to bind to CBS and induce its inactivation in vitro (Puranik et al., 2006; Taoka et al., 1999). These results are supported by in vivo findings, where CO overproduction in the liver has been seen to downregulate H_2S production and stimulate choleresis. In contrast, in CBS-knockout mice, CO overproduction could not cause either of those effects (Shintani et al., 2009). CO can also exert additional effects by inhibiting CBS, one of which includes activation of global protein methylation (Yamamoto et al., 2010). Additionally, there is evidence that CBS activity can inhibit H_2S production by CSE, such that CO inhibition of the former can lead to an upregulation of H_2S production by CSE (Kabil et al., 2016). Thus, CO can exert direct actions on H_2S-producing enzymes, while also indirectly affecting their activity by interfering with their own interactions. Correspondingly, in aortic smooth muscle cells, inhibition of endogenous CO production led to the upregulation of H_2S content and CSE expression (Jin et al., 2006), and in a murine model of gastric ulcers, exogenous CO administration increased endogenous H_2S production and mRNA expression of CSE and CBS (Magierowski et al., 2018). The upregulation of CSE in both studies aligns with the previous discussion of CO enhancing CSE activity by relieving the negative feedback of CBS; however, the upregulation of CBS in the latter is a curious finding. It is possible that the inhibition of CBS activity by CO may activate compensatory mechanisms, which upregulate CBS production to restore H_2S production by this enzyme.

There is also some evidence that H_2S can impact CO availability. In the same in vitro study with aortic smooth muscle cells, inhibition of endogenous H_2S production increased CO levels and HO-1 expression, whereas both decreased with the administration of NaHS

(Jin et al., 2006). These gasotransmitters can work together in different pathological contexts to exert a protective effect against various pathologies. In a murine model of chronic kidney disease-induced cognitive impairment, both NaHS and CO-releasing molecule (CORM)-3 reversed cognitive impairment and reduced oxidative stress; the protective effects of NaHS were abrogated by HO inhibition and CO depletion, and similarly, the effects of CORM-3 were abrogated by inhibition of endogenous H_2S production (Hamidizad et al., 2022). Thus, both gasotransmitters were interdependently neuroprotective. Yet in the gastric mucosa, whereas the protective effects of H_2S have been found to be dependent upon endogenous CO, CO could exert protective effects independent of endogenous H_2S (Magierowski et al., 2016; Magierowski et al., 2018). Thus, there seems to be a significant amount of crosstalk between these two gasotransmitters, and further characterization of the precise interactions may be useful so that combination therapies with CO and H_2S can be designed, similar to the NO- and H_2S- donating NSAIDs which have already demonstrated promising effects in several contexts (Kashfi et al., 2015).

3. The Triple Crown: NO, CO, and H_2S in carcinogenesis

There is significant evidence to suggest dual pro- and anti- cancer effects of NO, CO, and H_2S due to their roles in apoptosis, cancer invasion and metastasis, angiogenesis, and immunomodulation (Figs. 2,3,4). In addition, each of these gasotransmitters may have use in the prevention and/or management of severe infection in cancer patients, who are often predisposed to this complication. The actions of the gasotransmitters in each of these arenas are dependent upon the

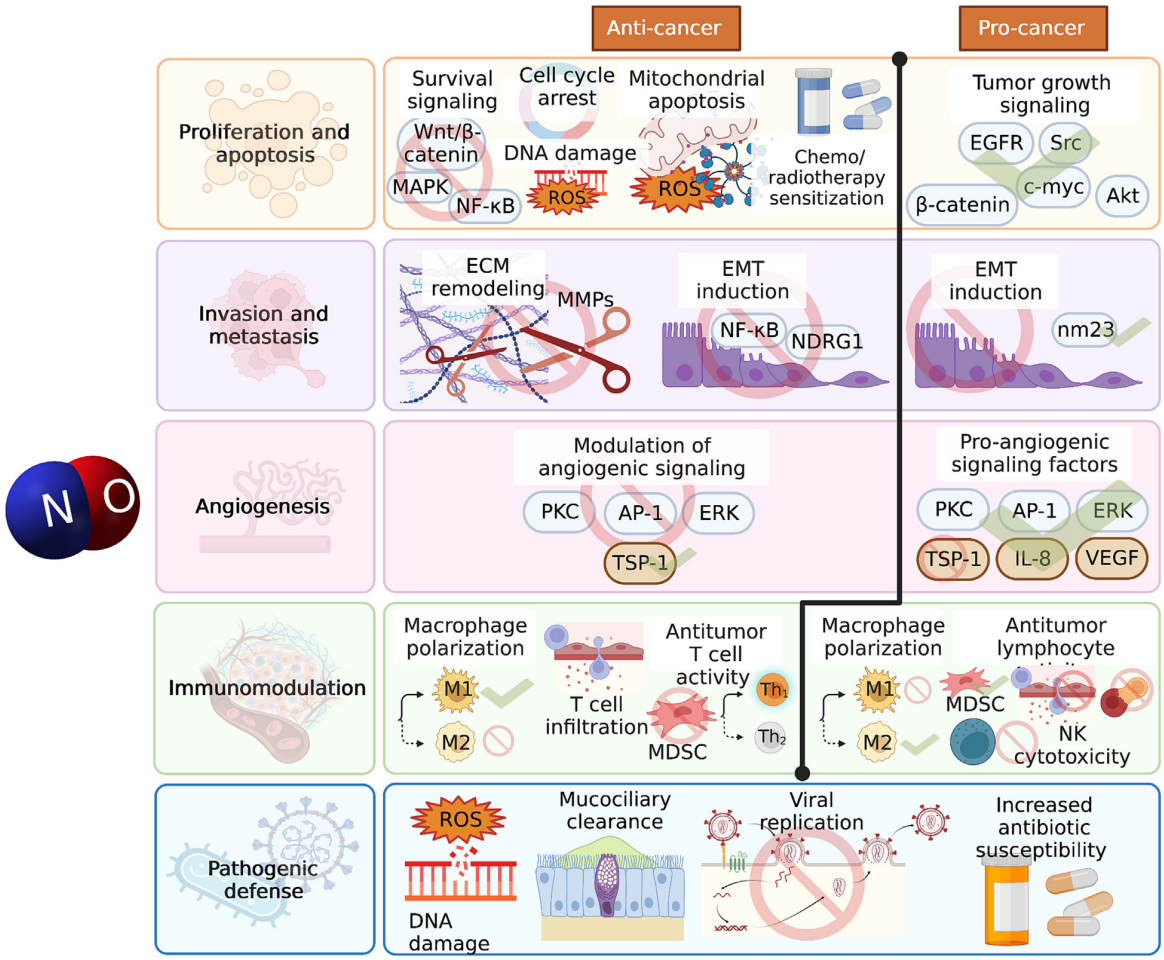

Fig. 2. NO effects in the context of cancer. NO has both cancer-combatting and cancer-promoting effects that may depend on factors such as concentration, flux, and physiological or pathological setting. NO can reduce cancer cell proliferation by inhibiting several cell survival signaling pathways, causing cell cycle arrest, and increasing cancer cell apoptosis by causing DNA damage, increasing oxidative stress, and shifting the balance of pro- and anti- apoptotic proteins in favor of mitochondrial apoptosis; NO has also been found to increase the sensitivity of cancer cells to existing chemotherapeutic and radiation treatments. On the other hand, NO may also have pro-proliferative effects in the context of cancer by enhancing several other tumor growth signaling pathways. NO can inhibit EMT through inhibition of signaling pathways implicated in this phenomenon, and can inhibit ECM remodeling by downregulating MMPs. Both of these reduce the ability of the cancer to invade and metastasize. Yet NO has also been found to induce EMT in separate studies through the activation of different pathways than those implicated in inhibiting EMT. In the context of angiogenesis, NO may either facilitate angiogenesis or inhibit it through the modulation of different signaling pathways involved in this process. NO can enhance the anticancer immune response by enhancing M1 macrophage polarization, enhancing T cell infiltration, selectively inducing Th_1 polarization, and inhibiting the immunosuppressive action of MDSCs. On the other hand, NO can suppress the host anticancer immune response by enhancing immunosuppressive MDSC accumulation, increasing M2 macrophage polarization, reducing NK cell cytotoxicity, and inhibiting cytotoxic T cell activity by reducing T cell activation and inducing apoptosis, hindering T cell infiltration, and facilitating the development of T cell tolerance. In addition to these actions, NO can play an important role in the increased infectious complications associated with cancer; this gasotransmitter has been shown to directly combat pathogens through ROS and DNA damage induction, increase mucociliary clearance, inhibit various steps of viral entry and replication, and increase the antibiotic susceptibility of bacteria.

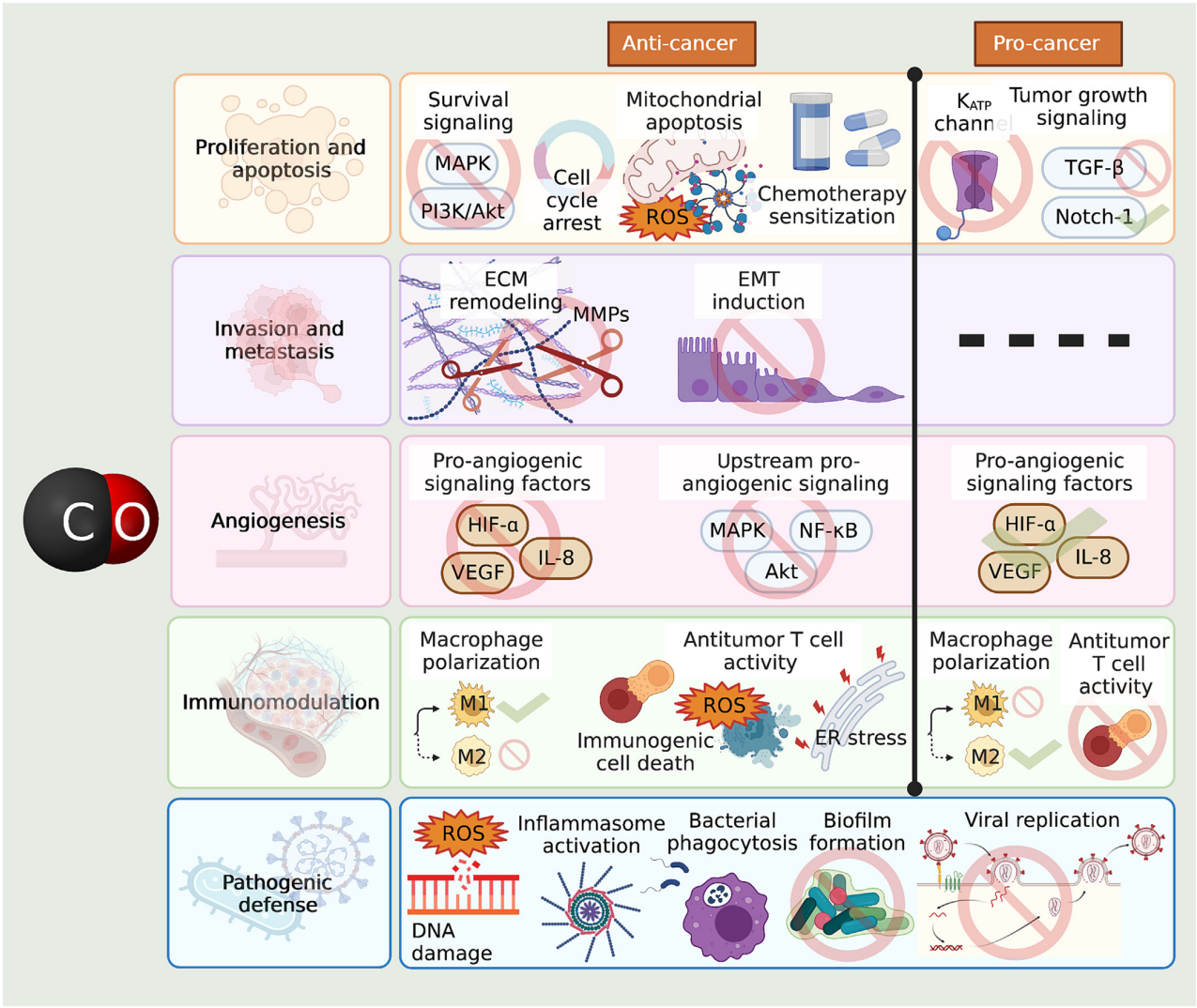

Fig. 3. CO effects in the context of cancer. CO has widespread effects on cancer proliferation and apoptosis, invasion and metastasis, angiogenesis, and host anticancer immunity. The gasotransmitter has both cancer-combatting and cancer-promoting effects in these arenas, which may depend on factors such as concentration, flux, and physiological or pathological setting. CO can reduce cancer cell proliferation by inhibiting several cell survival pathways, inducing cell cycle arrest, favoring mitochondrial apoptosis, and increasing cancer sensitivity to chemotherapy. On the other hand, CO has also been found to increase cancer cell proliferation by increasing the activity of different growth signaling pathways, and to increase resistance to oxidant-induced apoptosis through a mechanism involving the inhibition of K_{ATP} channels. CO can suppress cancer cell invasion and metastasis by inhibiting ECM remodeling through MMP downregulation, and by suppressing EMT. With regards to angiogenesis, the gasotransmitter can either increase or decrease angiogenesis by different, likely context-dependent effects on several angiogenic signaling pathways. CO can increase antitumor host immunity by inducing M1 macrophage polarization, inducing immunogenic cell death through ROS accumulation, and inducing moderate ER stress, which leads to protective autophagy and epigenetic reprogramming of T cell into a stronger antitumoral phenotype. Yet CO may also suppress host antitumor immunity by inducing M2 macrophage polarization and suppressing T cell activity. In the context of infection, CO can cause DNA damage by ROS induction, cause bactericidal inflammasome activation and phagocytosis of bacteria, inhibit biofilm formation, and inhibit viral replication.

physiological or pathological model, dosage, release kinetics, and the mode of gasotransmitter delivery.

3.1. Role in cancer cell proliferation and apoptosis

Inhibition of the growth and proliferation of cancer cells is an effective mechanism to disrupt cancer progression and is the goal of a range of cancer therapies, such as radiation therapy and cytotoxic chemotherapeutic agents. There are several mechanisms to halt cancer growth, including induction of cell cycle arrest, inhibition of cell survival and growth signaling pathways such as phosphoinositide 3-kinase (PI3-K)/Akt, c-Jun N-terminal kinases (JNK), and p38 MAPK pathways—which are often aberrant in cancer (Noorolyai et al., 2019; Samatar & Poulikakos, 2014; Wagner & Nebreda, 2009)—and induction of apoptotic cell death. Through the course of their development, cancer cells acquire many mutations that enable their uncontrolled proliferation and resistance to many cancer therapies (Fernald & Kurokawa, 2013). These mutations encompass, among others, (1) mutations in tumor suppressors including p53, which stops cell cycle progression and activates the transcription of pro-apoptotic proteins (Rivlin et al., 2011), (2) mutations in caspase genes (Soung et al., 2004; Sun et al., 2007) (3) overexpression of anti-apoptotic B-cell lymphoma 2 (Bcl-2) protein (Campana et al., 1993), (4) increased levels of inhibitor of apoptosis proteins (IAP), including survivin (Hernandez et al., 2011; Small et al., 2010), X-linked inhibitor of apoptosis protein (XIAP) (Yu et al., 2018), and cellular inhibitor of apoptosis protein 1 (cIAP1)

