NLRP3 and IL-1β in macrophages as critical regulators of metabolic diseases

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Abstract

The activation of the NLRP3 inflammasome leads to the autocleavage and activation of caspase-1. Caspase-1 cleaves several substrates, including the pro-inflammatory cytokine IL-1β. Inflammation, in particular IL-1β, has long been associated with the progression of metabolic disorders, and recent evidence suggests that the NLRP3 inflammasome plays a critical role in this inflammation. This review concentrates on the activation of NLRP3 during the development of metabolic disorders and the effect this activation has on the inflammatory state as well as the metabolic state of the cell.

Innate Immune System

The innate immune system is the first line of defence against invading pathogens. There are several families of receptors called pattern-recognition receptors (PRRs) that recognize highly conserved pathogen-associated molecular patterns (PAMPs) as well as host-derived danger signals called damage-associated molecular patterns (DAMPs). There are several families of PRRS including Toll-like receptors (TLRs), Nod-like receptors (NLRs), C-type lectin receptors (CLRs) and RIG-1-like receptors (RLRs). Once these PRRs have been activated they induce signalling cascades, which lead ultimately to the induction of a variety of pro-inflammatory cytokines. This review concentrates on the PRR NACHT, leucine rich repeat (LRR) and PYD domains-containing protein 3 (NLRP3), which is a member of the NLR family.

To date 22 NLR family members have been identified in humans [1]. They are cytosolic receptors, which detect microbial products or stress signals. A subset of NLRs activates multiprotein complexes, called inflammasomes that lead to the activation of caspase-1. There are four inflammasomes known to date involving NLRP1, NLRP3, NLRP4 and AIM2. The best characterized is the NLRP3 inflammasome. A wide range of DAMPs activate this inflammasome including endogenous markers of cellular and metabolic distress such as monosodium urate (MSU), ATP, amyloid-β, islet amyloid polypeptide (IAPP) or mitochondrial dysfunction, exogenous agents such as asbestos, silica or alum and obesity-related factors such as ceramide, fatty acids, hyperglyceamia or reactive oxygen species (ROS) [2]. Several PAMPs can also activate this inflammasome such as sendai virus, influenza virus or listeria [3].

NLRP3 consists of a pyrin domain, a NACHT domain and a LRR motif. The activation of the LRR leads to the oligomerization of NLRP3 via homotypic interaction between the NACHT domains of NLRP3. The pyrin domains then interact with the pyrin domain of ASC. This leads to the recruitment of procaspase-1 via a CARD–CARD interaction with an apoptosis-associated speck-like protein containing a CARD (ASC). The clustering of procaspase-1 results in autocleavage and activation. Caspase-1 then cleaves several pro-inflammatory cytokines including pro-IL-1β and pro-IL-18, resulting in their activation and secretion. The generation of mature IL-1β and IL-18 involves two signals. TLR ligands, such as lipopolysaccharide (LPS), induce the expression of pro-IL-1β and pro-IL-18, while the NLR inflammasome cleaves the pro-forms to produce active IL-1β and IL-18. These are important mediators of the immune response and inflammation. IL-1β binds to the IL-1 receptor resulting in the production of more inflammatory mediators influencing cell migration and immune cell infiltration [4]. IL-1β also promotes the generation and maintenance of interferon (IFN)-γ and IL-17 producing T-cells, which have been implicated in autoimmune disorders such as multiple sclerosis and type 1 diabetes [5].

Other PRRs, such as TLRs, are known to bind their PAMPs and DAMPs directly, but because of the vast array of DAMPs and PAMPs that activate the NLR inflammasome it is unlikely that they all bind directly to the NLRs. The mechanism by which these DAMPs and PAMPs activate the inflammasome remains unclear and has been the subject of much debate in the literature [3]. Current opinion suggests that the agonists influence cellular processes or organelles, such as K+ efflux, lysosomal destabilization or mitochondrial dysfunction and ROS production, to activate a signalling pathway that leads to inflammasome activation. There are several lines of evidence for this that are discussed below.

