REVIEW

# The NLRP3 Inflammasome: A Sensor for Metabolic Danger?

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Interleukin-1β (IL-1β), reactive oxygen species (ROS), and thioredoxin-interacting protein (TXNIP) are all implicated in the pathogenesis of type 2 diabetes mellitus (T2DM). Here we review mechanisms directing IL-1β production and its pathogenic role in islet dysfunction during chronic hyperglycemia. In doing so, we integrate previously disparate disease-driving mechanisms for IL-1β, ROS, and TXNIP in T2DM into one unifying model in which the NLRP3 inflammasome plays a central role. The NLRP3 inflammasome also drives IL-1β maturation and secretion in another disease of metabolic dysregulation, gout. Thus, we propose that the NLRP3 inflammasome contributes to the pathogenesis of T2DM and gout by functioning as a sensor for metabolic stress.

Type 2 diabetes mellitus (T2DM) manifests when pancreatic β cells fail to compensate for chronic elevated blood glucose (hyperglycemia) that occurs when glucose uptake in the periphery becomes dysregulated during insulin resistance. Insulin is secreted by pancreatic β cells upon hyperglycemia and regulates glucose utilization within the body. In healthy individuals, postfeeding hyperglycemia is transient, as insulin stimulates glucose uptake and restores normoglycemia. Insulin resistance, a state that precedes T2DM, prolongs hyperglycemia by inhibiting the action of insulin. It is becoming increasingly apparent that chronic, low-grade systemic inflammation accompanies obesity, insulin resistance, and T2DM and contributes to the progression from obesity to T2DM (*1*). Elevated proinflammatory cytokines can contribute to insulin resistance by antagonizing insulin signaling, thereby inhibiting insulin-dependent glucose uptake and contributing to failing glucose tolerance (*2*). Local inflammation in the insulin-secreting pancreatic islets is also implicated; immune cell infiltration and local cytokine production accompany the early stages of disease as β cells begin to fail to maintain normal blood glucose levels (*3*). These local inflammatory processes, coupled with the toxic effects of glucose, lead to the accelerated loss of β cell mass through cell death and severely impair the insulin-secreting capabilities of the remaining β cells in both T2DM patients and animal models (*4*–*6*). Expression of the potent proinflammatory cytokine, interleukin-1β (IL-1β), is elevated in the circulation and in pancreatic islets during the progression from obesity to T2DM, and IL-1β is implicated as an important driver of disease [reviewed in (*2*)]. Similarities to IL-1β–mediated pathology in islet destruction during type 1 autoimmune diabetes have led to the proposal that IL-1β presents a common final pathway for autoimmune diabetes and T2DM (*7*).

## Does IL-1β Contribute to Pancreatic Islet Dysfunction in T2DM?

Mechanisms of pancreatic islet failure in T2DM are beginning to be clarified, and, although somewhat controversial, an emerging literature suggests a pathogenic role for IL-1β. Pancreatic islets of T2DM patients contain a smaller β cell mass compared with nondiabetic controls, as a result of increased β cell death (*5*, *6*). This appears to be a direct consequence of prolonged hyperglycemia; although acute exposure of human pancreatic islets to glucose induced β cell proliferation and triggered insulin secretion (*4*), chronic exposure to elevated glucose inhibited β cell insulin secretion and induced cell death in an IL-1β–dependent manner (*8*, *9*). The potent proinflammatory properties of IL-1β are tightly regulated by expression, processing, secretion, and antagonism by a natural inhibitor (*10*). Initially, IL-1β expression was thought to be specific to cells of the immune system, and to macrophages in particular, but it is now clear that cells outside the immune system can express IL-1β (e.g., keratinocytes) (*11*). Pancreatic islets of T2DM patients and rodent models of T2DM exhibit immune cell infiltration, including macrophages (*3*), and these cells are likely to contribute to intra-islet IL-1β production; however, β cells can also secrete IL-1β in response to prolonged elevated glucose exposure (*8*, *12*). Furthermore, unlike normal controls, human and mouse pancreatic islets and purified human β cells under metabolic stress in T2DM express IL-1β (*8*, *12*). Although β cells secrete less IL-1β than macrophages (*13*), it is sufficient for a clear autocrine effect on β cell viability and insulin-secretion capacity that can be blocked by antagonism or ablation of IL-1β (*8*, *14*, *15*). The extreme sensitivity of β cells to IL-1β is likely to be conferred by high expression of the IL-1 type I receptor (IL1R1) chain in these cells (*16*). IL-1β induced within the islet impairs β cell insulin secretion (*17*, *18*) and induces Fas death receptor–dependent, apoptotic β cell death in a manner resembling glucose-dependent cell death (*8*), which suggests that the proapoptotic effects of glucose are at least partly mediated by IL-1β. Indeed, IL-1β deficiency (*14*) or IL-1R blockade by the IL-1 receptor antagonist (IL1RA) (*8*) improved β cell function and blocked the cytotoxic effects of chronic elevated glucose exposure to cultured mouse or human islets, respectively. Likewise, in vivo administration of IL1RA to mice fed a high-fat diet improved glucose tolerance and insulin secretion, as well as pancreatic islet survival and function (*15*). Collectively, these reports suggest that glucose-induced IL-1β is a key mediator of islet dysfunction and destruction.