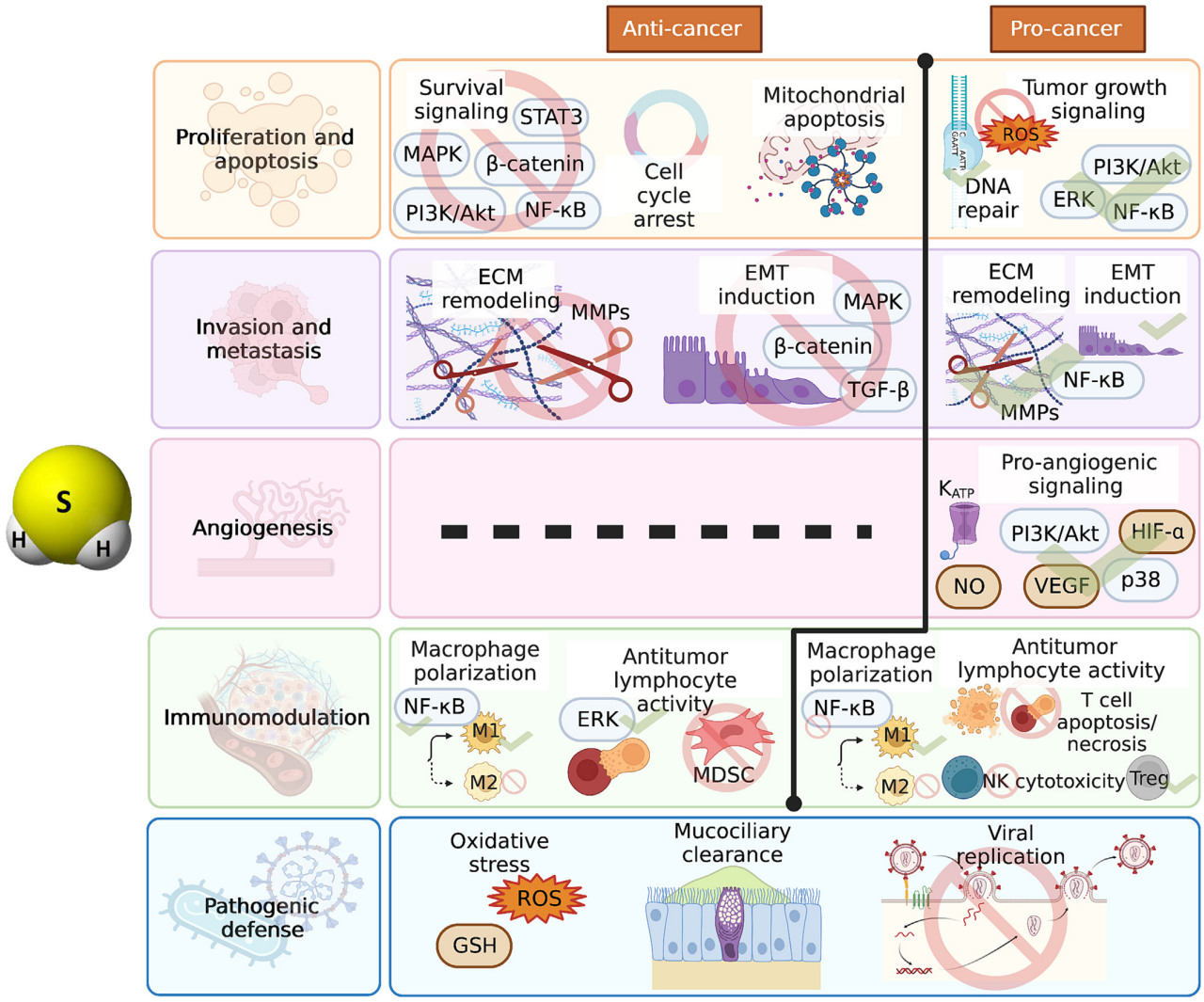

Fig. 4. H_2S effects in the context of cancer. H_2S also has both cancer-promoting and cancer-combatting effects resulting from its impact on cell proliferation and apoptosis, invasion and metastasis, angiogenesis, and antitumoral immunity. H_2S can inhibit tumor proliferation by inhibiting various growth signaling pathways, inducing cell cycle arrest, and increasing cancer cell apoptosis. Contrarily, H_2S can increase cancer proliferation and protect against apoptosis by activating various growth signaling pathways, maintaining DNA repair mechanisms, and suppressing ROS production. The gasotransmitter has been seen to both increase and suppress EMT induction and ECM remodeling through modulation of several different signaling pathways. In the context of angiogenesis, only a pro-angiogenic effect has been reported through increased pro-angiogenic signaling; mechanistically, NO and K_{ATP} channels have been found to be involved in the pro-angiogenic effect of H_2S. H_2S can boost anticancer immunity by increasing M1 macrophage polarization, enhancing T cell activation, and suppressing the immunosuppressive MDSCs; yet immunosuppressive activity of H_2S has also been described, including M2 macrophage polarization, T cell death, impaired NK cell cytotoxicity, and enhanced Treg differentiation. In the context of infection, H_2S exerts antimicrobial actions through increased oxidative stress upregulation of the antioxidant and antiviral agent GSH, increased mucociliary clearance, and inhibition of viral replication.

(Esposito et al., 2007), and (5) increased activation of cell survival signaling pathways such as the PI3-K/Akt pathway (Noorolyai et al., 2019), MAPK pathway (Braicu et al., 2019), and Wingless/Integrated (Wnt)/β-catenin pathway (Jackstadt et al., 2020). NO, H_2S. and CO have all separately demonstrated the ability to either induce or protect against cancer cell growth and apoptosis through impacts on some of these survival adaptations.

3.1.1. Nitric oxide in cancer cell proliferation and apoptosis

NO has both pro- and anti-proliferative effects (Fig. 2), which may depend on the physiological or pathological system in which its effects are observed. NO has shown pro-apoptotic activity against many cancers, including colon cancer (Oláh et al., 2018), pre-B acute lymphoblastic leukemia (Khan et al., 2012), and bladder carcinoma (Fabbri et al., 2005), among others. Experimental upregulation of NO production through NOS2 transduction was found to almost completely inhibit the growth of prostate, gastric, colon, fibrosarcoma, breast, ovarian, renal cell carcinoma, and bladder tumor cell lines, which was linked to the induction of apoptosis (Le et al., 2005).

The cancer-targeting apoptotic effects of NO have been linked to multiple mechanisms, one of which is the induction of oxidative stress either through increased ROS production (Khan et al., 2012) or depletion of antioxidant machinery such as glutathione stores (Gao et al., 2005), leading to subsequent caspase activation and the mitochondrial apoptotic pathway. Increased oxidative stress can induce apoptosis via its known ability to cause DNA damage and impair DNA repair mechanisms. Indeed, there is evidence that NO can induce double-stranded DNA breaks in multiple myeloma cells, and its cytotoxic effects have been associated with the activation of the JNK pathway and activation of both intrinsic and extrinsic apoptotic pathways

(Kiziltepe et al., 2007). In addition, there is evidence to suggest the ability of NO to affect the Bax/Bcl-2 ratio in favor of a pro-apoptotic balance in experimental cancer models (Singh et al., 2012); in one study, the treatment of both non-metastatic and metastatic melanoma cells with NO donors resulted in dose-dependent apoptotic cell death of both cell populations, an effect that was associated with the downregulation of Bcl-2, and which was significantly reduced with Bcl-2 transfection (Xie et al., 1997). Interestingly, more aggressive cancer cells may be able to adopt mechanisms to resist the anticancer effects of NO by suppressing its release; in one study with melanoma cells, while IL-1α and interferon (IFN)-γ were able to induce NO production, Bcl-2 downregulation, and subsequent apoptotic cell death in nonmetastatic cells, these effects were minimal in the metastatic cells (Xie et al., 1997). In other words, the more aggressive metastatic cells were resistant to an increase in NO production and subsequent apoptosis upon exogenous stimulation. Correspondingly, in a murine model, endogenous NO production was inversely correlated with the survival of melanoma cells to produce metastases (Dong et al., 1994). These findings suggest the downregulation of NO production as a pro-survival mechanism of aggressive cancer cells, which indicates a benefit to exogenous NO administration, especially against more aggressive cancers.

In addition to the direct induction of apoptosis, the suppression of several pro-survival signaling pathways is another mechanism through which NO inhibits cancer growth. The S-nitrosylating NO donor GSNO has, for instance, been found to inhibit the proliferation of both chemoresponsive and chemoresistant ovarian cancer cell lines by abolishing growth factor signaling, and was found to potentiate the toxicity of cisplatin therapy in vivo (Giri et al., 2014). Furthermore, NO has been reported to induce apoptosis through the suppression of NF-κB (Khan et al., 2012; Williams et al., 2003), a transcription factor known to participate in carcinogenesis (Khan et al., 2013) and whose suppression using agents other than NO has also been found to be sufficient to induce apoptosis in acute lymphoblastic leukemia cells (Khan et al., 2012; Meng et al., 2010). Along with the suppression of NF-κB, the inhibition of colon cancer and breast cancer cell growth by NO-donating aspirin was associated with inhibition of the β-catenin/T-cell factor (Tcf) signaling pathway and upregulation of cyclooxygenase (COX)-2 (Nath et al., 2009; Williams et al., 2003). The Wnt/β-catenin pathway has been identified as a pro-survival pathway implicated in cancer progression (Khan et al., 2007), and its inhibition is thus a mechanism for combatting cancer. The inhibition of Wnt signaling by NO has been further elucidated as having a dual mechanism based on a murine model of colon cancer – low concentrations of NO were seen to block the formation of β-catenin/Tcf complexes, and the additional mechanism of β-catenin cleavage was seen at higher concentrations (Gao et al., 2005). In addition to its impact on NF-κB and Wnt/β-catenin pathways, NO has also been seen to modulate MAPK signaling. Classical MAPK signaling involves three pathways—p38 MAPK, JNK, and extracellular signal-regulated kinase (ERK)1/2 (Zhang & Liu, 2002). In a model of photo-induced carcinogenesis, topical NO administration using NO-exisulind reduced UVB-induced phosphorylation of the MAPK proteins ERK 1/2 and p38 (Singh et al., 2012). Inhibition of these pro-survival pathways is thus a major mechanism through which NO can combat cancer growth.

NO may also inhibit cancer growth by directly influencing cell cycle progression. There is evidence from a range of cancer cell lines, including pancreatic, colon, prostate, lung, tongue, skin, cervix, and breast cancer cells that NO induces cell cycle arrest in G_2/M (Gao & Williams, 2012; Kashfi et al., 2002). Further investigation has revealed that NO can impact cell cycle progression by modulating the expression and activity of cell cycle regulatory proteins: increasing cyclin B1 expression, decreasing cyclin D1 and CDC25C expression, and increasing the phosphorylation of cyclin-dependent kinase (CDK)1 (Gao & Williams, 2012). Considering the reversal of these effects with the administration of the antioxidant *N*-acetyl-cysteine, redox signaling was identified as the likely mediator of these effects (Gao & Williams, 2012).

Aligning with its growth-inhibitory effects, NO has been found to increase the effects of various anticancer therapies. iNOS transfection has been demonstrated to enhance cisplatin toxicity in radiation-induced fibrosarcoma cells (Adams et al., 2009). Similarly, the treatment of prostate cancer cells with NO donors sensitized them to apoptosis by TNF-related apoptosis-inducing ligand (TRAIL) through NF-κB inactivation and inhibition of Bcl-related gene expression (Huerta-Yepez et al., 2004). These studies indicate that both endogenous and exogenous sources of NO can increase the pro-apoptotic effects of other anticancer agents. There have also been reports of radiosensitizing effect of NO and iNOS on colorectal cancer cells (Chung et al., 2003; Wang et al., 2004). In one of these studies, increased NO was associated with increased tumor vascularity, which although generally considered as a cancer-promoting hallmark, was suggested as a mechanism to increase the radioresponsiveness of the tumor (Wang et al., 2004). A second mechanism for the enhanced radiosensitivity was also found, involving NO-induced increase in the expression and activation of p53 (Cook et al., 2004; Wang et al., 2003). It seems that a functional p53 protein would be key to this effect, which may introduce a problem in the large proportion of p53-mutant tumors. Based on a separate study, the effect of NO on cancer growth may indeed depend on whether the tumor cells have functional or mutated p53; this study demonstrated that NO reduced the growth of colorectal cancer cell lines expressing wild-type p53, whereas it accelerated growth in their mutant p53 counterparts (Ambs et al., 1998). These results suggest that the genotype of the cancer is an important consideration and may affect whether NO exerts the desired anticancer effects or does the opposite.

While the above studies indicate very promising, pro-apoptotic anticancer effects of NO, there is also evidence to the contrary. In a murine model of renal cell carcinoma, NO administration was found to be unable to affect the primary tumor burden in the mice, although it was able to reduce metastases and therefore improve survival (Weiss et al., 2010). Thus, in this case NO was unable to induce sufficient apoptosis to reduce the tumor burden, contrary to the previous studies demonstrating significant pro-apoptotic effects of the gasotransmitter; still, the beneficial effects of NO remained due to its ability to suppress the spread of the cancer. On the other hand, in a model of human breast cancer, NO induced the activation of epidermal growth factor receptor (EGFR) and steroid receptor coactivator (Src) through a mechanism involving S-nitrosylation which led to further activation of oncogenic pathways including cellular myelocytomatosis (c-Myc), Akt, and β-catenin, inhibited the tumor suppressor protein phosphatase 2A (PP2A)-c, and thus increased cancer cell proliferation and led to increased resistance of the cancer cells to adriamycin and paclitaxel chemotherapies (Switzer et al., 2012). This directly contradicts prior studies in which NO was seen to inhibit c-Myc, Akt, and β-catenin signaling. Similarly, exogenous NO administration has been shown to protect neuroblastoma cells against H_2O_2-induced apoptosis (Yoo et al., 2018). A separate study with several different tumor models in vitro and in vivo also demonstrated that iNOS-derived NO production by tumor-associated M2-polarized macrophages protected tumor cells against apoptosis induced by cisplatin therapy by inhibiting acid sphingomyelinase (Perrotta et al., 2018), whereas iNOS inhibition suppressed melanoma growth and synergized with cisplatin therapy in vivo (Sikora et al., 2010). The reason for these conflicting study results may be attributable to various factors, including method of NO augmentation, specific cancer model used, release kinetics, and concentration of gasotransmitter used. A bell-shaped effect of NO on the growth of colon cancer cells has been reported; whereas endogenous NO promoted colon cancer cell proliferation, the inhibition of endogenous CO production as well as exogenous administration suppressed cancer cell proliferation (Oláh et al., 2018).

3.1.2. Carbon monoxide in cancer cell proliferation and apoptosis

There is a wide range of evidence to support an anti-proliferative, pro-apoptotic effect of CO in different cancer models (Fig. 3). A series of studies with photoactive CORMs have demonstrated their ability to induce apoptosis in the malignant cell lines HeLa and MDA-MB-231 human breast cancer cells with an efficacy comparable to approximately 3-day incubation with 10–25 μM 5-fluorouracil, a widely used cytotoxic chemotherapy (Carrington et al., 2013; Carrington et al., 2014; Chakraborty et al., 2015). Recently, the antigen-specific delivery of CO using photoactivatable antibody-photoCORM has also demonstrated promise in selective CO delivery and cytotoxicity toward cancer cells in an ovarian cancer model (Kawahara et al., 2020).

Further exploration with another photoactive CORM, $[Mn(CO)_3Br(\mu\text{-bpcpd})]_2$ (MnCORM) with lung, cervical, breast, and colon cancer cell lines revealed that apoptosis was induced through the intrinsic pathway by increasing ROS, resulting in the loss of mitochondrial membrane potential and corresponding increases in Bax, cytochrome *c* release, caspases −3 and −9, and a decrease in anti-apoptotic Bcl-2 levels (Vidhyapriya, Divya, Bala and Sakthivel, 2018). These findings have found confirmation in other studies using CORM-2 with non-small cell lung cancer (Shao et al., 2018) and pancreatic cancer (Yan et al., 2018). CO was also found to induce cell death in human lung carcinoma cells through mitochondrial exhaustion (Wang et al., 2021) and in breast cancer cells through metabolic starvation by inhibiting aerobic glycolysis (Guan et al., 2019). Thus, CO may induce apoptosis through direct targeting of cancer cell metabolism and mitochondrial apoptosis.

CO may also inhibit the proliferation of cancer cells through modulation of cell cycle regulatory proteins, demonstrated by the downregulation of cyclin D1 and CDK4 upon CORM treatment of MCF7 and MDA-MB-231 breast cancer cells (Lee, Chen, et al., 2014). Cyclin D1 and CDK4 are both involved in promoting cell cycle progression and their upregulation in different cancers has been associated with poorer prognosis (Bahnassy et al., 2004; Dong et al., 2001; Kenny et al., 1999; Wu et al., 2011), thus the ability of CO to downregulate these proteins can exert anticancer effects by suppressing cell cycle progression. CO was also able to downregulate human telomerase reverse transcriptase (hTERT) (Lee, Chen, et al., 2014), which is implicated in conferring cancer cells with replicative immortality, motility, and a stem cell phenotype (Hannen & Bartsch, 2018). Importantly, this gasotransmitter has also demonstrated the ability to modulate the expression of p53, a tumor suppressor protein responsible for cell cycle arrest and apoptosis where needed, mutations of which can promote cancer development and resistance to cancer drug resistance (Hientz et al., 2017; Hu et al., 2021). Interestingly, CORM treatment was found to increase p53 expression in MCF7 cells, which had wild-type p53, while it downregulated p53 expression via ubiquitination in MDA-MB-231 cells, which had mutant p53 (Lee, Chen, et al., 2014). This indicates that CO therapy may both, boost the tumor suppressive activity of p53 in cancer cells where p53 function remains normal, while eliminating mutant p53 that may promote cancer cell growth and drug resistance (Hientz et al., 2017, Hu et al., 2021). An earlier study with chronic lymphocytic leukemia cells showed a similar pattern, where inhibition of heat shock protein 90 (Hsp90) downregulated mutant p53 while upregulating wild-type p53 (Lin, Rockliffe, et al., 2008). This suggests the possibility that CO may affect p53 through an Hsp90-dependent mechanism; indeed, both CORM treatment and HO-1 induction resulted in downregulation of Hsp90-client proteins, including Akt, estrogen receptor alpha (Erα), and CDK4, indicating inhibition of Hsp90 by this gasotransmitter (Lee, Chen, et al., 2014). Akt is a serine/threonine kinase whose aberrant activation is oncogenic and has been seen in many cancers, and its functions are reviewed in detail in (Revathidevi & Munirajan, 2019). This highlights another avenue through which CO can inhibit cancer proliferation: through downregulation of growth signaling pathways that can increase tumor growth. The modulation of Akt activity by CO was also reported in a model of pancreatic cancer, where decreased activating phosphorylation of Akt was seen in association with CO (Vítek et al., 2014). Other findings that have been linked with the CO-mediated induction of apoptosis in lung tumors were increased expression of CD86, a molecule necessary for antigen presenting cells (Axelsson et al., 2020), and activation of MAPK/ERK1/2-c-myc pathway in the tumor microenvironment (TME) (Nemeth et al., 2016), a pathway which has also been identified to be important in solid tumor growth (Zuo et al., 2023).