Extracellular ATP is known to activate NLRP3 [6]. ATP is released during cellular injury or necrosis and activates the P2X7 receptor, an ATP-gated channel, resulting in a rapid K+ efflux, leading to inflammasome activation. Inhibition of K+ efflux by increased extracellular K+ concentrations prevents NLRP3 activation by a wide array of NLRP3 agonists including ATP, MSU, asbestos and nigericin [7]. While K+ efflux appears to be essential it is not sufficient to activate the NLRP3 inflammasome.

For large particulates, such as asbestos, silica and MSU, the activation of NLRP3 and release of IL-1β require phagocytosis as the inhibitor cytochalasin D, which disrupts actin filamentation, inhibited the production of mature IL-1β by these compounds [8]. Recent studies suggest that inefficient clearance of the particle following phagocytosis leads to the lysosomal destabilization and the release of cathepsin B into the cytosol. The inhibition of cathepsin B using inhibitors

prevented the activation of the NLRP3 inflammasome in response to particulates [9]. However, controversy remains over the role of cathepsin B as Dostert et al. showed no impairment in activation of the inflammasome by silica or asbestos in macrophages from cathepsin B-deficient mice [10]. This may be because of the redundancy among the lysosomal cathepsins. The secretion of IL-1β by non-crystalline activators of NLRP3, such as R837 and nigericin, is unaffected by the inhibition of phagocytosis.

A role for ROS in NLRP3 activation by several activators including ATP [11], MSU [7], asbestos and silica [8] has been shown. The ROS inhibitors N-acetyl-l-cysteine (NAC) and (2R,4R)-4-aminopyrolidine 2,4-dicarboxylate (APDC) inhibited the production of IL-1β by MSU, asbestos and ATP [10]. Dostert et al. showed this ROS production was reliant on NAPDH oxidase as an inhibitor of NADPH, diphenylene iodonium (DPI), prevented L-1β production [8]. Wen et al. showed that the activation of NLRP3 by palmitate, a saturated fatty acid, required increased mitochondrial ROS, a direct result of autophagy suppression [12]. This will be discussed in more detail later.

Zhou et al. have shown a role for TXNIP in NLRP3 activation by certain stimuli [13]. In resting cells, TXNIP is associated with the oxidoreductase thioredoxin. Inflammasome activators, such as uric acid crystals, cause an increase in ROS, resulting in dissociation between TXNIP and thioredoxin and an association between NLRP3 and TXNIP. ROS inhibitors suppress this association in human macrophages. TXNIP knockdown results in decreased caspase-1 activation and IL-1β secretion following NLRP3 activation. TXNIP appears to act only through NLRP3 as TXNIP knockdown has no effect on NLRP4 or AIM2 signalling. Masters et al. however found no involvement of TXNIP in the activation of NLRP3 by IAPP amyloids in macrophages [14].

Lee et al. showed that in mice calcium-sensing receptor (CASR) activates NLRP3 via increased intracellular Ca2+ and decreased cellular cyclic AMP (cAMP) [15]. CASR activates NLRP3 via the activation of phospholipase C which in turn catalyses inositol-1,4,5-triphosphate production inducing Ca2+ release from the endoplasmic reticulum. This results in spontaneous assembly of the NLRP3 inflammasome. CASR can also decrease cAMP levels. cAMP binds NLRP3 to directly prevent inflammasome assembly, therefore reducing cAMP.

Several of these NLRP3 activators, such as ATP, K+ efflux, ROS production and TXNIP, are key components of metabolic stress thus suggesting a significant role for NLRP3 in metabolic disorders.

The Role of the Inflammasome in Metabolic Disorders

Chronic inflammation has long been associated with metabolic disorders, such as type 2 diabetes (T2D), gout and atherosclerosis. The incidence of metabolic disorders is on the rise and constitutes one of the major threats to global health. Therefore, a true understanding of the progression of these diseases is more important than ever. Inflammatory cytokines such as interleukins and tumour necrosis factor (TNF) have been implicated in the development of several metabolic disorders.