Elevated circulating IL-1β is a risk factor for the development of T2DM in humans (*1*), and mouse models and human clinical trials suggest that IL-1β antagonism may be a promising treatment for T2DM. Despite inhibiting basal β cell proliferation, insulin secretory function, and glucose tolerance compared with control mice, IL-1β deficiency protected mouse islets from the toxic effects of prolonged hyperglycemia (*14*). This suggests that low IL-1β expression has a positive physiological function in healthy animals, consistent with the beneficial effects of low-dose IL-1β on β cell proliferation and insulin secretory function (*14*, *19*), whereas high concentrations of IL-1β negatively affect β cell function and mediate glucotoxicity. Indeed, IL1RA suppressed the toxic effects of both IL-1β and glucose in human and rat pancreatic islets (*8*, *20*), and injection of IL1RA (*15*) or a neutralizing antibody against IL-1β (*21*) protected against the diabetic effects of a high-fat diet in mice. IL-1β antagonism in this context inhibited β cell death, promoted β cell mass, potentiated β cell glucose-induced insulin secretion, and improved insulin sensitivity (*15*, *21*). Consistent with these results, a recent human clinical trial using IL1RA to treat T2DM ameliorated systemic inflammation and significantly improved glycemic control and β cell function (*22*, *23*).

## How Is IL-1β Secretion Regulated?

Until recently, the mechanisms underlying glucose-regulated IL-1β secretion were unclear. The production of active IL-1β is tightly regulated, requiring at least two independent signals for induction and maturation. IL-1β is induced by proinflammatory signaling through Toll-like receptors (TLRs) or by cytokines, such as tumor necrosis factor or IL-1β itself; however, this proform of IL-1β is inactive and requires processing by the cysteine protease, caspase-1, for maturation and secretion (*24*). IL-1β maturation is controlled by multiprotein, caspase-1–activating

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platforms called inflammasomes. The NLRP3 (also known as NALP3) inflammasome is the most fully characterized of the inflammasomes and contains the adaptor protein apoptosis-associated specklike protein (ASC); the proinflammatory caspase, caspase-1; and NLRP3. NLRP3 belongs to the nucleotide-binding oligomerization domain (NOD)–like receptor (NLR) family (also referred to as the nucleotide-binding domain and leucine-rich repeat–containing receptors by the Human Genome Organization and in the accompanying reviews) of pattern recognition receptors that include the NODs [NOD1 and 2, NLRC3 or NOD3, NLRC5 or NOD4, NLRX1 or NOD5, and the major histocompatibility complex II transactivator (CIITA)], the NLRPs (NLRP1 to 14), NAIP, and NLRC4 (or IPAF) (*25*). Of these, NLRP1, NLRC4, and NLRP3 can form caspase-1–activating inflammasomes. The HIN-200 family member, AIM2, can also drive assembly of a caspase-1–activating inflammasome (*26*). A variety of pathogen- and host-derived "danger" signals activate the NLRP3 inflammasome, including whole pathogens; pathogen-associated molecular patterns (PAMPs); other pathogen-associated molecules (e.g., bacterial pore–forming toxins and malarial hemozoin); host-derived indicators of cellular damage ("danger-associated molecular patterns" or DAMPs); and environmental irritants (Table 1). The potent immunomodulatory functions of the NLRP3 inflammasome are highlighted by several related autoinflammatory diseases, collectively called cryopyrin-associated periodic syndrome (CAPS), in which activating NLRP3 mutations result in dysregulated IL-1β production and inflammation [reviewed in (*25*)].