Importantly, CO administration may also increase the cytotoxic effects of various existing chemotherapies. In two separate studies, CO exposure through administration of either HisAgCCN, a photocatalytic nanomaterial that can convert endogenous CO_2 to CO, or air exposure at 250 ppm, was found to synergize DNA-damaging doxorubicin and camptothecin chemotherapies in inhibiting prostate cancer growth; these studies reported increased oxidative stress (Zheng et al., 2017) and mitotic catastrophe followed by mitochondrial collapse (Wegiel et al., 2013) as the mechanisms of apoptosis induction. Interestingly, both studies also demonstrated protective actions of CO for normal cells against chemotherapy-induced cell death (Wegiel et al., 2013; Zheng et al., 2017), an indication that CO therapy have a use in the selective targeting of cancer cells. A separate study with doxorubicin-resistant MCF-7/ADR tumors showed that thermal-induced CO-releasing platforms reversed the resistance to therapy by causing mitochondrial exhaustion, resulting in ATP depletion and blocking ATP-dependent efflux of doxorubicin, while also inducing apoptosis through caspase-3 upregulation (Li, Dang, Liang and Yin, 2019b). CO treatment has also been found to synergize with a multitude of other chemotherapeutic agents, including the experimental chemotherapeutic agent tirapazamine by inducing mitochondrial exhaustion apoptosis in breast cancer (Li et al., 2019a), the microtubule-targeting paclitaxel by inhibiting CYP3A4/2C8 (Kawahara et al., 2021), and, in ovarian cancer, the cytotoxic DNA-damaging agent cisplatin by inhibiting CBS, thus reducing glutathione and metallothionein, which may be implicated in cisplatin resistance (Kawahara et al., 2019). Interestingly, while CO may increase the sensitivity of cancer cells to cisplatin-induced apoptosis, it was protective against cisplatin-induced apoptosis in non-cancerous renal tubular cells (Tayem et al., 2006); these opposing effects in cancerous vs non-cancerous cells may indicate a beneficial selectivity of this gasotransmitter's pro-apoptotic effects.

In contrast to the anti-proliferative and pro-apoptotic effects of CO on various cancer models as described above, exogenous administration of CO has been found to increase the resistance of medulloblastoma cells to oxidant-induced apoptosis (Al-Owais et al., 2012), and protect hepatocellular cancer cells against cell cycle arrest induced by the anti-proliferative cytokine transforming growth factor (TGF)-β1 (Park et al., 2018); mechanistically, these findings were linked to an inhibitory effect of CO on potassium (K^+) channels, and CO-induced Smad3 phosphorylation through the ERK 1/2 pathway, respectively. Similarly, inhibition of HO-1 was found to reduce, whereas HO-1 inducers increased, the size and number of tumorspheres in breast cancer stem cells (Kim et al., 2018). These effects were attributed to HO-1-derived CO, as CORM-2 treatment increased the proportion of MDA-MB-231 retaining cancer stem cell properties, and increased the expression of neurogenic locus notch homolog protein 1 (*Notch-1*), which was accompanied by an increase in tumorsphere formation (Kim et al., 2018). The reason behind these conflicting effects of CO is not entirely clear, although it is possible that the experimental setup, including the CO administration strategy, concentration, route, release kinetics, and the type of cancer may play a role. Interestingly, one in vitro study demonstrated a bell-shaped effect of CO on the proliferation of colon cancer cells: endogenous CO production was found to promote their proliferation, whereas both inhibition of endogenous CO production and exogenous administration suppressed proliferation (Oláh et al., 2018). Thus, it is possible that while physiologic H_2S levels promote cancer growth, both supraphysiological and below physiological levels causes cancer growth inhibition.

3.1.3. Hydrogen sulfide in cancer cell proliferation and apoptosis

Exogenous H_2S administration using H_2S-releasing NSAIDs has demonstrated the potential to exert growth inhibitory effects against several cancer cell lines in vitro, including colon, breast, T-cell leukemia, pancreatic, prostate, and lung cancers (Chattopadhyay, Kodela, Nath, Barsegian, et al., 2012). There is evidence to suggest a protective role of CSE, in particular, against cancer. For instance, the analysis of human melanoma samples revealed that the highest levels of CSE were found in primary tumors, whereas metastases, especially those involving the lymph nodes, had severely reduced CSE (Panza et al., 2015a), raising the possibility of CSE being a protective factor whose loss allows increased tumor aggressiveness. Correspondingly, in further investigation with melanoma cell lines both CSE overexpression and exogenous H_2S administration inhibited cell proliferation and induced apoptosis; likewise, L-cysteine administration to mice bearing melanoma tumors was protective against tumor growth, whereas CSE inhibition abolished this protective effect (Panza et al., 2015b). Interestingly, H_2S donor S-propargyl-cysteine (SPRC), which was seen to have significant anti-cancer effects both in vitro and in vivo in gastric cancer, was also seen to upregulate CSE expression and activity (Ma et al., 2011). This suggests the possibility that exogenous administration of H_2S can be used to upregulate the innate antitumor defense provided by endogenous H_2S production.

Mechanistically, H_2S employs both pro-apoptotic and anti-proliferative effects to combat cancer growth (Fig. 4). Exogenous H_2S administration using various H_2S donors in vitro has been seen to cause cell cycle arrest in the G_0/G_1 phase in melanoma cells (Panza et al., 2015b), gastric cancer cells (Ma et al., 2011), urothelial bladder carcinoma cells (Panza, Bello, Smimmo, Brancaleone, Mitidieri, Bucci, Cirino, Sorrentino, and R. d'Emmanuele di Villa Bianca, 2022), colon cancer cells (Chattopadhyay, Kodela, Nath, Barsegian, et al., 2012, Wu et al., 2012), cisplatin-resistant lung cancer cells (Ma et al., 2018), and breast cancer cells (Chattopadhyay, Kodela, Nath, Dastagirzada, et al., 2012). Separate studies also reported H_2S to cause G_2/M arrest in breast cancer cells (Lee et al., 2011) and pancreatic adenocarcinoma cells, the latter of which was also found to have S phase arrest (Citi et al., 2019). Cell cycle arrest by exogenous H_2S administration has been associated with the upregulation of the cyclin-dependent kinase inhibitor $p21^{cip}$ (Takeuchi et al., 2008; Wu et al., 2012), suppression of cyclin D1 and CDK4 expression (Panza, Bello, Smimmo, Brancaleone, Mitidieri, Bucci, Cirino, Sorrentino, and R. d'Emmanuele di Villa Bianca, 2022) and inhibition of inactivation phosphorylation of the cell cycle regulatory Retinoblastoma (Rb) protein (Takeuchi et al., 2008).

In combination with cell cycle arrest, H_2S also induces apoptosis to further inhibit cancer growth (Lee et al., 2011, Ma et al., 2011, Chattopadhyay, Kodela, Nath, Dastagirzada, et al., 2012, Chattopadhyay, Kodela, Olson, & Kashfi, 2012, Panza et al., 2015b). The pro-apoptotic effects of H_2S involve several mechanisms, including induction of a shift to a pro-apoptotic state by affecting the balance of pro- and anti-apoptotic proteins. In vitro, the H_2S donor diallyl trisulfide (DATS) has been found to downregulate the anti-apoptotic proteins XIAP and Bcl-2 in urothelial bladder carcinoma cells (Panza, Bello, Smimmo, Brancaleone, Mitidieri, Bucci, Cirino, Sorrentino, and R. d'Emmanuele di Villa Bianca, 2022), and similarly, NaHS downregulated Bcl-xL in lung cancer cells (Ma et al., 2018). In addition to the downregulation of anti-apoptotic proteins, exogenous H_2S administration using NaHS also upregulated pro-apoptotic and cell cycle inhibitory proteins p53 and its activated phosphorylated form, p21, caspase-3, and Bax (Ma et al., 2018). These findings have been supported in vivo in mice bearing gastric cancer tumors, where SPRC was seen to increase Bax and p53 expression while decreasing the expression of Bcl-2 (Ma et al., 2011). The downregulation of anti-apoptotic proteins has been attributed to H_2S-induced inhibition of NF-κB activation, which plays an anti-apoptotic role through upstream upregulation of these proteins (Panza et al., 2015a, De Cicco et al., 2017). A separate study using H_2S-releasing aspirin further elucidated that the inhibition of NF-κB DNA binding activity is associated with prevention of IkappaKinase activation, leading to inhibition of phosphorylation-mediated degradation of IκBα, ultimately preventing the translocation of NF-κB-p65 into the nucleus (Chattopadhyay, Kodela, Nath, Dastagirzada, et al., 2012). Additionally, reduced activation of the β-catenin (Huang et al., 2015), signal transducer and activator of transcription (STAT)3 (Lu et al., 2014), PI3-K/Akt pathways and MAPK/ERK pathways (Panza et al., 2015b, De Cicco et al., 2017), as well as the other two MAPKs, JNK and p38 (Pei et al., 2011) have been implicated in H_2S-mediated apoptosis. Interestingly, one study attributed the anti-proliferative effect of H_2S to induction of autophagy rather than apoptosis; mechanistically, this induction of autophagy was through H_2S stimulation of AMP-activated protein kinase (AMPK) phosphorylation, and inhibition of mammalian target of rapamycin (mTOR) phosphorylation (Wu et al., 2012). Yet another study identified both, apoptosis and autophagy, as the mechanism of anticancer activity exerted by DATS (Panza, Bello, Smimmo, Brancaleone, Mitidieri, Bucci, Cirino, Sorrentino, and R. d'Emmanuele di Villa Bianca, 2022).

A drawback of many currently available cancer therapies is a lack of selectivity for cancerous tissue, leading to significant damage to normal tissue. In one study, H_2S donor NaHS demonstrated a similar drawback, being non-selective in its growth inhibitory effects on colon cancer cells and non-cancerous colon epithelium (Wu et al., 2012). The possibility of H_2S damaging normal non-cancerous tissues aligns with the known cellular cytotoxicity of H_2S (Jiang et al., 2016) that for so long led to it being known as nothing more than a toxic gas. On the other hand, however, several studies have demonstrated selectivity in the growth-inhibitory actions of various H_2S donors; for instance, H_2S-releasing aspirin was seen to preferentially inhibit the growth of breast cancer cells compared to normal mammary epithelial cells (Chattopadhyay, Kodela, Olson, & Kashfi, 2012), and GYY4137 was able to inhibit the growth of seven different cancer cell lines without any effect on non-cancer fibroblast cells (Lee et al., 2011). Additionally, in one study, the continuous exposure of cancer cells, but not non-cancerous cells, to GYY4137 resulted in increased glycolysis and lactate overproduction alongside reduced pH regulatory activity, leading to intracellular acidification and cell death (Lee, Teo, et al., 2014). Thus, there may be an optimal therapeutic administration strategy that maximizes cancer cell damage without allowing H_2S to exert toxic effects on the host. Considering the promise that H_2S may potentially act as a selective cancer therapy that minimizes damage to non-cancerous tissue, further investigation to elucidate the extent of H_2S selectivity is worthwhile.

Interestingly, an anti-apoptotic, pro-proliferative effect of H_2S has also been described in the context of cancer (Fig. 4). NaHS has been found to induce proliferation of colon cancer cells (Cai et al., 2010) and oral squamous cell carcinoma cells (Ma et al., 2015), the former through Akt and ERK phosphorylation and p21 inhibition to allow cell cycle progression (Cai et al., 2010), and the latter through downregulation of cell cycle regulatory genes RPA70 and Rb1, and upregulation of proliferating cell nuclear antigen (PCNA) and CDK4 (Ma et al., 2015). Many of same targets have been previously reported to be affected by H_2S in a completely opposite fashion, as highlighted in preceding sections. In addition to enabling proliferation itself, NaHS has also demonstrated the ability to protect colon cancer cells from apoptosis induced by the potential anti-tumor agent β-phenylethyl isothiocyanate (PEITC) in vitro (Rose et al., 2005).

One possibility accounting for the opposite effects of H_2S on cancer cell growth may be differences in the dosage and H_2S release kinetics of the exogenous donor used. In one study, whereas low dose NaHS (10–100 μM) enhanced the proliferation and viability of hepatocellular carcinoma cells, the same donor at higher concentrations (600–1000 μM) dose-dependently inhibited their proliferation (Wu et al., 2017). This supports the suggestion of a biphasic effect of this gasotransmitter. In addition to dose-dependent effects,

release kinetics may also play a role in these conflicting results. The slow donor GYY4137 has been seen to significantly reduce the growth of several cancer cell lines in vitro—30–70% reduction at 400 μM, and 75–95% reduction at 800 μM—including breast adenocarcinoma, acute promyelocytic leukemia, myelomonocytic leukemia, cervical carcinoma, colorectal carcinoma, hepatocellular carcinoma, and osteosarcoma. Yet in the same study, quick-releasing donor NaHS had no effects on cancer cell survival at the lower concentration, and yielded only a small reduction (15–30%) in the viability of three of the seven cell lines at the higher concentration (Lee et al., 2011). In a separate study using several H_2S donors, NaHS was the only one of all compounds tested that failed to demonstrate melanoma cell proliferation in vitro (Panza et al., 2015b), raising the possibility that the release kinetics and properties of this particular H_2S donor is the reason behind the discrepancy observed here, rather than an anti-apoptotic effect of H_2S itself. Additionally, as H_2S is a highly volatile compound, it is likely that exposure times were short, further impacting the results seen.

Yet other studies have implicated not only NaHS administration, but also CSE and CBS expression and activity in the pro-proliferative effects on cancer cells, indicating a more complex relationship than proposed above. Exogenous H_2S administration using NaHS as well as increased endogenous production through CBS overexpression was seen to protect neuroblastoma cells from apoptosis induced by a dopaminergic neurotoxin; these effects were associated with activation of the protein kinase C (PKC)/PI3K/Akt pathway (Tiong et al., 2010). Thus, the overexpression of endogenous H_2S-producing enzymes may contribute to cancer growth and progression, contrary to the benefits observed previously with exogenous H_2S supplementation. Correspondingly, CBS overexpression has been documented in ovarian carcinoma (Bhattacharyya et al., 2013) and both CSE and CBS overexpression has been reported in hepatocellular carcinoma (Pan et al., 2014; Zhen et al., 2015). Inhibition of these enzymes has been found to inhibit tumor growth, increase apoptosis, and sensitize cancer cells chemotherapy (Bhattacharyya et al., 2013; Pan et al., 2014). Differences between in vitro and in vivo anticancer activity of H_2S may at least partly contribute to these contradictory findings, as in one study NaHS was seen in vitro to increase responsiveness of tumor cells to radiotherapy, whereas no effects on tumor growth was seen in vivo (De Preter et al., 2016). Still, given that both anti- and pro- apoptotic effects have been seen in vitro and in vivo, other factors as donor molecule chosen, concentrations tested, release kinetics, etc., may together be responsible for such alternating findings.

Mechanistically, the demonstrated anti-apoptotic and pro-proliferative effects of H_2S observed from these studies have been attributed to a variety of mechanisms, including activation of NF-κB (Zhen et al., 2015) possibly through sulfhydration of the enzyme (Sen, Paul, et al., 2012a), and activation of Akt alongside suppression of ROS production (Taniguchi et al., 2011), and stimulation and maintenance of DNA damage repair mechanisms (Szczesny et al., 2016; Zhao et al., 2014). NaHS administration has also been seen to induce survivin expression (Cai et al., 2007), a known inhibitor of apoptosis and downstream product in the PI3-K/Akt pathway. Inhibition of H_2S-producing enzymes, on the other hand, has been found to be responsible for increasing ROS and disruption of mitochondrial activity (Bhattacharyya et al., 2013), suppressing PI3K/Akt/mTOR signaling (Khan et al., 2022), activating cell cycle regulatory proteins p53 and p21, decreasing Bcl-2/Bax ratio, and inhibiting of ERK1/2, leading to suppression of EGFR survival signaling (Pan et al., 2014). These findings are surprising in that many of these very same pathways were found to be utilized by endogenous and exogenous H_2S to exert anti-tumor activity, raising questions as to the reason behind these findings.

3.1.4. Gasotransmitters in combination in cancer cell proliferation and apoptosis

In addition to the individual potential benefits of NO, H_2S, and CO in various cancer models, the development of dual gasotransmitter-releasing compounds, mainly NO- and H_2S- releasing NOSH-aspirin, illustrate that combination therapy with two or more of these gasotransmitters with other pharmacological agents is another possible strategy. NOSH-aspirin has been found to inhibit tumor growth in xenograft colon cancer murine models (Chattopadhyay, Kodela, Nath, Barsegian, et al., 2012, Kodela et al., 2015), with a growth reduction of 85% reported (Chattopadhyay, Kodela, Nath, Barsegian, et al., 2012). Another NO- and H_2S- donating compound, NOSH-sulindac, has also been seen to inhibit the growth of 12 cancer cell lines from 6 different tissues by inhibiting cell proliferation, inducing apoptosis, and causing G_2/M cell cycle block (Kashfi et al., 2015).

The anticancer effects of NOSH-aspirin have been attributed to growth inhibition due to cell cycle arrest in G_0/G_1, which both decreases cell proliferation and contributes to increased induction of apoptosis, as seen in pancreatic and colon cancer cells (Chattopadhyay, Kodela, Nath, Barsegian, et al., 2012, Chattopadhyay et al., 2020). Interestingly, NOSH-aspirin was found to be 9000 times more potent in inhibiting colon cancer growth than the sum of its parts, determined through comparison with combinations of aspirin, NO- and H_2S- donating compounds, which suggested that the biological activity of NOSH-aspirin may not be entirely attributed to the synergistic effects of its individual components (Chattopadhyay, Kodela, Nath, Dastagirzada, et al., 2012). Interestingly, the same group also found that the growth-inhibiting effect of NOSH-aspirin on colon cancer cells significantly differs based on its positional isomers and the presence of different electron -donating or -withdrawing groups on its benzoate moieties (Vannini, MacKessack-Leitch, et al., 2015), suggesting an ability to fine-tune and enhance the anti-proliferative and pro-apoptotic effects of the individual gasotransmitters through synthesis of hybrid compounds. Other mechanisms through which NOSH-aspirin induces apoptosis include increased expression of iNOS and p53 – both involved in ROS- and reactive nitrogen species (RNS)- induced apoptosis (Banerjee et al., 2014), and decreased expression of NF-κB and Forkhead box (Fox)-M1 (Chattopadhyay et al., 2020).