Type 2 Diabetes

In healthy individuals insulin is released from pancreatic β-cells to promote glucose uptake in muscle and reduce gluconeogenesis in the liver and lipolysis in adipose tissue. Overnutrition and obesity are strong risk factors for T2D. Obesity leads to excess lipid storage in adipocytes, leading to increased stress signals and an influx of macrophages into these insulin-producing tissues resulting in chronic inflammation [16]. Sustained overnutrition leads to chronic hyperglycaemia, which in turn leads to insulin resistance. Over time the body can no longer compensate for insulin resistance and this leads to defective nutrient metabolism and elevated levels of glucose circulating in the blood, leading to the development of T2D. The chronic inflammation associated with obesity has been shown to contribute directly to the development of insulin resistance and ultimately T2D. Studies have shown that TLR4 and NLRP3 play a key role in this inflammation with TNF and IL-1β as key inflammatory cytokines [17, 18]. IL-1β is of particular interest as increases in IL-1β leads to the generation of more inflammatory mediators via the IL-1 receptor [19]. IL-1β causes a shift in adipocytes to a more insulin-resistant phenotype during differentiation. Injection of IL-1β results in insulin resistance in mice and IL-1β null mice do not develop insulin resistance when fed a high-fat diet (HFD). Elevated IL-1β levels in circulation are associated with increased risk of developing T2D [20] and Sauter et al. showed that administration of the IL-1 receptor agonist (IL-1Ra) in vivo improved glucose tolerance and insulin sensitivity and prevented diabetes in mice fed a HFD [21]. Further evidence of the importance of IL-1β in the progression of metabolic disorders comes from the encouraging results in T2D patients treated with the IL-1 receptor antagonist anakinara [22]. Recent studies suggest that IL-1β produced in response to obesity-induced chronic inflammation functions in at least three ways to promote insulin resistance. It prevents the translocation of the glucose transporter 4 (GLUT4) to the plasma membrane following exposure to insulin. IL-1β decreased the expression and phosphorylation of the insulin receptor substrate 1 (IRS1) in human adipocytes [23]. It also induces the expression of TNF, which is known to contribute to insulin resistance [24].

Because of the central role of the inflammasome in the generation of active IL-1β, several studies have concentrated on the role of inflammasomes in metabolic disorders. As mentioned above, obesity is a strong risk factor in metabolic

disorders such as T2D. Obesity causes an increase in the release of ceramides, saturated fatty acids, ROS, mitochondrial dysfunction and ATP from necrotic adipocytes. These obesity-associated DAMPs activate NLRP3 and this activation prevents adipocyte differentiation and insulin signalling leading to the development of insulin resistance [12, 13, 25]. In mice lacking NLRP3 or other components of the inflammasome such as ASC or caspase-1, glucose tolerance and insulin sensitivity were improved following feeding on a HFD [13]. Wen et al. and Vandanmagsar et al. have shown a direct association between NLRP3 activation and the development of insulin resistance [12, 25]. They also show that the activation of inflammasomes in macrophages can induce insulin resistance in other cell types such as hepatocytes or T cells. Palmitate, one of the most abundant saturated fatty acids in the plasma of patients with T2D, is known to activate the NLRP3-inflammasome, via the suppression of AMPK activation [12]. The role of AMPK will be discussed in more detail later in the review. Wen et al. showed that IL-1β, produced by the activation of NLRP3 by LPS and palmitate, impairs insulin signalling in a mouse cell line and in primary hepatocytes. Further proof of the involvement of the NLRP3 inflammasome in the development of T2D came when Wen et al. showed that NLRP3 −/− or pycard (ASC) −/− mice demonstrate increased insulin sensitivity and better glucose metabolism in comparison to wild-type (WT) mice when fed a HFD [12]. Palmitate can be further converted into sphinganine, dihydroceramide and ceramide. Ceramide has also been shown to activate caspase-1 and IL-1β via the NLRP3-inflammasome [25]. In contrast, oleate, an unsaturated fatty acid does not activate the inflammasome [12].