Upon activation, NLRP3 is thought to oligomerize via homotypic interactions between NACHT domains and thereby presents clustered pyrin (PYD) domains for interaction with the PYD domain of ASC (Fig. 1). ASC assembly, in turn, presents clustered caspase activation and recruitment domains (CARDs) for interaction with the CARD of procaspase-1. Procaspase-1 clustering enables autocleavage and activation, and activated caspase-1 can cleave other cytosolic targets, including the proinflammatory cytokines IL-1β and IL-18. An unconventional pathway that awaits clarification directs secretion of the cleaved, mature cytokines.

Pathways leading to inflammasome activation are a matter of debate, and several models have been suggested that may not be mutually exclusive (Fig. 1). Extracellular adenosine triphosphate (ATP) is an NLRP3-activating DAMP that is released at sites of cellular injury or necrosis. ATP stimulates rapid $K^+$ efflux from the purinergic P2X7 receptor, an ATP-gated ion channel (*27*), and triggers gradual recruitment and pore formation by the pannexin-1 hemichannel (*28*). It has been proposed that NLRP3 senses either low intracellular $K^+$ or a breakdown in membrane integrity or that hemichannel pore formation allows extracellular NLRP3 agonists to access the cytosol, to activate NLRP3 directly (*28*). Given that a direct interaction between NLRP3 and its activators has not been demonstrated and the structural diversity among agonists, it seems unlikely that NLRP3 directly senses its activating stimuli. Membrane disruption may also drive NLRP3 activation in response to particulate or crystalline activators. Under this model, inefficient clearance of phagocytosed material leads to phagosomal destabilization and release of the proteinase cathepsin B into the cytosol, which contributes to inflammasome activation through an undetermined mechanism (*29*). The proposed role for cathepsin B, however, may be based on off-target effects of the cathepsin B inhibitor (*30*). Moreover, cathepsin B–deficient macrophages respond normally to particulate NLRP3 agonists (*31*).

A crucial function of ROS in NLRP3 activation has also been proposed (*31*–*33*) and is strongly supported by recent mechanistic data (*13*). ROS is normally produced within resting cells (e.g., by cellular metabolism); however, ROS induced by cellular infection or stress can cause oxidative stress. Where examined, all known NLRP3 activators, including ATP and activators that require phagocytosis, induce ROS. Moreover, ROS inhibition by treatment with ROS scavengers blocks inflammasome activation by a range of NLRP3 agonists [reviewed in (*24*)], which suggests that ROS generation is a necessary upstream event for inflammasome activation. For these reasons, we favor a model in which, instead of sensing PAMPs or DAMPs per se, the NLRP3 inflammasome is activated by ROS generated as a cellular response to these ligands and is thereby a more general sensor of cellular stress. Future work is required to clarify the role of ROS in NLRP3 activation. For example, a recent report suggested that caspase-1 activity can be inhibited by oxidation and