Whereas pro-apoptotic effects are widely described with the use of NOSH-aspirin in different cancer models, it seems that normal, non-cancerous cells are protected from these effects. In fact, whereas NOSH-aspirin significantly induced apoptosis in pancreatic cancer cells, the treatment had no inhibitory effects on the regular pancreatic epithelial cells at the same concentration (Chattopadhyay et al., 2020). These selective cancer cell-targeting actions are promising in their ability to combat the cancer while minimizing treatment-related toxicities, which continues to be a widespread issue in many current cancer therapy regimens.

3.2. Role in tumor invasion and metastasis

The ability to invade surrounding tissue and spread, or metastasize, to distant sites is identified as a hallmark of cancer (Fouad & Aanei, 2017). Cancer metastasis is an event that is associated with significantly high mortality (Dillekås et al., 2019; Globus et al., 2021) and is thus an important target for improving prognosis among cancer patients.

For cancerous cells to metastasize, they must first detach from the original mass, invade the extracellular matrix (ECM) and break through the basement membrane, after which they can enter into a circulatory vessel, travel to a new location, extravasate from the vessel, and establish a new niche in which to grow (Fouad & Aanei, 2017). For these steps to occur and allow tumor metastasis, cancer cells take advantage of several molecular changes that are not available to normal cells.

Starting from the first step, in the case of normal epithelial cells, detachment from the ECM results in a process of programmed cell death termed anoikis (Taddei et al., 2012). Invasive cancerous cells can acquire changes that render them resistant to anoikis, through mechanisms such as a switch in the expression of cell adhesion molecules including integrins, increased ROS production, and other changes reviewed in (Taddei et al., 2012). The collection of changes that confer cancer cells

with mesenchymal properties and the abilities for detachment, resistance of anoikis, motility, production of their own ECM, and ultimately invasion is termed epithelial-mesencymal transition (EMT) (Kalluri & Weinberg, 2009). EMT is characterized by the downregulation of epithelial markers such as E-cadherin and upregulation of mesenchymal markers in their place, such as N-cadherin (Loh et al., 2019).

Remodeling of the ECM is another process taken advantage of by cancer cells. Cancer cells can hijack the degradation of the ECM by matrix metalloproteinase (MMP) enzymes. In the physiologic system, MMPs are important for cell proliferation, tissue remodeling, wound healing, the immune response, and angiogenesis (Yan & Boyd, 2007). Cancer cells can take advantage of MMPs to invade through the ECM and ultimately metastasize. Increased levels of different MMPs have been reported in multiple different cancer types, along with an association to poorer prognosis (Hadler-Olsen et al., 2013). Therefore, inhibition of MMPs is a possible therapeutic avenue in combatting cancer. There is evidence that NO, H_2S, and CO may target some of these mechanisms of invasion and metastasis, as discussed in the following sections.

3.2.1. Nitric oxide in cancer cell invasion and metastasis

There is a wide range of evidence to suggest a role of NO in suppressing cancer invasion and metastasis (Fig. 2), indicating the importance of endogenous NO production in the host defense against cancer. In fact, the lack of host iNOS, as investigated in one study using iNOS-null mice, was associated with increased experimental metastases of three iNOS-null fibrosarcoma cell lines (Wei et al., 2003). The anticancer defense of iNOS-derived NO is further supported by reports that the upregulation of iNOS inhibited the migration and metastasis of several cancer models both in vitro and in vivo, including oral cancer (Harada et al., 2004), ovarian cancer (Giri et al., 2014), as well as orthotopic xenograft models of renal cell carcinoma, pancreatic cancer, colon cancer, and prostate cancer (Le et al., 2005). In addition to exerting antimigratory and anti-invasive effects on the primary tumor, endogenous NO production also defends secondary sites from the establishment of a new metastasis, as seen in a murine model of lymphoma, in which NO produced by the liver endothelial cells was credited with the resistance against liver metastasis in a T-cell-dependent manner (Rocha et al., 1995).

Mechanistically, there are several ways in which NO exerts its anti-invasive and anti-metastatic effects. As previously mentioned, EMT is one of the major events in metastasis of carcinomas, and NO has demonstrated the potential to curtail this transition. In a murine model of UVB-induced photo-carcinogenesis, topical treatment of the mice with the NO donor NO-exisulind reduced the overall aggressiveness of the tumor, increased the expression of the epithelial marker E-cadherin, reduced levels of various EMT markers, including fibronectin and N-cadherin, and downregulated EMT inducers such as Snail, Slug, and Twist (Singh et al., 2012). These EMT inducers have been associated with cancer chemoresistance (Haslehurst et al., 2012), reduced overall survival (Wushou et al., 2014), and recurrence (Moody et al., 2005), thus their downregulation by NO would be greatly beneficial in hindering cancer spread. A separate study exploring the mechanism of EMT inhibition by NO in prostate metastatic cell lines further elucidated that NO inhibits the transcription factor NF-κB, of which Snail is one downstream product; in this way, NO has two major effects – it downregulates the EMT-inducer Snail, and also upregulates the metastasis suppressor Raf-1 kinase inhibitor protein (RKIP), which is typically inhibited by Snail (Baritaki et al., 2010). A separate pathway through which NO has been suggested to suppress EMT is through the upregulation of the metastasis-suppressing protein N-Myc-downstream-regulated gene 1 (NDRG1), an effect associated with the interaction of NO with the chelatable iron pool, as seen in a model of triple negative breast cancer (Hickok et al., 2011). The EMT-suppressing effects of NO may not just be limited to cancer models, as exogenous NO administration was seen to suppress EMT in alveolar epithelial cells exposed to the EMT-inducing cytokine TGF-β, whereas inhibition of NOS enzymes by L-NAME treatment resulted in spontaneous EMT (Vyas-Read et al., 2007).

In addition to preventing EMT, NO can reduce tumor invasion and metastasis by directly interfering with ECM remodeling. MMP-9, a protease involved in ECM remodeling, is one of the most widely investigated MMPs in the context of cancer. NO has been found to downregulate MMP-9 by destabilizing MMP-9 mRNA in rat glomerular mesangial cells (Eberhardt et al., 2002); this effect was further demonstrated to arise by inhibiting the expression of the mRNA-stabilizing factor HuR (Akool et al., 2003). The downregulation of MMP-9 by NO was also found to involve the inhibition of PKCδ in a breast cancer cell line in which TPA was used to induce MMP-9 (Jespersen et al., 2009). On the other hand, iNOS upregulation in tumor-associated macrophages was associated with decreased MMP-2 and MMP-9 expression, and was credited with the synergistic anti-metastatic effects of combined IL-2/anti-CD40 immunotherapy; exogenous NO administration confirmed that NO was responsible for these actions (Weiss et al., 2010). These results highlight the possibility of exogenous NO administration to reduce tumor invasion by thwarting ECM remodeling and emphasize the importance of an NO-producing M1 macrophage phenotype to the host defense against cancer. Thus, considering the finding that cancers are able to induce phenotypic switching of macrophages to the anti-inflammatory M2 phenotype (Sousa et al., 2015), augmenting NO either by exogenous administration of modulating endogenous signaling may function to restore the host defense against cancer invasion.

Despite the large amount of evidence suggesting a beneficial, anti-metastatic effect of NO on cancer cells, select studies have reported that NO may also be able to increase cancer migration (Fig. 2). In one study, *Rhus Coriara* extract, an agent that was found to reduce breast cancer cell migration and invasiveness, was also found to downregulate iNOS and NO production (El Hasasna et al., 2016), raising the possibility that reducing NO levels is a part of the anticancer effects. Correspondingly, iNOS expression has been reported as having a strong association with lymph node metastasis and downregulation of the non-metastatic protein 23 (nm23) protein (Dueñas-Gonzalez et al., 1997); in fact, NO administration was even found to induce EMT in breast cancer cells, as seen with the reduced cell-to-cell adhesion, decreased E-cadherin, COX-2 overexpression, which has been associated with EMT induction (Neil et al., 2008; Ogunwobi & Liu, 2011), and increased vimentin (Switzer et al., 2012). Correspondingly, in a mammary-adenocarcinoma cell line, NOS inhibitors NMMA and L-NAME significantly reduced invasiveness whereas stimulation of iNOS-derived NO production using LPS and IFN- γ treatment stimulated invasion (Orucevic et al., 1999). A separate study confirmed the role of iNOS, in particular, in inhibiting cancer invasion, as selective inhibition of this enzyme reduced the invasion of human colorectal adenocarcinoma cell line by almost 50% (Siegert et al., 2002).

One explanation for the differing effects of NO on the invasive ability of cancers is that the gasotransmitter may differentially modulate tumor metastasis based on the identity of the tumor. This is illustrated in one study in which NO was associated with strikingly opposing effects on melanoma and ovarian sarcoma cells lines; whereas the ovarian sarcoma cells produced larger and more metastases in NOS 2-null mice than mice expressing NOS 2, melanoma cells did the opposite (Shi et al., 2000). In the same study, NOS 2-expressing macrophages activated to produce NO had cytotoxic effects on ovarian sarcoma, but not melanoma cells, and the cytotoxic effects were reversed with the inhibition of NOS 2 (Shi et al., 2000). Additionally, the previous described concentration-dependent effects may also be a factor.

3.2.2. Carbon monoxide in cancer cell invasion and metastasis

Both in vitro and in vivo, CO has demonstrated the ability to inhibit the migration, invasion, and metastasis of several cancers (Fig. 3), including breast (Lin, Shen, et al., 2008), colorectal (Lv et al., 2019), prostate (Yan et al., 2018), and non-small cell lung cancers. Mechanistically, one of the ways in which CO may inhibit cancer invasion and

metastasis is through inhibition of EMT, as was demonstrated in models of pancreatic (Yan et al., 2018) and tongue squamous cell carcinoma (Dai et al., 2022). Moreover, low-dose CO was found to inhibit the migration of breast, pancreatic, colon, prostate, liver, and lung cancer cell lines, and inhibit the lung metastasis of breast cancer and liver metastasis of pancreatic cancer in mice; mechanistically, the effects involved blocking the transcription of heme transporters and reducing the level of cytochrome P4501B1 (Zhang et al., 2022), the latter of which has been implicated in cancer metastasis via induction of EMT (Kwon et al., 2016). In non-cancer models as well, CO may be important in preventing EMT, illustrated by the increase in EMT seen with HO-1 deficiency in the kidneys (Kie et al., 2008); in this case, however, it is possible that other products of HO-1 played a role.

In addition to its impact on reducing EMT, CO can also reduce ECM remodeling by downregulating MMP-2, MMP-7, and MMP-9 (Lin, Shen, et al., 2008; Lv et al., 2019; Megías et al., 2007). As previously mentioned, the ECM-degrading actions of these enzymes are exploited by cancer cells to facilitate invasion through the ECM, and it follows that downregulating MMPs will reduce invasiveness and improve prognosis by allowing for localized therapies such as surgical resection of the tumor tissue prior to spread. Furthermore, in an in vivo study with prostate cancer cells, transfection with HO-1 created tumors with reduced MMP-9 positive staining (Ferrando et al., 2011), suggesting that this effect can be seen with both exogenously administered and endogenous increases in CO. Interestingly, the ability of CO to downregulate MMPs has also been seen in non-cancerous, alveolar epithelial cells (Desmard et al., 2005), and *Staphylococcus aureus (S. aureus)*-stimulated aortic endothelial cells (Tsai et al., 2018). In human breast carcinoma cells, through a mechanism involving the upregulation of HO-1, suppression of ERK phosphorylation and decreased c-Jun protein expression, and inhibition of activator protein 1 (AP-1) transcription factor activation by 12-O-tetradecanoylphorbol-13-acetate (TPA, a compound which increases MMP-9 activity), CO was also able to inhibit TPA-induced invasion of breast cancer cells (Lin, Shen, et al., 2008). Thus, the modulation of MMP activity may arise from effects on these upstream signaling pathways. IL-6 was also suggested to play a role in another study in which CORM-2 treatment downregulated MMP-7 expression (Megías et al., 2007). Further investigation into the precise mechanisms of the impact of CO on MMPs and EMT induction is warranted, as it seems a promising avenue for thwarting cancer migration and metastasis.

3.2.3. Hydrogen sulfide in cancer cell invasion and metastasis

H_2S administration using a variety of H_2S-releasing molecules, including SPRC, NaHS, acetyl deacylasadisulfide, the H_2S-releasing isothiocyanate erucin, and HA-ADT—a compound made from the combination of hyaluronic acid and 5-(4-hydroxyphenyl)-3*H*-1,2-dithiol-3-thione (ADT-OH)—has demonstrated the ability to suppress cancer cell migration, and invasion in vitro in gastric cancer cells (Ma et al., 2011; Zhang et al., 2015), colon cancer cells (Wu et al., 2012), breast cancer cells (Dong et al., 2019), pancreatic adenocarcinoma (Citi et al., 2019), metastatic melanoma cells (De Cicco et al., 2017) and in vivo reduce lung melanoma metastases (De Cicco et al., 2017).

Mechanistically, there is evidence that H_2S can hinder invasion and metastasis through the inhibition of EMT (Fig. 4), like the other two gasotransmitters. In A549 human alveolar epithelial cells, the inhibition of CSE using propargylglycine resulted in spontaneous EMT, with the corresponding downregulation in epithelial marker E-cadherin, upregulation in mesenchymal markers N-cadherin and vimentin, and increase in fibroblast-like morphologic features (Fang et al., 2010). Similar findings were reported in a separate study using human urothelial bladder cancer cells, in which H_2S treatment reduced epithelial markers Slug, zinc finger *E*-box binding homeobox 1 (ZEB-1), caveolin-1, and vimentin, alongside increased expression of E-Cadherin upon exogenous H_2S treatment (Panza, Bello, Smimmo, Brancaleone, Mitidieri, Bucci, Cirino, Sorrentino, and R. d′Emmanuele di Villa Bianca, 2022). These findings suggest an inhibitory role of endogenous H_2S production against EMT, both in cancer as well as non-cancer cells. Interestingly, the former study also demonstrated that the treatment of the A549 cells with TGF-β1, a known inducer of EMT, was seen to suppress CSE expression, while exogenous H_2S administration to the TGF-β1-treated cells reversed the EMT-suggestive changes through a mechanism dependent on decreasing Smad2/3 phosphorylation (Fang et al., 2010). These findings were confirmed in separate studies using the same A549 cell model, in which NaHS was seen to reverse paraquat-induced (Bai et al., 2019) and $NiCl_2$-induced migration and EMT through suppression of TGF-β1/Smad2/Smad3 signaling (Ye et al., 2020); the latter study also reported that there was no role of the MAPK signaling pathway in these effects (Ye et al., 2020). In contrast, in a study with breast cancer cells, the anti-EMT effects of H_2S—evidenced by decreased Snail expression—were seen alongside decreased phosphorylation of p38 MAPK (Lv et al., 2014), which has been reported to at least partially account for TGF-β1-induced EMT in alveolar epithelial cells (Chen et al., 2013), suggesting a p38 as a potential target of H_2S in inhibiting EMT. In addition to these pathways, in H_2S-releasing agent diallyl disulfide (DADS) was found to inhibit the β-catenin signaling pathway in breast cancer cells, which was linked to the EMT-suppressing effects of the gasotransmitter (Huang et al., 2015). The role of both ERK and β-catenin signaling in H_2S-mediated EMT inhibition has been confirmed in a non-cancer model using renal tubular epithelial cells (Guo et al., 2016).

Furthermore, H_2S has been found to hinder ECM remodeling through downregulation of MMPs (Fig. 4), a crucial step in cancer invasion. The downregulation of MMP-9 by exogenous H_2S administration using H_2S releasing molecules DADS and DATS has been noted in several models of breast cancer in vitro and in vivo (Huang et al., 2015; Xiong et al., 2018), and in one study, the downregulation in MMP-9 was observed alongside MMP-2 downregulation (Liu et al., 2015). Interestingly, in a separate study with breast cancer cells, NaHS administration led to the downregulation of MMP-2 expression but had no effect on MMP-9 (Ma et al., 2018). The downregulation of MMPs by H_2S has been attributed to several mechanisms, including suppression of the β-catenin pathway (Huang et al., 2015), suppression of NF-κB (Liu et al., 2015), upregulation of tristetraprolin (Xiong et al., 2018)—an RNA-binding protein that has been found to induce MMP-2 and MMP-9 mRNA degradation (Van Tubergen et al., 2013)—and the suppression of EGFR and the MAPK/ERK pathway (Liu et al., 2015; Wu et al., 2017). Importantly, like with proliferation, there may be a dual effect of H_2S on cancer cell migration, with migration being promoted at low concentrations and being significantly inhibited at higher concentrations (Wu et al., 2017). These dual effects coincided with the increase in EGFR and ERK phosphorylation at lower concentrations and reduction in their phosphorylation at higher concentrations (Wu et al., 2017).

Alternatively, H_2S may also play a role in increasing tumor migration, invasion, and metastasis (Fig. 4). Both, endogenous CBS-derived H_2S and exogenous H_2S through NaHS have been found to promote colon cancer cell migration in vitro, whereas inhibition of the enzyme suppressed these effects (Szabo, Coletta, Chao, Módis, et al., 2013). A similar finding was seen with non-small cell lung adenocarcinoma cells and patient specimens, which were found to have upregulated CBS, CSE, and MPST in comparison to non-cancerous tissue whereas inhibition of these enzymes reduced metastatic potential in vitro (Wang, Yan, et al., 2020). These findings suggest upregulation of endogenous H_2S production as a mechanism used by cancer cells to promote their invasiveness, rendering it as a potential target for combatting cancer. In fact, the CBS-suppressing ribosomal protein L3 was identified to potentiate the efficacy of 5-fluorouracil therapy in lung cancer by inhibiting cell invasion and migration (Russo et al., 2016). The invasion-promoting role of H_2S may, in contrast to the previously discussed studies, be the result of EMT induction. Supporting this possibility, NaHS administration in non-small cell lung

adenocarcinoma cells reduced E-cadherin and increased vimentin, indicating induction of EMT, and increased MMP-2 and MMP-9 expression, which allows for enhanced cell invasion (Wang, Yan, et al., 2020). Further investigation highlighted a role of hypoxia-inducible factor (HIF)-1α in these effects, as knockdown of HIF-1α reversed the H_2S-induced EMT phenotype (Wang, Yan, et al., 2020). A second study reported that the H_2S-induced increase in the migration of hepatocellular carcinoma cells involves the activation of NF-κB, as inhibition of this transcription factor reversed MMP-2 upregulation seen with NaHS exposure (Zhen et al., 2015). The role of the NF-κB activation by endogenous H_2S in cancer metastasis was also seen in pancreatic cancer cells; this activation led to increased IL-1β signaling and enhanced cancer invasiveness (Wang, Huang, et al., 2019). Interestingly, as described above, H_2S has also been found to inhibit invasion by suppressing NF-κB (Liu et al., 2015), entirely contrary to the results seen in (Wang, Huang, et al., 2019). Combined with the finding of the dual, concentration-dependent effects of NaHS in cancer invasion (Wu et al., 2017), there is a possibility that these seemingly contradictory effects may be two sides of the same coin, and therapeutic use of these agents is possible with careful tailoring of delivery concentrations and release kinetics.

3.3. Impact on angiogenesis

Angiogenesis involves the sprouting of new blood vessels from the existing vascular network and is considered a hallmark of cancer (Hanahan & Weinberg, 2011). Cancer cells, like normal cells, have requirements for oxygen, nutrients, and a mode to eliminate wastes, which a rich vascular supply provides. However, unlike normal cells in which angiogenesis is a tightly controlled and self-limiting process, in cancer there is a switch to an uncontrolled pro-angiogenic state which not only fulfills the nutritional and oxygen requirements of the cancer, but also provides a route of metastasis to other organs (Baeriswyl & Christofori, 2009). Interestingly, conditioned medium from cancer cells has been seen to induce endothelial cell growth (Lian et al., 2016), indicating that cancer cell secretions are responsible for creating a pro-angiogenic environment.

One of the main triggers for angiogenesis is hypoxia, which is a characteristic of cancer cells. Endothelial cells can sense hypoxia, which leads to the activation of the HIF family proteins that are responsible for various cell survival and angiogenic pathways (Fraisl et al., 2009). Angiogenic activators include, among others, vascular endothelial growth factor (VEGF), angiogenin, TGF-β, TNF-α, platelet-derived endothelial growth factor, and epidermal growth factor (Nishida et al., 2006). Of these, VEGF has received much interest and is a target of many anti-angiogenic cancer therapies (Rajabi & Mousa, 2017). Interestingly, each of the three gasotransmitters has demonstrated either or both pro- and anti- angiogenic properties that must be considered in the context of cancer.

3.3.1. Nitric oxide and cancer angiogenesis

NO has a dual anti-angiogenic and pro-angiogenic role as demonstrated in non-cancer as well as cancer models (Fig. 2). In the basal state, eNOS-derived NO is crucial for the maintenance of the endothelium, and low levels of NO from this enzyme can have a pro-angiogenic effect. In fact, the pro-angiogenic effect of prostaglandin E2 (PGE2) in human umbilical vein endothelial cells (HUVECs) was attributed to increased eNOS activity via the PKA/PI3-K/Akt pathway (Namkoong et al., 2005). These pro-angiogenic actions of NO align with the findings of eNOS recruitment under hypoxic conditions PI3/Akt activation and Hsp90-eNOS binding (Chen & Meyrick, 2004), as well as eNOS induction by the pro-angiogenic signal protein VEGF through hsp90-dependent Akt-mediated activation of the enzyme (Brouet et al., 2001). On the other hand, both sodium nitroprusside (SNP) and L-arginine treatment has demonstrated the ability to curtail angiogenesis in an in vivo model of the chick embryo chorioallantoic membrane, whereas NOS inhibition had the opposite effect (Pipili-Synetos et al., 1993).

These opposing effects seem to be concentration and flux dependent. The biphasic effects of NO have been illustrated in three different endothelial cell lines, where cGMP-dependent stimulatory effects of NO on cell proliferation, adhesion, and chemotaxis were observed at lower levels of DETA-NO treatment, whereas inhibitory effects were observed at higher levels (Isenberg et al., 2005). There is evidence to suggest that the dual pro- and anti-angiogenic activity of NO is associated with its biphasic effect on the activation of PKC, ERK, and the downstream transcription factor AP-1, which has known pro-angiogenic effects mediated through VEGF (Jia et al., 2016; Stanley et al., 2005) and MMPs (Jin et al., 2011; Singh et al., 2010); corresponding to its effects on angiogenesis, NO activated these proteins at low concentrations and inhibited them at higher concentrations (Jones et al., 2004). In addition to these pathways, the concentration-dependent regulation of angiogenesis by NO may also involve its effects on the expression of the anti-angiogenic protein thrombospondin-1 (TSP-1). The regulation of this protein by NO has been seen to be triphasic, with TSP-1 expression decreasing at 0.1 μM DETA-NO, rebounding at 100 μM, and decreasing at 1000 μM (Ridnour et al., 2005). These effects were associated with increased phosphorylated ERK (p-ERK), the inhibition of which abolished the pro-angiogenic activity of DETA-NO (Ridnour et al., 2005). Interestingly, exogenous TSP-1 has been found to reduce NO-induced ERK phosphorylation, suggesting a feedback regulation cycle between these two signaling molecules (Isenberg et al., 2005; Ridnour et al., 2005).

Many of the studies conducted with cancer models have demonstrated pro-angiogenic effects of this gasotransmitter, which is a potential limitation in its use in cancer. Exogenous administration of NO has been found to increase VEGF expression in glioblastoma and hepatocellular carcinoma cells (Chin et al., 1997), and furthermore, iNOS expression in lung cells was linked to increased vascularization and VEGF expression compared to iNOS-deficient lines (Ambs et al., 1998). These findings suggest that both endogenous and exogenous NO sources exert pro-angiogenic effects. Similarly, iNOS upregulation, which was associated with increased VEGF and tumor vascularity, has been observed in cancerous tissue compared to normal mucosa, and in metastatic tumors compared to non-metastatic ones (Cianchi et al., 2003; Gallo et al., 1998). Thus, iNOS upregulation may be a characteristic of cancer aggressiveness as a result of angiogenesis, and inhibition of endogenous NOS production may counter cancer angiogenesis and therefore metastasis as well. In fact, studies using non-specific NOS inhibitors, iNOS and eNOS short hairpin RNA (shRNA), and an iNOS-selective inhibitor have reported downregulation of pro-angiogenic genes and proteins, reduced tumor neovascularization, and correspondingly, increased necrotic tumor tissue (Gao et al., 2019; Jadeski & Lala, 1999). Interestingly, however, while iNOS gene transfer was seen to upregulate pro-angiogenic molecules including VEGF and IL-8 in fibrosarcoma and colorectal adenocarcinoma models, the tumor cells were still unable to form metastases, and this dramatic loss of malignancy was attributed to the apoptotic effects of NO (Le et al., 2005). This suggests that the pro-angiogenic effect of NO might not sufficiently counteract its other anticancer effects.

Alternatively, by increasing tumor perfusion NO may enhance the ability of other cytotoxic therapies to reach the tumor and exert their damage; in one study, the enhanced blood perfusion of tumor tissue allowed increased tumoral accumulation of NO- and O_2- delivering ultrasound-responsive nanoparticles, which were used to enhance the anti-cancer effects of sonodynamic therapy and increase the immune response to the tumor (Ji et al., 2021). Still, the balance between the beneficial effects of increasing vs depleting tumor blood supply needs to be investigated further with respect to optimal concentration, to ensure the therapeutic effects of this gasotransmitter in cancer.

3.3.2. Carbon monoxide and cancer angiogenesis

Like NO, CO seems to have a dual role in stimulating or inhibiting angiogenesis (Fig. 3), which may depend on the physiological or pathological context in which it is acting. In astrocytes, CORM-2 administration was found to induce angiogenesis by increasing pro-angiogenic VEGF levels through upregulation of the HIF-α protein, which was done using two pathways: promoting HIF-α translation and stabilizing the protein against degradation (Choi et al., 2010). Endothelial cells exposed to another CORM, CORM-401, also upregulated VEGF levels in vitro, as well as levels of IL-8 (Fayad-Kobeissi et al., 2016), a chemokine known to induce angiogenesis through endothelial cell proliferation (Li et al., 2003).

On the other hand, CO has in numerous studies displayed anti-angiogenic effects against cancer cells. Whereas CO increased IL-8 levels in endothelial cells in the study discussed previously (Li et al., 2003), in human gastric cancer cells, CORM-2 treatment decreased IL-1β-induced expression of IL-8, and inhibiting IL-8 using a neutralizing antibody reversed the stimulatory effect of the cancer conditioned medium on endothelial cell growth (Lian et al., 2016). This effect was the result of modulation of several pathways, including the inhibition of ROS-mediated NF-κB activation, inhibition of ERK1/2 activation, and suppression of MAPK-mediated AP-1 activation (Lian et al., 2016). These opposing effects in normal compared to cancerous tissue may suggest CO as a useful molecule in depriving neoplastic tissue of blood supply without negatively affecting the vascularization of normal tissue. This selectivity may increase the utility of CO compared with many current anti-angiogenic cancer therapies whose side effects, including impaired wound healing, endothelial dysfunction, hypertension, and increased clotting risk, result from their lack of such selectivity (Rajabi & Mousa, 2017). Other studies with CO in both in vitro and in vivo cancer models have shown its ability to reduce de novo angiogenesis by inhibiting phosphorylation of p-Akt—of which angiogenesis is one downstream effect—reducing VEGF levels and inhibiting VEGFR2 phosphorylation, and decreasing the migration and tube-forming ability of endothelial cells; these effects were seen with pancreatic, colorectal, triple-negative breast cancers, and, interestingly, in HUVECs (Ahmad et al., 2015; Kourti et al., 2019; Kourti et al., 2021; Lv et al., 2019; Vítek et al., 2014). The anti-angiogenic effects of CO on non-cancerous HUVECs suggests that the selectivity of CO for cancer may not be absolute.

Yet CO may not have anti-angiogenic effects against all cancers. Increased HO-1 expression has been seen to induce VEGF secretion and angiogenesis and correlate to increased vascular density in models of prostate cancer (Birrane et al., 2013), melanoma (Was et al., 2006), glioma (Nishie et al., 1999), and non-small cell lung cancer (Skrzypek et al., 2013), whereas it decreased neovascularization and VEGFR2 expression in PC3 cancer cells (Ferrando et al., 2011). It is worth noting here that although HO-1 is responsible for producing CO, it also yields other products such as biliverdin and ferrous iron; therefore, it is possible that CO is not the mediator behind these effects. Still, a dose-dependent increase in vascular permeability and tumor blood supply was observed with treatment using both CORM-2 and HO-1 induction in S180 solid tumors (Fang et al., 2012), thus, the possible role of CO in increasing tumor blood supply cannot be ignored, albeit this effect was through increasing vascular permeability rather than angiogenesis. Further studies on the precise role of CO on angiogenesis in the context of different cancers would be worthwhile.

3.3.3. Hydrogen sulfide and cancer angiogenesis

Based on the available evidence, H_2S seems mainly to be a pro-angiogenic signaling molecule (Fig. 4), which may contraindicate its use in cancer. Both in vitro and in vivo, exogenous administration of H_2S and its precursors, L-cysteine and 3-MP, has been found to increase endothelial cell growth, proliferation, migration, microvessel formation, and accelerate wound healing through increased neovascularization (Cai et al., 2007; Coletta et al., 2012; Coletta et al., 2015; Papapetropoulos et al., 2009). Likewise, the endogenous production of H_2S has been demonstrated to have the same pro-angiogenic effects, whereas inhibition of H_2S-producing enzymes suppresses angiogenesis (Papapetropoulos et al., 2009). All three H_2S-producing enzymes have been identified as having a role in this regard. The pro-angiogenic role of CSE is demonstrated by the marked reduction of the pro-angiogenic effects of VEGF upon CSE silencing, with a corresponding enhancement in the outgrowth of branching microvessels with CSE upregulation; this suggests endothelial H_2S synthesis to be crucial for VEGF signaling (Coletta et al., 2012). VEGF stimulation of endothelial cells also increases H_2S production (Papapetropoulos et al., 2009), suggesting a self-reinforcing cycle of events to ensure angiogenesis in conditions where it is needed. Correspondingly, CSE expression is upregulated in hypoxic conditions, further supporting its role in angiogenesis and protection against insufficient oxygen delivery (Wang et al., 2014). Because hypoxia is a major feature of solid tumors and is associated with tumor progression and increased treatment resistance (Brahimi-Horn et al., 2007), it is possible that H_2S production by tumor tissue promotes tumor survival through its effects on vascularity. CBS is also involved in angiogenesis, and silencing of this enzyme was seen to significantly decrease HUVEC proliferation, diminish the pro-angiogenic effects of VEGF, and reduce transcription of the VEGF receptor VEGF receptor 2 (VEGFR2) and neuropilin 1—both essential for endothelial function—whereas exogenous H_2S administration using NaHS and GYY4137 reversed these effects by stabilizing the transcription factor specificity protein 1 through protein S-sulfhydration (Saha et al., 2016). Lastly, the 3-MP/3-MST/H_2S pathway has also been seen to promote angiogenesis both in vitro and in vivo (Coletta et al., 2015).

Mechanistically, the pro-angiogenic effects of H_2S involve several mechanisms. There is evidence to indicate a role of the PI3-K/Akt pathway—which is downstream of VEGFR2 activation—in H_2S-induced angiogenesis, and in one study blocking PI3-K was seen to suppress the pro-angiogenic effects of H_2S in vitro (Cai et al., 2007). Additionally, exogenous administration of H_2S and NaHS has been found to induce activating phosphorylation of the downstream signaling molecule Akt (Cai et al., 2007; Coletta et al., 2012; Wang et al., 2009). Interestingly, one study that reported involvement of the PI3-K/Akt pathway also ruled out any effects of H_2S on the phosphorylation of p38 and ERK (Cai et al., 2007), while a separate study reported the opposite: that H_2S increased the phosphorylation of both of these molecules to induce angiogenesis, and that inhibition of the PI3-K/Akt pathway did not affect the migration of H_2S-exposed endothelial cells (Papapetropoulos et al., 2009). The latter demonstrated that inhibition of p38 abolished H_2S-induced motility of endothelial cells, further supporting its role in angiogenesis, and highlighted the role of K_{ATP} channels in p38 phosphorylation, where blocking these channels inhibited p38 phosphorylation while enhancing their opening increased p38 phosphorylation (Papapetropoulos et al., 2009). Whether this pathway or the PI3-K/Akt pathway, or both, are involved in H_2S-induced angiogenesis is not clear.

As previously mentioned, the signaling and actions of VEGF are intertwined with H_2S production and release, illustrated by the finding that CSE silencing reduces the pro-angiogenic effect of VEGF (Coletta et al., 2012). The increased vessel growth and capillary density upon NaHS treatment in a rat model of hind limb ischemia was found to be associated with increased VEGF expression and VEGFR2 phosphorylation (Wang et al., 2009), and indeed, H_2S has been found to upregulate HIF-1α and VEGF mRNA and protein levels and increase HIF-1α binding activity under hypoxic conditions (Liu et al., 2010). HIF-α, the upstream regulator of VEGF expression, is necessary for the pro-angiogenic effects of H_2S, as HIF-α silencing suppressed these effects in vitro (Zhou et al., 2015). Similarly in ex vivo renal artery culture, triple gene therapy with CBS, CSE, and 3-MST, as well as H_2S treatment, led to increased

VEGF and reduced antiangiogenic factor endostatin (Sen, Sathnur, et al., 2012). On the other hand, no change in VEGF levels were seen in NaHS-treated endothelial cells in other studies (Cai et al., 2007; Tao et al., 2013), raising the question of whether the upregulation of VEGF and HIF-1α is a direct effect of H_2S or a result of other influences such as hypoxia. There is also evidence that H_2S can directly activate VEGFR2 through cleavage of an inhibitory disulfide bond of the receptor, allowing VEGFR2 phosphorylation, accompanied by downstream phosphorylation of PI3-K and Akt; interestingly, Akt was not a direct target of H_2S, rather its phosphorylation was a downstream effect of VEGFR2 activation (Tao et al., 2013). This suggests the possibility that the previous studies indicating Akt phosphorylation by H_2S as a mechanism for angiogenesis were describing a downstream effect of H_2S on VEGFR2 (Tao et al., 2013).