**Fig. 1.** Current models for activation of the NLRP3 inflammasome. NLRP3 oligomerization and recruitment of ASC and procaspase-1 trigger autoactivation of caspase-1 and the maturation and secretion of proinflammatory cytokines, such as IL-1β. Mechanisms leading to NLRP3 inflammasome activation are a matter of debate. Three models are widely favored in the literature and may not be mutually exclusive: (1) The NLRP3 inflammasome is activated by extracellular ATP by one of the following mechanisms: The purinergic P2X7 receptor–activated pannexin-1 pore allows cytoplasmic entry of extracellular factors that are direct NLRP3 ligands, or NLRP3 senses either $K^+$ efflux or a loss of membrane integrity. (2) Crystalline or particulate structures are phagocytosed, which leads to lysosomal rupture and cytoplasmic release of lysosomal content. This pathway is sensitive to the cathepsin B inhibitor, Ca-074-me, which suggests that cathepsin B potentiates this process. (3) All NLRP3 agonists trigger the production of ROS, which leads to the activation of the NLRP3 inflammasome via the ROS-sensitive TXNIP protein (see Fig. 3). LRR, leucine-rich repeat.

**Table 1.** NLRP3 inflammasome activators. Details of individual NLRP3 inflammasome activators are reviewed in (*24*, *25*).

| Activator class | Activator | Disease associations |
|---|---|---|
| Whole pathogen | *Candida albicans* | Infection |
| | *Saccharomyces cerevisiae*[*] | Infection |
| | *Staphylococcus aureus* | Infection |
| | *Listeria monocytogenes* | Infection |
| | Influenza virus | Infection |
| | Sendai virus | Infection |
| | Adenovirus | Infection |
| Pathogen-associated molecules | Bacterial pore–forming toxins | Infection |
| | Hemozoin | Cerebral malaria |
| Environmental insults | Silica | Silicosis |
| | Asbestos | Asbestosis |
| | Skin irritants | Contact hypersensitivity reactions |
| | Ultraviolet light | Sunburn |
| Endogenous danger signals | ATP | Injury or necrotic cell death |
| | Glucose | Metabolic syndrome |
| | MSU | Gout |
| | Calcium pyrophosphate dihydrate (CPPD) | Pseudogout |
| | Amyloid β | Alzheimer's disease |
| | Hyaluronan | Injury |
| Adjuvant | Alum | |

[*]Viable (*52*) but not heat-killed (*53*) *S. cerevisiae* activates the NLRP3 inflammasome.

glutathionation (*34*); whether this represents a negative feedback pathway to limit ROS-regulated caspase-1 function is presently unclear. Furthermore, although ROS appears to be necessary, it is not sufficient for NLRP3 activation, as some ROS-inducing agents (e.g., cytokines and nonimidazoquinoline TLR agonists) are not sufficient to trigger NLRP3 inflammasome activation. This implies either a specific requirement for the type or location of ROS or that ROS cooperates with a second, unidentified pathway for NLRP3-dependent caspase-1 activation. NLRP3 inflammasome activation can be suppressed by culturing cells in medium containing a high concentration of $K^+$ [reviewed in (*24*)], which implies a requirement for $K^+$ efflux for NLRP3 activation. The interplay between $K^+$ efflux and ROS generation is unclear, but it is possible that intracellular $K^+$ concentrations modulate ROS production or that low intracellular $K^+$ is required independently of ROS for NLRP3 activation.

Recent identification of a ROS-dependent NLRP3 ligand revealed several molecular events that may direct inflammasome activation (Fig. 2). NLRP3 agonists trigger the association of NLRP3 with thioredoxin-interacting protein (TXNIP), also known as vitamin $D_3$ up-regulated protein 1 (VDUP1), in human macrophages, and this association is suppressed by inhibiting ROS (*13*). In unstimulated cells, TXNIP is bound to the oxidoreductase thioredoxin; however, this complex dissociates when intracellular ROS increases. Free thioredoxin is then able to perform its function as a ROS scavenger. Dissociation of TXNIP from thioredoxin allows interaction with NLRP3 in a ROS-dependent manner (*13*). Furthermore, TXNIP knockdown or deletion suppresses caspase-1 activation and IL-1β secretion in response to NLRP3 agonists in human or mouse macrophages (*13*), and knockdown of the TXNIP inhibitor, thioredoxin, augments inflammasome activation in human macrophages (*31*). Taken together, these data suggest that TXNIP is an upstream activating ligand for NLRP3. Although unlikely, an indirect effect of TXNIP on NLRP3 activation via redox modulation, however, cannot be excluded at present. TXNIP-dependent inflammasome activation appears to be specific for NLRP3, as TXNIP deficiency did not affect the activity of other inflammasomes (e.g., NLRC4 and AIM2) (*13*).

### How Do TXNIP and NLRP3 Collaborate to Sense Metabolic Stress?

A large body of literature implicates a pathogenic role for TXNIP in T2DM, which, until recently, was not known to be linked to IL-1β. TXNIP deficiency improves glucose tolerance and insulin sensitivity in mice fed a high-fat diet (*35*, *36*). These attributes may be due to TXNIP-induced activation of NLRP3, because NLRP3 ablation also improves these metrics (*13*). TXNIP expression is induced by glucose (*13*, *37*), repressed by insulin (*38*), and elevated in T2DM (*38*, *39*). Glucose is a potent inducer of TXNIP in pancreatic islets but not in macrophages (*13*), which suggests that tissue macrophages do not contribute to glucose-dependent TXNIP induction within the islet. Pancreatic islets express all NLRP3 inflammasome components (NLRP3, ASC, and caspase-1) (*13*), albeit at lower levels than macrophages, which may reflect their reduced capacity to secrete IL-1β. Glucose-dependent IL-1β secretion is ablated in both TXNIP- and NLRP3-deficient mouse pancreatic islets and is also antagonized by ROS inhibitors (*13*). Taken together, these findings suggest that the NLRP3 inflammasome, in collaboration with ROS-liberated TXNIP, drives IL-1β secretion from pancreatic islets in response to chronic elevated glucose. Furthermore, they suggest that the TXNIP-dependent NLRP3 inflammasome, activated under conditions of metabolic stress, mediates IL-1β–driven islet failure during the progression of T2DM.

The concept that the NLRP3 inflammasome is activated by pathways that culminate in metabolic stress is further supported by the crucial role of NLRP3-dependent IL-1β production in a very different disease of metabolic dysregulation, gout. Gout is linked to dysregulated purine metabolism, which leads to elevated blood uric acid levels and monosodium urate (MSU) crystal deposition in joints, resulting in severe joint inflammation. It is interesting that metabolic syndrome, which often precedes development of T2DM, is a predisposing factor for gout. In this context, gout is likely to manifest as a consequence of increased purine intake. In gout, MSU activates the NLRP3 inflammasome and drives IL-1β production, leading to local pain and inflammation (*40*). Similar to inflammasome activation by glucose, MSU-dependent IL-1β maturation depends on collaboration between TXNIP and NLRP3 (*13*). Like metabolic syndrome, this condition can be ameliorated by changes in diet. In the case of gout, this involves decreasing the intake of gout-inducing purine-rich foods (e.g., beer and seafood). Acute gout attacks can also be successfully treated with IL1R antagonists (*41*, *42*).

### Does the NLRP3 Inflammasome Contribute to T2DM Progression?

In the majority of cases, T2DM is a complex disorder in which there is substantial interaction between environmental factors, such as food intake and exercise, and genetic predisposition. A number of genetic variants were shown to associate with β cell decline in T2DM in recent genome-wide association studies (*43*). Although components of the inflammasome pathway were not implicated, a number of potassium channel variants, presumed to mediate their diabetic effects through modulation of insulin secretion, may also modulate activation of the $K^+$-sensitive NLRP3 inflammasome. There is a clear link,