H_2S-induced angiogenesis also seems to involve an NO-dependent mechanism. NOS inhibition using L-NAME has been seen to abolish the proliferation of endothelial cells induced by H_2S exposure in vitro, and in vivo, eNOS-deficient mice completely lack the microvessel outgrowth-promoting effect of H_2S (Coletta et al., 2012). The opposite was also true: H_2S was required for the pro-angiogenic effects of NO donor therapy (Coletta et al., 2012). Thus, reducing the bioavailability of either one of these gasotransmitters while administering the other may allow therapeutic use of one of these gasotransmitters while reducing its potential to induce a harmful pro-angiogenic effect. Further investigation revealed that the angiogenesis-stimulating effects of these gasotransmitters converges on the cGMP/PKG pathway, as inhibiting sGC abolished the pro-angiogenic effects of both (Coletta et al., 2012). This is plausible, given that NO is a known activator of sGC which leads to cGMP production (Bryan et al., 2009), while H_2S is a known inhibitor of PDE5A (Bucci et al., 2010), leading to reduced breakdown and increased accumulation of cGMP. Furthermore, H_2S also exerts redox regulation on sGC and thereby enhances its response to NO, allowing more efficient cGMP production (Zhou et al., 2016). Additionally, H_2S stimulates phosphorylation of Akt, which led to activating phosphorylation of eNOS, demonstrating further cooperation between the two gasotransmitter (Coletta et al., 2012). Supporting the role of NO in H_2S-induced angiogenesis, H_2S has been found to promote ischemic vascular remodeling with increased HIF-1α and VEGF activity in an NO-dependent manner (Bir et al., 2012), as well as NO-dependent monocyte recruitment and arteriogenesis (Kolluru et al., 2015).

The combination of these findings gives a strong indication that H_2S facilitates tumor progression and spread through the formation of new vascular networks. The overexpression of H_2S-producing enzymes and increased H_2S levels have been reported in various tumors, including colon cancer (Szabo, Coletta, Chao, Modis, et al., 2013), non-small cell lung adenocarcinoma (Wang, Yan, et al., 2020), hepatocellular carcinoma (Zhen et al., 2015), and Von Hippel Lindau clear cell renal cell carcinoma (Sonke et al., 2015). Aligning with the previous discussion, in these cancer models H_2S has been seen to increase tumor neovascularization alongside HIF-1α activation and VEGF upregulation, whereas inhibition of H_2S production reverses these pro-angiogenic effects (Szabo, Coletta, Chao, Módis, et al., 2013, Sonke et al., 2015, Zhen et al., 2015, Wang, Yan, et al., 2020). Interestingly, one study demonstrated a difference in the pro-angiogenic effects of H_2S on breast cancer endothelial cells vs non-cancerous endothelial cells; whereas NaHS treatment induced cytosolic Ca^{2+} release in both cell types, at low concentrations (1–10 μM) it promoted VEGF-induced migration and invasion of the cancer endothelial cells while failing to do so in the non-cancerous endothelial cells (Pupo et al., 2011). This indicates that H_2S may have a harmful level of selectivity, preferentially promoting cancer angiogenesis and invasion. Overall, the evidence seems to indicate that the pro-angiogenic effects are a drawback to its use in the context of cancer and suggest the need to combine any potential H_2S therapy with known antiangiogenic agents or other cytotoxic agents that can take advantage of the increased tumor blood supply induced by H_2S exposure.

3.4. Impact on the immune system

Evasion of the host immune response is a hallmark of cancer (Mortezaee, 2020), which proves as a major obstacle to the development of effective anticancer therapeutic strategies. There is an entire branch of cancer therapies—termed immunotherapy—that focuses on restoring the host immune response to cancer, an approach that has already demonstrated great promise (Farkona et al., 2016). However, the dysfunction and exclusion of T cells is a major limitation to the efficacy of such therapy (Jiang et al., 2018), indicating the need for additional strategies that further boost antitumor immune function.

The cytotoxic $CD8^+$ T cell population is one of the main cell types involved in the cytotoxic anticancer immune response, and intratumoral infiltration of these cells has been associated with improved prognosis and increased survival in several cancers (Ali et al., 2014; Hiraoka et al., 2006; Naito et al., 1998; Shimizu et al., 2019). Unfortunately, cancer cells are able to acquire several adaptations that suppress both $CD8^+$ T cell infiltration into the cell and the cytotoxic effects of this cell, including through recruitment of immunosuppressive myeloid-derived suppressor cells (MDSCs) (Lesokhin et al., 2012), increased levels of which has been associated with poorer survival (Jordan et al., 2013), induction of immunosuppressive Treg cells (Chen et al., 2005a, Chen et al., 2005b), and anti-inflammatory M2 polarization of tumor-associated macrophages (Lepique et al., 2009; Pu et al., 2021). Targeting any of these immunosuppressive steps may significantly augment the antitumor immune response. In addition to their other actions, each of the gasotransmitters has been found to play a role in immunomodulation to some degree, with some promising effects and some potential drawbacks to their use.

3.4.1. Nitric oxide immunomodulation in cancer

A large proportion of the studies investigating the immunomodulating actions of NO have described the gasotransmitter to have an immunosuppressive role (Fig. 2), which may contraindicate its use in the context of cancer. In fact, NO is involved in the suppression of T cell proliferation by mesenchymal stem cells (Sato et al., 2006), and there is evidence to suggest that cancer cells may take advantage of the immunosuppressive activity of NO and use it to escape immune surveillance. In one study, the coculture of melanoma cells with peripheral blood mononuclear cells (PBMCs) from healthy volunteers demonstrated the former's ability to suppress the IFN response in PBMCs, an effect that was negatively correlated with NOS1 expression (Liu et al., 2014); interestingly, increased NOS1 expression was also associated with reduced responsiveness of melanoma metastases to adoptive T cell transfer immunotherapy (Liu et al., 2014). Not only NOS1, but the other NOS enzymes also play a role in this regard. Tumor-recruited myeloid-derived suppressor cells (MDSCs)—which have a purpose of inhibiting cytotoxic T cells and thus allowing tumor growth and metastasis—have been found to be dependent upon tumor-expressed iNOS to induce T cell suppression, whereas iNOS inhibition reduces MDSC accumulation and immunosuppressive activity, and increases intratumoral $CD8^+$ T cell infiltration and cytotoxic activity both in vitro and in vivo (Dufait et al., 2015; Jayaraman et al., 2012). Therapeutic targeting of MDSC-mediated immunosuppression is of great interest in combatting cancer, as there is evidence that MDSC accumulation is a limitation of adoptive immunotherapy with cytotoxic T cells, as seen in a murine model of melanoma, where the MDSCs then resulted in NO-mediated immunosuppression that was reversed using the NO scavenger carboxy-PTIO (Hirano et al., 2015). Further study has revealed two different subpopulations of MDSCs—granulocytic and monocytic MDSCs—both of which inhibit T cell function through NO-dependent pathways; however, while granulocytic MDSCs exert their effects through

eNOS-derived NO, monocytic MDSCs do so through iNOS-derived NO (Raber et al., 2014). Thus, all three NOS isoforms seem to be implicated in cancer-induced T cell suppression.

There are several pathways through which NOS activity can suppress T cell function. One of these involves the nitration of tyrosine residues necessary for T lymphocyte activity. A study with organ cultures of human prostate adenocarcinoma revealed increased nitrotyrosine in the immunosuppressed tumor-infiltrating lymphocytes, whereas inhibition of iNOS and arginase, another enzyme involved in L-arginine metabolism, was seen to reduce tyrosine nitration and reinstate T cell antitumor activity (Bronte et al., 2005). It is possible that NO itself may not be to blame for this, as increased arginase activity can lead to L-arginine depletion leading to increased NOS production of superoxide anions; these then react with NO to form peroxynitrite, a damaging radical known to cause tyrosine nitration, inhibiting T cell activation and inducing T cell apoptosis in vitro (Brito et al., 1999). There is support for these findings from an in vivo murine model, in which the hyperproduction of peroxynitrite and ROS by MDSCs induced nitration of the T cell receptor (TCR)/CD8 complex, thwarting T cell binding to peptide-specific major histocompatibility complex (MHC) molecules, leading to T cell tolerance (Nagaraj et al., 2007); interestingly, the ability of these cells to induce T cell tolerance remained even in iNOS-deficient mice, suggesting the upregulation of ROS rather than NO to be the culprit behind the immunosuppressive effects, further supporting that it is peroxynitrite, and not specifically NO, that is responsible for this effect (Nagaraj et al., 2007). Other studies have highlighted additional mechanisms for T cell suppression, including iNOS-derived NO-mediated inhibition by MDSCs of IL-2R signaling pathways required for T cell activation (Mazzoni et al., 2002), peroxynitrite-mediated nitration of the CCL2 chemokine, which hinders T cell infiltration and sequesters these cells in the stroma surrounding the tumor (Molon et al., 2011), and inhibition of vascular *E*-selectin expression, an adhesion molecule whose expression was positively correlated with the intratumoral infiltration of CLA^+ memory T cells (Gehad et al., 2012). The immunosuppressive effects on T cells in these studies were reversed with the inhibition of NOS enzymes (Mazzoni et al., 2002) or suppression of peroxynitrite production (Molon et al., 2011).

While anti-tumor T cell activity is inhibited by these agents, immune-suppressing T cell phenotypes may be differentially impacted. In one study, iNOS-expressing mice were found to have increased an pro-tumor, IL-17-secreting phenotype of γδ T cells compared to their iNOS-deficient counterparts, leading to the recruitment of MDSCs and impaired cytotoxicity of γδ T cells toward melanoma cells (Douguet et al., 2016). On the other hand, in a study with melanoma tumor-bearing mice, iNOS inhibition was associated with suppression of intratumoral MDSCs, pointing again to an immunosuppressive role of iNOS (Jayaraman et al., 2014). iNOS deficiency was also associated with an upregulation of immunosuppressive $Fox3p^+$ Treg cells, suggesting the enzyme to protect against Treg accumulation while simultaneously increasing immunosuppression-inducing MDSCs (Jayaraman et al., 2014). In this same study, host iNOS inhibition was unsuccessful in impacting tumor growth by itself, but in combination with Treg depletion using low-dose cyclophosphamide, $CD8^+$ T cell infiltration was boosted, and tumor growth was significantly arrested (Jayaraman et al., 2014).

Immune cell populations other than T cells are also seen to be impacted. MSDCs from patients with cancers of different origins inhibited natural killer (NK) cell antibody-dependent cellular cytotoxicity, an effect involving NO production by MDSCs and subsequent NK cell protein nitration (Stiff et al., 2018). The results were confirmed in vivo, as inhibition of iNOS in mice bearing breast cancer tumors enhanced NK cell antibody-dependent cytotoxicity, and inhibiting NO production by MDSCs enhanced the efficacy of anti-cancer monoclonal antibody (mAb) therapy with trastuzumab (Stiff et al., 2018). Antigen presentation by dendritic cells to $CD4^+$ is another immune function inhibited by MDSCs via NO production, and correspondingly, NOS inhibition has been found to restore T cell proliferation in this context (Markowitz et al., 2017). By way of reversing NO/NOS/peroxynitrite-mediated immunosuppression, the anti-cancer activity of several potential cancer therapies, including the alpha-garactosylceramide (Ito, Ando, Ogiso, et al., 2015) and toll-like receptor agonists (Ito, Ando, & Seishima, 2015), has been reported to be increased by the inhibition of NOS enzymes in murine cancer models. A phase 1/2 trial of NOS inhibitor L-NMMA with the anti-microtubule agent taxane also demonstrated promising results in treating patients with chemorefractory breast cancer, warranting further investigation in clinical trials (Chung et al., 2021). Overall, NOS inhibition has earned much interest in the context of cancer therapy.

While these studies point to a detrimental role of NO in the setting of cancer, there is evidence to suggest that exogenous NO administration may be beneficial in this context, though counterintuitive. Illustrating this point, the NO donor GSNO, when administered to ovarian tumor-bearing mice, slowed tumor growth in association with decreased levels of MDSCs, reversed the suppression of T cell proliferation, and increased pro-inflammatory, IFN-γ-producing $CD4^+$ and $CD8^+$ T cell populations (Rattan et al., 2018). Within the $CD4^+$ T cell population, a higher ratio of Th_1/Th_2 cells is favorable for antitumor immunity. Importantly, at low concentrations, NO has been found to selectively induce Th_1 but not Th_2 differentiation (Niedbala et al., 1999) by cGMP-dependent induction of IL-12 receptor used by the former cell population without any effect on the IL-4 receptor used by the latter (Niedbala et al., 2002). Exogenous NO may also exert its immunoprotective effects by downregulating NOS activity. In one study, the furoxan-based NO donor AT38 was seen to block the production of peroxynitrite and downregulate intratumoral iNOS in several murine cancer models, leading to a significant increase in the intratumoral T cell infiltration (Molon et al., 2011). Mechanistically, these effects were linked to reduced CCL-2 nitration, which enhanced tumor eradication by adoptive cell therapy and caused sequestration of the immunosuppressive $Foxp3^+/CD4^+$ Treg cells at the periphery of the tumor, in contrast to the effect observed on cytotoxic T cells (Molon et al., 2011). From these findings, it seems that iNOS overactivity can interfere with antitumor T cell function through the production of reactive nitrogen species and subsequent protein modifications, whereas NO administration can be beneficial in curtailing this enzyme. Thus, the previously described detrimental effects of iNOS in cancer may, rather than a contraindication to NO administration, be mitigated by exogenous administration of NO. The beneficial effects of exogenous NO administration on T cell activity are supported by the results of another study in which NO-releasing aspirin reversed the immunosuppression exerted by MDSCs, restoring T cell proliferation in response to alloantigens in vitro (De Santo et al., 2005). The same study demonstrated that in tumor-bearing mice, NO-aspirin reduced the activity of the NOS and arginase enzymes, inhibited intratumoral peroxynitrite formation, and enhanced the efficacy of DNA cancer vaccination (De Santo et al., 2005). The increase in T cell proliferation may arise from the impact of NO on the required step of antigen presentation; in a previously discussed study in which NO was implicated in suppression of dendritic cell antigen presentation, pre-treatment with the NO-releasing aspirin derivative NCX-4016 was used to inhibit NO production by MDSCs and found to increase T cell proliferation in the context of dendritic cell antigen presentation (Markowitz et al., 2017). In each of these studies, NO donors were used to block the activity of iNOS to achieve their beneficial immune-boosting effects. Administering exogenous NO to inhibit NOS activity, and therefore peroxynitrite production, is a strategy that likely takes advantage of the extensive feedback regulation of NO on NOS activity; NO has been seen to inhibit the activity and expression eNOS and iNOS through inhibitory S-nitrosylation of the enzyme and inhibition of NF-κB (Katsuyama et al., 1998a, Grumbach et al., 2005, Altaany et al., 2014). Thus, the extensive preceding discussion of the evidence that iNOS plays a role in cancer-mediated immunosuppression does not preclude the use of exogenous NO—in fact, NO itself can be used to offset the deleterious immune effects of excessive iNOS activity.

NO may also boost the anti-tumor activity of immune cells besides T cells. In one study, inflammatory M1 macrophages were seen to prevent repolarization into M2 macrophages by inhibiting mitochondrial oxidative phosphorylation, likely by NO production, as inhibition of NO production reversed these effects and allowed the phenotypic switch to anti-inflammatory M2 macrophages (Van den Bossche et al., 2016). In this way, NO seems to be key to maintaining a pro-inflammatory macrophage phenotype, which is especially important in cancer states where cancer cells induce macrophage polarization to M2 phenotype to escape immune surveillance. Indeed, NO- and O_2 co-delivering ultrasound-responsive nanoparticles enhanced sonodynamic therapy and promoted polarization of macrophages from an M2 to an M1 phenotype after ultrasound radiation (Ji et al., 2021). Additionally, this therapy induced mitochondrial dysfunction by peroxynitrite production, promoted dendritic cell maturation, and depleted MDSCs (Ji et al., 2021).

Because these immune cells work in conjunction with other immune cells rather than in isolation, NO-mediated induction of macrophage switching may also boost the anti-tumor activity of other immune cells. In fact, in murine models of pancreatic carcinomas, the polarization of tumor-associated macrophages into an iNOS-expressing pro-inflammatory M1 phenotype by local low dose gamma-radiation was responsible for increased recruitment of $CD8^+$ T cells into tumor tissue by causing endothelial activation and subsequent upregulation of adhesion molecules, inducing the expression of Th_1 chemokines, and suppressing angiogenic, immunosuppressive, and tumor growth factors (Klug et al., 2013). The upregulation of adhesion molecules, in particular vascular cell adhesion molecule 1 (VCAM-1), by iNOS-expressing macrophages was also seen in a murine model of pancreatic neuroendocrine tumors, promoting T cell infiltration into the tumor tissue (Sektioglu et al., 2016); furthermore, co-transfer of $CD8^+$ T cells with iNOS-expressing macrophages, but not iNOS-deficient macrophages, induced a markedly pro-inflammatory TME, with simultaneous downregulation of angiogenesis-associated genes (Sektioglu et al., 2016). Interestingly, the effects of NO were demonstrated to be biphasic in vitro, where low levels of NO donor glyceryl trinitrate (10 μM and 50 μM) induced the expression of adhesion molecules in HUVECs in an NF-κB-dependent manner, whereas higher levels (250 μM and 500 μM) were suppressive (Sektioglu et al., 2016), thus emphasizing the importance of considering dosage when using this gasotransmitter for therapeutic purposes.