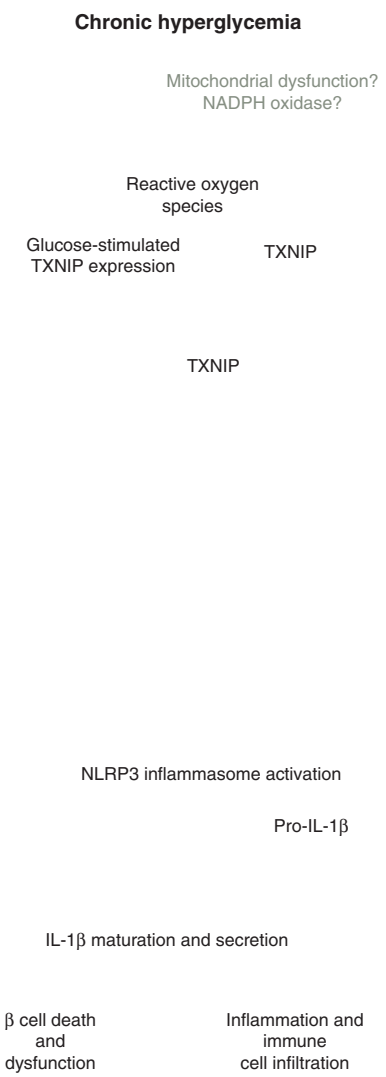


**Fig. 2.** Proposed model of NLRP3 inflammasome activation leading to pancreatic islet dysfunction in T2DM. Chronic hyperglycemia leads to ROS production, probably through overstimulation of the mitochondrial electron transport chain as a consequence of increased glycolysis. Glucose induces TXNIP expression, and ROS triggers the dissociation of TXNIP from thioredoxin (TXN), which results in increased TXNIP availability for activation of the NLRP3 inflammasome and caspase-1–dependent IL-1β maturation. The autocrine and/or paracrine action of secreted IL-1β mediates glucose-induced β cell death and dysfunction. β cell failure is further augmented by the local proinflammatory milieu created by infiltrating immune cells. β cell failure impairs glucose-stimulated insulin secretion and so contributes to decreased glucose uptake in the periphery and the maintenance of chronic hyperglycemia.

however, between prolonged hyperglycemia, whether driven by genetic or environmental factors, or both, and pancreatic islet failure. It is in this context that the data reviewed here suggest a pathogenic role for the NLRP3 inflammasome.

The evidence presented above suggests the following model for NLRP3 inflammasome activation in pancreatic islet failure during T2DM progression (Fig. 2). Chronic islet exposure to elevated glucose triggers ROS generation, through mechanisms that are currently unclear. Glucose was reported to induce ROS generation via the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system in rat pancreatic islets and a β cell line (*44*); however, it is more likely that increased glycolysis drives ROS production by increasing the activity of the mitochondrial electron transport chain (*45*). Indeed, mitochondrial dysfunction and oxidative stress in pancreatic islets are strongly implicated in T2DM progression (*45*). Elevated glucose also induces high expression of TXNIP, which together with its ROS-dependent dissociation from thioredoxin, switches TXNIP function from thioredoxin repressor to NLRP3 inflammasome activator. Once activated, caspase-1 cleaves pro-IL-1β to its mature form, and IL-1β is secreted and can signal in an autocrine and/or paracrine manner to promote β cell death and to impair β cell function.

Additional mechanisms may contribute to islet dysfunction and destruction. IL-1β signaling is likely to trigger secretion of other chemotactic factors to direct further immune cell infiltration. The combined effects of the proinflammatory milieu and activated immune cells would augment β cell death and would suppress β cell secretory functions. TXNIP was reported to contribute to β cell destruction (*39*); however, whether this is dependent on IL-1β is unclear. Inhibition of glucose uptake in the periphery by TXNIP (*38*) may also contribute to pancreatic islet failure by reducing blood glucose utilization and thereby sustaining hyperglycemia.

A number of questions remain unresolved, including the mechanism of pro-IL-1β induction in pancreatic islets. Potential mechanisms include induction by an autoamplification loop or by elevated circulating free fatty acids, which can signal through TLR4 (*46*, *47*). Alternatively, islet oxidative stress that is associated with T2DM (*45*) may activate the IL-1β promoter via the nuclear factor κB transcription factor (*48*). Any of these pathways would also promote secretion of other proinflammatory cytokines and chemokines, which would drive islet infiltration by immune cells and thereby amplify the local proinflammatory milieu. The specific contribution of intra-islet macrophages to IL-1β–mediated β cell dysfunction is currently uncertain.

Relative insulin resistance in the periphery, coupled with insufficient pancreatic insulin

**Fig. 3.** Model for the role of ROS, TXNIP, and IL-1β in pancreatic β cell failure in T2DM. During the early stages of disease, pancreatic β cells can compensate for relative insulin resistance in the periphery by increasing the production of insulin and thereby ameliorate hyperglycemia. Increasing insulin resistance, however, overwhelms β cell compensatory mechanisms, leading to decreased insulin signaling and insulin-dependent glucose uptake, and contributing to sustained hyperglycemia. Prolonged hyperglycemia in pancreatic islets leads to the induction of ROS, which triggers TXNIP-dependent activation of the NLRP3 inflammasome, culminating in the secretion of mature IL-1β. Elevated IL-1β causes β cell death and dysfunction, leading to decreased glucose-stimulated insulin secretion and exacerbating chronic hyperglycemia. In the periphery, the combination of decreased insulin signaling and elevated glucose induces expression of TXNIP. High TXNIP expression, coupled with decreased insulin signaling, antagonizes glucose uptake and inhibits the return to normoglycemia. Glucose-induced NLRP3 inflammasome activation outside of the pancreatic islets may also contribute to elevated IL-1β, insulin resistance, and T2DM progression.

secretion during hyperglycemia, establishes a vicious cycle that drives the progression from insulin resistance to T2DM (Fig. 3). TXNIP is implicated as a disease-driver in both pancreatic islets and the periphery: TXNIP mediates glucose-induced cell death in islets and antagonizes glucose uptake in the periphery (*38*, *39*). The available data suggest a model in which hyperglycemia induces, whereas insulin signaling suppresses, TXNIP expression. Thus, the high-glucose and low-insulin signaling state in T2DM results in elevated TXNIP expression in both pancreatic islets and the periphery. High TXNIP expression within the islet sensitizes the cells to TXNIP-dependent cell death and NLRP3 inflammasome activation, whereas high TXNIP expression in the periphery further antagonizes glucose uptake and contributes to hyperglycemia. A major open question is whether extra-pancreatic tissues under metabolic stress (e.g., chronic hyperglycemia) drive NLRP3 inflammasome activation and IL-1β production in a manner similar to that of pancreatic islets, to contribute to IL-1β–dependent insulin resistance within tissues. The potential cooperation of TXNIP and NLRP3 in glucose-dependent inflammasome activation outside of the pancreatic islet awaits clarification and future research.

## Concluding Remarks

T2DM manifests when blood glucose levels become so unbalanced, because of high nutrient consumption and poor peripheral glucose uptake, that the compensatory functions of pancreatic β cells become overwhelmed. Studies of IL-1β–deficient mice demonstrate that IL-1β has important homeostatic functions in glucose tolerance that may be linked to the ability of acute, low-dose IL-1β to stimulate pancreatic β cell proliferation and insulin secretory function. Furthermore, IL-1β suppresses appetite (*49*). Thus, glucose-dependent IL-1β secretion may be an important physiological compensatory mechanism for the maintenance of normoglycemia. Chronic elevation of IL-1β in T2DM, however, suggests a pathological role for IL-1β in disease progression. In gout, NLRP3-dependent IL-1β production in response to metabolic stress in the form of MSU is a well-established driver of disease. The evidence presented in this review suggests that NLRP3-dependent IL-1β production during metabolic stress, in this case chronic hyperglycemia, may also contribute to the progression of T2DM. This new hypothesis should be the focus of future investigations into the disease-driving mechanisms of T2DM. In support of a pathological role for the NLRP3 inflammasome in T2DM, the antidiabetic drug, glibenclamide, which is used to stimulate β cell insulin secretion, also suppresses glucose-induced inflammasome activation and downstream IL-1β release (*13*, *50*, *51*). Furthermore, antagonists of IL-1β or its receptor are proving highly effective for the treatment of T2DM in both mouse models and human clinical trials. The recent finding that the NLRP3 inflammasome forms a nexus linking TXNIP, oxidative stress, and IL-1β production during metabolic stress provides new avenues for research and therapy for T2DM, a disease often described as the next global pandemic.

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