3.4.2. Carbon monoxide immunomodulation in cancer

CO has demonstrated several immunomodulatory effects, with evidence of both immunosuppressive and immune boosting effects (Fig. 3). In the context of LPS stimulation of macrophages in vitro and in vivo LPS challenge of mice, CO was seen to exhibit potent anti-inflammatory effects including downregulation of pro-inflammatory cytokines TNF-α, IL-1β, and MIP-1β, and upregulation of the anti-inflammatory cytokine IL-10 through a mechanism involving the MAPK pathway (Otterbein et al., 2000). A separate study identified the nuclear hormone peroxisome proliferator-activated receptor-γ (PPARγ) as mediating the anti-inflammatory effects of CO on LPS-stimulated macrophages (Bilban et al., 2006). In inflammatory conditions, such as LPS stimulation in vitro (Mu et al., 2022) and acute pancreatitis in vivo (Taguchi et al., 2018), CO release from different CO donors has also been reported to induce anti-inflammatory M2 macrophage polarization, suggesting that the gasotransmitter has an anti-inflammatory role in setting of increased inflammation. Interestingly, another in vitro study demonstrated that while CORM-3 treatment promoted the M2 phenotype and upregulated iNOS expression in unstimulated alveolar macrophages, it reduced iNOS expression in macrophages stimulated by LPS/IFN-γ (Yamamoto-Oka et al., 2018), suggesting that the effects of CO differ based on the level of inflammation present within the system tested.

In addition to inducing anti-inflammatory macrophage polarization, which is beneficial in many disease models but may protect cancer cells from cell death, CO has also demonstrated suppressive effects on T lymphocytes. CO has been found to suppress T cell proliferation and cell cycle entry by inhibiting the secretion of IL-2, possibly through inhibition of ERK (Pae et al., 2004). There is also evidence that CO may induce $CD4^+$ T cell apoptosis through Fas/CD95-induced apoptosis, in part attributable in part to the inhibition of ERK and MAPK, as seen upon exposure of Jurkat T cells to CO (Song et al., 2004). Furthermore, this gasotransmitter has been found to decrease $B220^+$ $CD4^-$ $CD8^-$ T cells in a murine model of systemic lupus erythematosus (Mackern-Oberti et al., 2015), and to be protective against intestinal inflammation by suppressing Th17 cell differentiation (Takagi et al., 2018). Thus, CO has been found to suppress the immune activity of several different T cell populations, which is a possible drawback to its use in cancer, considering the importance of these cells in anti-tumor host immunity. In fact, increased HO-1 expression has been associated with reduced sensitivity to chemotherapeutic agent pirarubicin in patient colorectal tumor tissues (Yin et al., 2014), which may be linked to the immunosuppressive effects of CO as discussed. Overall, these studies seem to suggest a harmful immunosuppressive effect of CO in the context of cancer.

There is also evidence to suggest an immunoprotective effect of CO. In one study, CORM treatment was found to reduce the immunosuppressive effects of solar-simulated ultraviolet (UV) radiation and the epidermal UVB byproduct *cis*-UCA through a mechanism involving guanylyl cyclase (Allanson & Reeve, 2005). Further study in a murine model of solar-simulated UV radiation-induced photocarcinogenesis revealed that topical CORM-2 treatment inhibited early tumor appearance, reduced tumor multiplicity, induced the regression of established tumors, and delayed malignant progression; correspondingly, CO reduced expression of immunosuppressive IL-10 and increased immune boosting IL-12 (Allanson & Reeve, 2007). These findings suggest an immunopotentiating ability of CO in the context of cancer.

There are several different effects through which CO may yield its immunoprotective effects against cancer, one of which is through the induction of immunogenic cell death. Immunogenic cell death, which results in the release of DAMPs that stimulate the immune system toward recognizing and combatting cancer cells, is one avenue that is currently being investigated for cancer immunotherapy. Interestingly, exogenous CO administration was seen to induce immunogenic cell death in both in vitro and in vivo models of 4 T1 breast cancer (Xiao et al., 2021) and in a murine model of melanoma, in which CO administration suppressed lung metastasis (Zhai et al., 2021). Based on these studies, CO-induced immunogenic cell death is successful in stimulating the anti-tumor immune response in vitro and in vivo, with increased dendritic cell maturation, increased $CD4^+$ and $CD8^+$ T cells, and improved ratio of these cell types to Treg cells; furthermore, CO therapy in the former study enhanced the anti-tumor effect of anti-PDL1 immune checkpoint therapy (Xiao et al., 2021). The immunoprotective role of CO in cancer has been implemented in a study developing a cancer nanovaccine using soft X-ray-triggered CO releasing lanthanide scintillator nanoparticles (ScNPs: $NaLuF_4$:Gd,Tb@$NaLuF_4$) combination with a PhotoCORM, which has demonstrated promise in reversing the immunosuppressive TME, activating the adaptive anti-tumor immunity, and therefore causing systemic tumor growth inhibition through ROS generation and the induction of immunogenic cell death (Li, Jiang, et al., 2021). The potential enhancement of the anti-tumor immune response by CO can also increase the efficacy of other currently used cancer chemotherapies. For instance, enhanced effects of doxorubicin therapy has been seen with the use of different CO -generating or -releasing compounds (Wang, Zhang, et al., 2019; Zhao et al., 2022); in one study, the therapeutic effect was increased from 29% to 82.4% in vitro (Zhao et al., 2022). Thus, combination therapy with CO and immunotherapies or other chemotherapies that ultimately require cancer clearance by the immune system is an avenue to augmenting current therapeutic approaches to cancer. In addition to boosting antitumoral T cell activity through induction of immunogenic cell

death, evidence from melanoma antigen-specific T cells has demonstrated that CO boosts T cell antitumor activity in vivo by inducing moderate endoplasmic reticulum stress; mechanistically, this leads to transient activation of ERS sensor protein kinase R-like endoplasmic reticulum kinase (PERK) which induces protective autophagy and epigenetic reprogramming of T cells into a stronger anti-tumoral phenotype (Chakraborty et al., 2022). Considering the promising findings of T cell activity enhancement, further investigation of the effects of CO on the T cell responses to cancer may be warranted.

Moreover, in direct contrast to the M2-polarizing activity of CO described previously in inflammatory models, CO has been found to induce anti-tumor macrophage activity in the cancer setting. Exogenous CO administration in a murine model of lung cancer led to inhibition of tumor growth by increasing cancer cell apoptosis; this effect was associated with increased infiltration of $CD169^+$ macrophages into the TME (Nemeth et al., 2016). This macrophage subtype has been recognized to have a critical role in anti-tumor immunity through cross-presentation of tumor antigens to $CD8^+$ T cells (Asano et al., 2011). Additionally, CO treatment was associated with skewing of the macrophages into CD86/CD197-positive M1 phenotype alongside suppression of the MMR-expressing M2 phenotype in the TME; mechanistically, the reprogramming of macrophages by CO into an anti-tumoral phenotype was found to be mediated by ROS-dependent activation of MAPK/ERK1/2-c-myc signaling and Notch 1-dependent negative feedback on HO-1 (Nemeth et al., 2016). Thus, in addition to boosting anti-tumoral immunity through immunogenic cell death-mediated immune activation, CO treatment may also result in enhanced anti-tumoral effects through macrophage activity.

3.4.3. Hydrogen sulfide immunomodulation in cancer

While there has been a large amount of investigation into the immune modulation by H_2S, as reviewed in (Dilek et al., 2020), unlike with the other two gasotransmitters, few studies have examined the cancer-specific immunomodulatory role of H_2S. Thus, the following discussion presents evidence from several non-cancer models that may perhaps carry over to the cancer setting.

There is evidence to suggest that H_2S plays a role in modulating lymphocyte activity (Fig. 4), in particular T cells, which are especially important in the antitumor response. In one study, physiological levels of H_2S were found to enhance TCR-stimulated polyclonal and antigen-specific T cell activation, as demonstrated by increases in IL-2, CD69, and CD25 (Miller et al., 2012). Furthermore, T cell activation also led to increased CSE and CBS, whereas silencing of the latter impaired T cell activation that was reversed upon exogenous H_2S supplementation, suggesting a self-reinforcing cycle of T cell activation through H_2S (Miller et al., 2012). Further investigation revealed that H_2S-induced T cell activation occurs through ERK1/2 phosphorylation, and inhibition of mitogen-activated protein kinase kinase (MEK)-dependent ERK phosphorylation can suppress T cell activation; in fact, the inhibitory effect of TSP-1 through CD47 was suggested to involve inhibition of ERK phosphorylation, and furthermore, TSP-1 also suppressed activation-dependent CBS and CSE expression in the T cells (Miller et al., 2013). From these studies, physiological levels of H_2S seem to promote T cell activation.

On the other hand, there is also evidence that H_2S can impair the anti-tumor lymphocytic response (Fig. 4). Supraphysiological levels of H_2S using NaHS have been seen in vitro to impair lymphocyte proliferation and induce lymphocyte cell death by necrosis—not apoptosis—through the loss of mitochondrial membrane potential (Mirandola et al., 2007). The toxicity of H_2S toward T cells in this study was specific to $CD8^+$ and NK cells, sparing $CD4^+$ T cells, and interestingly, glutathione was protective against the cytotoxicity of H_2S (Mirandola et al., 2007). Similarly, H_2S was found to be necessary for gingiva-derived mesenchymal stem cell-induced Fas/FasL-mediated T cell apoptosis in vitro (Yang et al., 2018). In cancer models, CBS and CSE knockdown in breast cancer cells enhanced their susceptibility to NK and T cell cytotoxicity by allowing increased expression of co-stimulatory ligands on the cancer cells (Youness et al., 2021). Interestingly, CO was found to increase the sensitivity of breast cancer cells to doxorubicin therapy by inhibiting CBS and thus reducing antioxidant capacity (Kawahara et al., 2017), aligning with the pro-cancer role of CBS and further supporting the previously discussed anti-tumor potential of CO treatment. Additionally, H_2S has been found to be essential for $Foxp3^+$ Treg cell differentiation and function (Yang et al., 2015), and H_2S depletion in colorectal cancer-bearing mice correspondingly decreased $CD4^+CD25^+Foxp3^+$ Treg cells, while increasing the $CD8^+$ T-cell/Treg ratio, along with enhanced efficacy of anti–programmed cell death ligand 1 (PDL1) and anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) immunotherapies (Yue et al., 2023). Taken together, these studies suggest that the effect of H_2S on T cell function are biphasic, as with many of its other effects. This is supported by the results of another study, in which both fast- and slow- donors NaHS and GYY4137, respectively, stimulated proliferation in of lymphocytes healthy and systemic lupus erythematosus patients at lower concentrations and were inhibitory at higher concentrations (Han et al., 2013). In this study, the inhibitory effects of H_2S were further demonstrated to arise from modulation of the Akt/glycogen synthase kinase-3 beta (GSK3β) (Han et al., 2013).

Some of the effects of H_2S on immune cells are mediated through its effects on MDSCs, an immunosuppressive cell type recruited by cancer cells. In melanoma-bearing mice, DATS was found to inhibit tumor growth through downregulation of MDSCs in the spleen, blood, and TME, alongside an increase in dendritic cells and $CD8^+$ T cells within the spleen, although no increase in either of the immune cells was seen in the tumor tissue (De Cicco et al., 2020). These effects were at least partially attributable to suppression of immunosuppressive genes in MDSCs, which was linked to restoration of T cell proliferation (De Cicco et al., 2020). In an alternative murine model of *H. pylori*-induced colitis, oral H_2S administration using DATS was able to suppress the recruitment of G-MDSCs to the colon (De Cicco et al., 2018).

H_2S also has varying impacts on macrophages, another immune cell type that can either facilitate an increased immune response to the cancer or exert an immunosuppressive role allowing cancer cells to escape immune detection. In inflammatory conditions such as LPS stimulation, H_2S seems to exert an anti-inflammatory effect on macrophages, reducing the pro-inflammatory mediators TNFα, IL-6, PGE_2, and suppressing the expression of IL-1β, COX-2 and iNOS through NF-κB inhibition; these anti-inflammatory effects were further confirmed in vivo in an LPS sepsis mouse model (Huang et al., 2016). In fact, LPS has been seen to induce increased CSE expression and H_2S in macrophages (Zhu et al., 2010a). Similarly, pre-treatment of RAW 264.7 macrophages in vitro with H_2S donor JK1 reversed M1 polarization induced by LPS stimulation, yet in this study, H_2S also induced M2 polarization in the absence of a pro-inflammatory stimulus (Wu et al., 2019). On the other hand, NaHS administration has been seen to induce pro-inflammatory cytokine release in monocytes through ERK-dependent NF-κB activation (Zhi et al., 2007), and to increase early macrophage infiltration of infarcted myocardium in vivo, an effect associated with the internalization of β1 integrin and activation of downstream Src-focal adhesion kinase (FAK)/Pyk2-Rac signaling (Miao et al., 2016). CSE silencing produced the opposite effects, supporting the role of endogenous H_2S production in macrophage infiltration (Miao et al., 2016). Further support for a pro-inflammatory effect of H_2S involving macrophages comes from a murine model of mechanical load-induced tooth movement, in which exogenous H_2S administration increased M1 macrophage levels whereas CBS inhibition did the opposite; the pro-M1 polarization effects of H_2S were attributed to activation of the STAT1 pathway (He et al., 2020).

There is evidence for dual effects of H_2S on other aspects of the immune response and inflammation (Fig. 4). H_2S was seen to promote the survival of neutrophils by inhibiting their apoptosis through the inhibition of p38 and caspase 3; intriguingly, H_2S also reduced

lymphocyte survival in this study (Rinaldi et al., 2006). The gasotransmitter has also been seen in separate studies to decrease leukocyte adherence to the endothelium through the activation of K_{ATP} channels (Zanardo et al., 2006) vs increase neutrophil adhesion and locomotion through the same K_{ATP}-dependent mechanism (Dal-Secco et al., 2008). Given the role of H_2S in protecting the endothelium in the basal state, it is likely that in physiological conditions the gasotransmitter has antiadhesive activity but promotes endothelial activation and inflammation in pathological conditions. In addition to these effects, H_2S deficiency can also accelerate cellular senescence in response to oxidative stress, whereas H_2S is protective via the activation of antioxidant regulator nuclear factor erythroid 2-related factor 2 (Nrf2) (Yang et al., 2012); while beneficial in reducing inflammation in hyperinflammatory states, this may be detrimental when trying to combat, as it may defend these cells against oxidative stress-induced death.

Yet in one study, both the anti-inflammatory and antitumor effects of H_2S were emphasized as being important for combatting cancer. The combination of H_2S with photothermal therapy (PTT) was found to increase immunogenicity of the latter, as demonstrated by increased tumor-infiltrated $CD8^+$ T cells accompanied by lowered $CD4^+$ T cells (Li, Xie, et al., 2021). At the same time, anti-inflammatory effects of H_2S were seen through reduction of the PTT-induced proinflammatory cytokines TNF-α, IL-6, and IL-1β; this was an added benefit of H_2S therapy, as the pro-inflammatory effect of PTT can reduce its ability to trigger immunogenicity, cause permanent tissue injury with possible tumor regeneration (Li, Xie, et al., 2021). In fact, different approaches to curtail the pro-inflammatory response caused by PTT are being investigated (Dong et al., 2018), indicating the importance of the anti-inflammatory effects seen with H_2S. Thus, the seemingly conflicting effects of H_2S on the immune/inflammatory response may work to synergistically promote antitumor effects of other therapies.

3.5. Impact on cancer-associated infectious complications

Immunosuppression is an adverse effect of a wide range anticancer therapies, including cytotoxic chemotherapies, radiotherapy, and hematopoietic stem cell transplants, which leave cancer patients vulnerable to infections (Bodey, 1986). Bacterial pathogens are a notable cause of infection among cancer patients, particularly gram-negative bacteria that are often antibiotic-resistant (Marin et al., 2014; Perez et al., 2014; Vahedian-Ardakani et al., 2019). Those with hematological malignancies are also especially at risk of opportunistic fungal infections (Pagano et al., 2017; Segal et al., 2007; Shariati et al., 2020). Additionally, as illustrated recently by the increased susceptibility to COVID-19 infection and poor outcomes in the recent pandemic (Wang, Sun, et al., 2020; Zhang et al., 2020), cancer-related immunosuppression can predispose patients to increased severity of viral infections as well. With the increased susceptibility to such a wide range of pathogens, it follows that infectious disease is a leading non-cancer cause of death among cancer patients (Zaorsky et al., 2017). This issue is present even among young adult cancer populations, and in one study, an alarming standardized mortality ratio of 5.13 was seen in adolescent and young adult cancer patients for infectious disease (Anderson et al., 2019). Cancer patients have also been found to have an almost 10-fold increased risk of sepsis in comparison to non-cancer patients (Danai et al., 2006), accounting for >20% of all sepsis hospitalizations in the US (Hensley et al., 2019), and having higher rates of mortality from sepsis compared to non-cancer patients (Abou Dagher et al., 2017). Curtailing infections from a wide range of pathogens is thus of great interest in the context of cancer; all three gasotransmitters have roles in this regard, and thus are worth investigating specifically in the setting of cancer.

3.5.1. Nitric oxide and infection

Increased levels of NO and its derivatives during infection and their association with reduced disease severity, as seen with various viral (Kharitonov et al., 1995; Sanders et al., 2004), parasitic (Anstey et al., 1996; Evans et al., 1993), and bacterial pathogens (Wheeler et al., 1997), suggests a role of NO in innate host defense. Correspondingly, reduced NO levels can be found in individuals with cystic fibrosis (Lundberg et al., 1996) and Kartagener syndrome (Lundberg et al., 1994), both of which are known for a predisposition to recurring infections, further highlighting the importance of NO for thwarting infection. NO demonstrates a very broad range of direct antimicrobial activity against different viruses (Akaberi et al., 2020; Keyaerts et al., 2004; Regev-Shoshani et al., 2013; Rimmelzwaan et al., 1999; Sanders et al., 1998), both gram-positive and gram-negative bacteria (Miller et al., 2009; Ormerod et al., 2011), fungi (Ahmadi et al., 2016; Deppisch et al., 2016; Stasko et al., 2018), and protozoa (Anstey et al., 1996, Evans et al., 1993) (Fig. 2). Consistent with its ability to combat a wide range of pathogens, the antimicrobial actions of the gasotransmitter involve multiple mechanisms, making it unique compared to current antimicrobial therapies, and reducing the likelihood of antimicrobial resistance; indeed, NO resistance among pathogens has not been reported to our knowledge (Privett et al., 2012; Rouillard et al., 2021).

The activation of mucociliary clearance, which is especially important for the removal of pathogens from the respiratory tract (Jiao et al., 2011; Nagaki et al., 1995), is the first line of defense against pathogens provided by NO. The gasotransmitter also has more specific antimicrobial actions, including protein modifications and induction of DNA damage through oxidative and nitrosative stress (Fang, 1997). With viruses, NO can inhibit replication and entry into host cells by nitration, S-nitrosylation, and oxidation of proteins essential for these functions (Colasanti et al., 1999; Xu et al., 2006). The specific protein target varies based on the identity of the virus; for instance, while NO inhibited HIV-1 reverse transcriptase by oxidation of a cysteine residue (Persichini et al., 1999), in dengue virus type-2 it inhibited the RNA-dependent RNA polymerase (Takhampunya et al., 2006). Other reported antiviral mechanisms include inhibition of ribonucleotide reductase and transcription factors,disruptions in post-translational modifications, etc., as described in(Colasanti et al., 1999).

With respect to bacteria, while NO alone may not directly exert antibacterial effects, its reaction products and combination with other agents may still be promising to combat bacterial infections. For instance, whereas NO had minimal direct antibacterial effects on *E. coli* (Pacelli et al., 1995) and *S. typhimurium* (De Groote et al., 1995), it was found to increase the DNA-damaging effects of hydrogen peroxide in the case of the former, and in the latter, exert bacteriostatic and bactericidal effects through its products S-nitrosoglutathione (GSNO) and peroxynitrite, respectively. Interestingly, more recent studies have also found NO treatment to significantly enhance the efficacy of tetracycline therapy against both gram -positive and -negative bacteria (Reger et al., 2017a; Reger et al., 2017b). Interestingly, NO has been found to increase susceptibility bacterial to conventional antibiotics and slow the development of antibiotic resistance (Rouillard et al., 2021), which is especially important for cancer patients who are susceptible to multidrug resistant bacterial infections. Additionally, the co-release of NO and CO has been found to be superior in treating methicillin-resistant *S. aureus* (MRSA) infection in a murine skin wound model vancomycin, suggesting the combined use of these gasotransmitters may be especially beneficial in the context of bacterial infection (Gao et al., 2022).

NO has demonstrated fungicidal activity as well (Stasko et al., 2018); in fact, the antifungal activity of amphotericin B against *C. neoformans* has been linked to the upregulation of the NO pathway in macrophages (Mozaffarian et al., 1997; Tohyama et al., 1996). Overall, this broad range antimicrobial activity is likely to be beneficial in the context of cancer, considering the immunosuppressed state induced by cancer therapeutics and susceptibility of these patients to potentially life-threatening infections.

It should be noted that there is also evidence that NO can sometimes perpetuate infection rather than curtail it. The gasotransmitter has been identified as one defense utilized by bacteria against immune oxidative

attack (Gusarov & Nudler, 2005; Shatalin et al., 2008) and has been associated with resistance of the bacterial pathogens to a range of antibiotics (Gusarov et al., 2009), directly contrary to the increased antibiotic susceptibility and delayed development of antibiotic resistance described more in a more recent study (Rouillard et al., 2021). With viral infections as well, inhaled NO failed to improve the outcome in mice infected with severe influenza (Darwish et al., 2012), and in fact, NOS inhibition using non-specific inhibitor L-NMMA improved survival and pulmonary compliance in a murine model of HSV-1 pneumonitis despite a higher viral load, suggesting that the inflammatory response rather than the virus itself was the reason for the damage (Adler et al., 1997). The reasons for these contradictory findings are not entirely clear; perhaps the effects of NO depend on the identity of the pathogen, and/or the methodological differences such as dosage and release kinetics of NO administration strategies play a role. In any case, while NO has demonstrated great promise in preventing and combatting a wide range of infectious pathogens, understanding the settings in which its use would be beneficial vs harmful is critical, especially when dealing with immunosuppressed cancer patients.

3.5.2. Carbon monoxide and infection

CO has demonstrated a broad range of antimicrobial activity that may be promising for cancer patients predisposed to infection (Fig. 3).

A large number of studies have indicated direct antibacterial actions of CO, covering gram-positive, gram-negative, aerobic, and anaerobic bacteria (Desmard et al., 2009; Nobre Lígia et al., 2007), and CO treatments can be tailored to preferentially target the bacteria while having no effect on host cells, as seen with a visible-light-induced CORM (Ward et al., 2014). The bactericidal activity of macrophages has been attributed to CO production, which leads to bacterial ATP depletion and NALP3 inflammasome activation, promoting bacterial phagocytosis (Wegiel et al., 2014). Thus, the exogenous supplementation of CO seems to be one potential avenue in combatting bacterial infections, and indeed, in a murine model of antibiotic-resistant *P. aeruginosa*, CORM-3 treatment reduced bacterial counts and improved survival in both immunocompetent as well as immunosuppressed hosts (Desmard et al., 2009).

In one study, CO administration was found to inhibit the growth of *S. aureus* and *E. coli* in culture most potently in near-anaerobic conditions, suggesting that the bactericidal effects of CO are not entirely dependent on its disruption of the electron transport chain through cytochrome *c* inhibition (Nobre Lígia et al., 2007). Further investigation has revealed several mechanisms by which CO may exert its antibacterial effects, including through the induction of significant transcriptional-level genome-wide changes (Davidge et al., 2009; McLean et al., 2013), direct DNA damage through ROS induction (Tavares et al., 2011), suppression of the bacterial respiration (Desmard et al., 2009; Wilson et al., 2012), and inhibition of bacterial biofilm formation (Murray et al., 2012; Nguyen et al., 2015). Importantly, CO treatment has also demonstrated promise against drug-resistant bacteria, such as multi-drug resistant uropathogenic *E. coli* (Sahlberg Bang et al., 2016) and methicillin-resistant *S. aureus* (Cheng et al., 2021), to which an increased susceptibility among cancer patients has been described (El-Gendy et al., 2018; Mahmoud et al., 2020).

CO may also have direct antiviral activity, although studies focusing on CO itself rather than the CO-producing enzyme HO-1 are relatively limited. Studies with HO-1 have demonstrated its antiviral actions against several viruses, including hepatitis B (Protzer et al., 2007), hepatitis C (Zhu et al., 2008), HIV-1 (Devadas & Dhawan, 2006), influenza A (Ma et al., 2016), and dengue virus (Tseng et al., 2016). As HO-1 is responsible not only for CO production, but also other products such as biliverdin and iron, it is not clear how much of these effects are attributable to CO. There are a few studies that have shown CO specifically to have antiviral actions, seen against the human pathogen enterovirus 71 through inhibition of its replication (Tung et al., 2011), and in several animal viruses, including porcine reproductive and respiratory syndrome virus (PRRSV) (Zhang et al., 2016), bovine viral diarrhoea virus (BVDV) (Ma et al., 2017), and spring viremia of carp virus (SVCV) (Li et al., 2018); the antiviral mechanisms in these studies were elucidated to involve cGMP/PKG and NF-κB pathways. Considering these findings, it is possible that CO has yet unexplored antiviral actions that may prove useful in the context of cancer, and further investigation in this area is warranted.

3.5.3. Hydrogen sulfide and infection

Like NO, H_2S has a range of antimicrobial actions (Fig. 4), although these are not as vast as those demonstrated by NO. As its first line of defense, H_2S increases mucociliary clearance of offending particles by reducing transepithelial Na^+ transport in lung tissue, reducing mucus viscosity (Agné et al., 2015; Althaus et al., 2012). H_2S also has direct antiviral actions against a range of enveloped RNA viruses, including through the inhibition of viral replication (Bazhanov et al., 2017; Li et al., 2015), entry (Pacheco, 2017), and syncytium formation, which is hypothesized to affect viral assembly/release (Li et al., 2015). A separate, indirect antiviral mechanism of H_2S may involve the upregulation of GSH levels (Kimura et al., 2009), which acts both as an antioxidant as well as an antiviral agent independent of its ROS scavenging activity (Diotallevi et al., 2017).

With regards to bacterial infection, there are conflicting reports of the role of H_2S. Separate studies have found that suppression of bacterial H_2S production rendered the microbes more susceptible to a range of antibiotics by protecting against oxidative stress (Seregina et al., 2022; Shatalin et al., 2011), suggesting a deleterious involvement of the gasotransmitter in the development of antibiotic resistance. On the other hand, H_2S has been found to inhibit the growth of several gram-positive and gam-negative bacteria, including *S. aureus*, *S. typhimurium*, *L. monocytogenes*, *B. subtilis*, *B. thuringiensis*, *E. coli*, *S. mitis*, *S. oralis*, and *E. aerogenes* (Fu et al., 2014; Fu et al., 2018; Ooi & Tan, 2016). Mechanistically, these studies revealed increased ROS and decreased GSH as the mechanisms by which H_2S exerted its antibacterial effects (Fu et al., 2018, Ooi & Tan, 2016), directly opposing the observation of H_2S protecting against oxidative stress in the previous studies (Seregina et al., 2022, Shatalin et al., 2011). Additionally, a bactericidal role of H_2S-containing thermal spring waters has been reported, leading to a suggestion that H_2S may have a role in new perspectives for pool treatment (Giampaoli et al., 2013). Interestingly, both toxic and protective effects of H_2S were seen in one study with the bacterium *Shewanella oneidensis*, where the simultaneous addition of H_2S with H_2O_2 enhanced the toxicity of the latter by increasing oxidative stress, while H_2S pre-treatment rendered the bacteria resistant to the H_2O_2 cytotoxicity by activating oxidative-stress-responding regulator OxyR (Wu et al., 2015); thus, timing seems to be a critical component in the effects of H_2S on bacterial pathogens.

Overall, the evidence suggests a benefit to H_2S therapy in cancer patients particularly in the context of viral infection.

4. Summary and perspectives

Overall, the potential for therapeutic application of NO, CO, and H2S in the context of cancer remains unclear. A large body of evidence from a range of experimental cancer models indicates favorable anti-cancer effects of each of these gases. All three have demonstrated an ability to inhibit cancer cell proliferation by inhibiting growth and survival signaling, induce cell cycle arrest and apoptosis, thwart cancer invasion and metastasis by reducing ECM remodeling and EMT induction, and induce anti-tumor immune defense. Additionally, all gasotransmitters have demonstrated tremendous potential in the defense against pathogens, which may be especially important in the context of cancer, considering the burden of immunosuppression that often accompanies this disease and its treatments. NO and CO have also demonstrated the ability to reduce cancer-related angiogenesis, although, in this

regard, H2S has demonstrated only pro-angiogenic effects. Despite these promising findings, there is also evidence to suggest NO, CO and H_2S have cancer-promoting activity, including through increased growth/survival signaling, increasing angiogenesis, and interfering with tumor-targeting immune defense, which is entirely contradictory to the anti-tumor effects that targeted the same aspects of cancer biology.

The reasons for these contradictory results largely remain to be elucidated. The apparent discrepancies between various studies stay even with a lens that focuses on each type of cancer separately, suggesting other players are involved in these baffling findings. Notably, some studies have emphasized the role of gasotransmitter donor dosage and release kinetics (Oláh et al., 2018; Wu et al., 2017), demonstrating that the same experimental system can yield opposite findings when these parameters are adjusted. However, it is challenging to establish dose-response curves for these gaseous molecules, leading to difficulties in defining quantitative relationships; this likely plays a significant role in the lack of consistency across studies, which makes it challenging to compare results between different studies. Additionally, the wide range of molecular targets with which these gasotransmitters can interact to elicit effects introduces another variable in interpreting study findings, necessitating affinity and dose-response considerations. As an example, CO itself has over 25 molecular targets, ranging from hemoglobin and cytochrome *c* oxidase to sGC and several ion channels, binding to each with different affinities (for more information, see (Zhengnan et al., 2022). Furthermore, when using exogenous donors, it is important to consider that some of these compounds have extensive activity independent of the gasotransmitter they release. Once again, using CO as an example, several CO-independent effects of different CORMs have been elucidated, ranging from ion channel modification to antimicrobial activity (Gessner et al., 2017; Juszczak et al., 2020; Southam et al., 2021), which introduces yet another element that can impact study results. Evidently, there are many issues to be further explored before any conclusions about NO, H_2S, and CO in the context of cancer can be made. Still, the preponderous weight of the data strongly suggests a promising anti-cancer potential for NO, CO, and H_2S, which merits further serious consideration and efforts to develop as therapeutics.

Decades of research have highlighted the enormous potential of NO, CO, and H 2S in various aspects of medicine, yet few gasotransmitter-releasing agents have reached the marketplace. In the context of cancer, this may be due to the scientific community's focus on chemoprevention rather than chemotherapy; for more details, see (Kashfi, 2018).

An area in which significant progress can be expected is the field of multifunctional compounds, that is, using clinically approved drugs with added NO-, CO-, or H_2S-donating moieties, either alone or in combination. In this regard, Otenaproxesul (ATB-346), an H_2S-releasing analog of naproxen, has completed phase 2 clinical trials to manage chronic pain, gastric ulcer, and osteoarthritis (NCT03978208, 2019) but not cancer. In addition, there are other H_2S-releasing compounds under evaluation for indications other than cancer; for example, a Phase 2a clinical study on the analgesic effect of GIC-1001 and GIC-1002 on visceral pain (NCT02276768; 2016) (NCT01926444; 2019).

With regards to NO, there are several ongoing clinical trials addressing its potential efficacy and application in several indications other than cancer. These include inhaled NO in cystic fibrosis (CF) patients (NCT02498535; 2021), a Phase 2 open-label study of a nebulized NO-generating solution in patients with CF (NCT05101915; 2022), and a Phase 1/2 study of inhaled sodium nitrite as an antimicrobial for Pseudomonas infection in CF (NCT02694393, 2022). The only NO-releasing agent clinically evaluated in managing cancer is an NO derivative of aspirin. A Phase 1 clinical trial of NO-releasing aspirin in preventing colorectal cancer in high-risk patients (NCT00331786; 2007) was terminated due to the possible genotoxicity of a potential metabolite (NicOx, 2007). Another NO-releasing NSAID, NO-naproxen (naproxcinod) that, was being evaluated for osteoarthritis of the knee and hip (NCT00504127; 2009) (Karlsson et al., 2009; Lohmander et al., 2005; Schnitzer et al., 2005; Schnitzer et al., 2010; Schnitzer et al., 2011) has completed Phase-III clinical trials. However, approval for NDA application was denied due to concerns by the FDA about this agent's gastrointestinal and cardiovascular effects over long-term use (NicOx, 2010).

Regarding CO, translation to the clinical setting is the current focus of an investigation. Several methods of exogenous CO delivery exist, including inhaled CO, light-activated CORMs, liquid-dissolved CO, and metal-based CORMs. A relatively new direction that has recently emerged is the synthesis of organic (non-metal-based, non-photo-activated) CO-releasing prodrugs, which are intended to release CO under physiological conditions in response to a chemical or biological triggers; for details, see (Ji & Wang, 2018). This new class of drugs may offer exciting new possibilities for organelle or biomarker-based targeting and enable a more accurate assessment of the biological effect of this gasotransmitter both in vitro and in vivo (Ji & Wang, 2018).

Phase II clinical trials using inhaled delivery and PEGylated hemoglobin-carrier delivery of CO for indications such as chronic obstructive pulmonary disease (COPD) (NCT00122694; 2006), idiopathic pulmonary fibrosis (NCT01214187; 2015) (Rosas et al., 2018), vaso-occlusive crises (NCT02672540, NCT02411708; 2017) and ulcerations (NCT02600390; 2016) of sickle cell disease, subarachnoid hemorrhage (NCT02323685; 2016) and kidney transplant (NCT02490202; 2016) (Siracusa et al., 2021) have been conducted. There is also an ongoing phase II clinical trial (May 2022) investigating the safety and efficacy of inhaled CO in the treatment of acute respiratory distress syndrome (ARDS) (NCT03799874). However, no trials are being conducted for treating cancer. As far as we know, CO-donating multifunctional donors have not yet been characterized.

To reiterate, one must also remember that NO, CO, and H_2S do not act in isolation but in concert, sometimes through overlapping signaling pathways. These interactions need to be further explicitly elucidated in the context of cancer, as they may potentially enhance or complement the efficacy of other therapeutics. Such efforts have demonstrated the utility of NOSH-aspirin (Chattopadhyay, Kodela, Nath, Barsegian, et al., 2012, Lee et al., 2013, Fonseca et al., 2015, Kodela et al., 2015, Chattopadhyay et al., 2020), NOSH-naproxen (Chattopadhyay et al., 2016; Kodela et al., 2013), and NOSH-sulindac (Kashfi et al., 2015), as dual NO- and H_2S-donating hybrids against cancer and other inflammatory-based diseases in preclinical studies.

Finally, selective inducers/inhibitors of the gasotransmitter-generating enzymes may serve as another possibility for therapeutic applications. Importantly, however, each of these scenarios has both benefits and drawbacks. For instance, selective inhibitors of CBS could potentially increase homocysteine levels and thus increase cardiovascular risks, and iNOS-specific inhibitors could induce immunosuppression.

Many scientific discoveries have had an element of serendipity, curiosity, and a prepared mind; the NO, CO, and H_2S arenas are no exception.

Authorship contributions

KK – formulated the general concept of this review, PPO and KK researched the literature and wrote the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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