IAPP is a protein secreted at the same time as insulin by β-cells in the pancreas [14]. IAPP forms amyloid deposits in the pancreas of patients with T2D. This is a marker of the progression of the disease and an indication of increased severity. A rare polymorphism in IAPP is associated with increased incidence and severity of T2D and this polymorphism leads to increased amyloid formation [26]. Master et al. showed that these amyloid structures activate the NLRP3 inflammasome, leading to IL-1β activation. This process appears to involve the phagocytosis of amyloid deposits into lysosomal deposits [14].

As mentioned previously, TXNIP may play a role in NLRP3 activation by certain stimuli [13]. TXNIP has also been shown to play a role in the development of T2D. The levels of TXNIP are increased in T2D, and TXNIP is associated with insulin resistance. TXNIP deficiency improves glucose tolerance and insulin sensitivity in mice fed HFD [27]. The lack of TXNIP also prevents glucose-induced IL-1β in pancreatic islets [13]. NLRP3 deficiency exhibits similar effects to those seen by TXNIP deficiency suggesting that the role of TXNIP in T2D may involve its interaction with NLRP3.

Atherosclerosis

Atherosclerosis is another disorder associated with chronic inflammation. It is characterized by accumulation of fats and cholesterol in the arterial walls and infiltration of immune cells into the atherosclerotic lesions [28]. In a similar manner to T2D, the progression of atherosclerosis pathogenesis is greatly affected by obesity-related factors. Several lines of evidence suggest a central role for the inflammasome in this disease. IL-1β levels are increased in arterial plaques and IL-1β levels correlate with disease severity [29, 30]. The presence of an IL1RN polymorphism, which increases IL-1β production, increases the risk of developing atherosclerosis [31]. Low-density lipoproteins accumulate in the artery walls and lead to the production of cholesterol crystals [28, 32], and these crystals are known to activate the NLRP3 inflammasome in mouse and human macrophages [32]. This activation is sensitive to treatment with cytochalasin D or bafilomycin, suggesting a need for phagocytosis and lysosome acidification in the activation of the inflammasome [8, 9].

Gout

Gout is the most common form of inflammatory arthritis in older men, affecting 1–2% of adults in the developed world. It is known as the 'arthritis of the rich' as it is associated with rich food, high in purines and alcohol. High concentrations of uric acid in the blood lead to the formation of MSU crystals. MSU was described as the causative effect of gout over 100 years ago [33] but the mechanism of action of MSU was only understood upon the discovery of NLRP3 a decade ago. IL-1β is a key inflammatory cytokine in the development of gout, promoting neutrophil recruitment into the synovium and joint fluid [34]. The importance of IL-1β in the progression of this disease has become evident from the effectiveness of IL-1β antagonists in treating this disease [35-37]. Mononuclear phagocytes are thought to play a central role in the recognition of MSU and the production of IL-1β [38]. Studies have shown a role for NLRP3 in this process [39] but the exact mechanism by which NLRP3 recognizes MSU remains unclear. As mentioned above, K+ efflux, phagocytosis, ROS production or TXNIP association may be involved in the activation of NLRP3 by MSU. Joosten et al. showed the need for free fatty acids (FFAs) along with MSU to activate IL-1β. They saw a significant reduction in IL-1β production in caspase-1 and ASC deficient mice, but no difference in NLRP3-deficient mice [40]. This disagrees with earlier studies and may point to a role for an alternative inflammasome in the activation of IL-1β. The role of TLRs in the immune response to MSU is unclear. One study indicated a role for TLR2 and TLR4 as macrophages from mice deficient in these TLRs showed reduced IL-1β production in response to MSU [41], while another study, in a peritoneal model of gout, showed no role for TLR2 or TLR4 but a role from the IL-1 receptor [42]. While certain aspects of the activation of IL-1β by MSU remain to be elucidated it is quite clear that this pathway is central to the development of gout and it seems likely that treatment for this disease in the future will centre on this pathway.

As mentioned previously, the production of active IL-1β requires two signals. A priming signal (signal 1), which leads to increased pro-IL-1β expression and an

activating signal (signal 2), which leads to the cleavage and activation of IL-1β. As outlined in this review, NLRP3 inflammasome activation (signal 2) leads to the release of active IL-1β in several auto-inflammatory diseases. It is known that several pathogenic components, such as LPS, can activate TLRs, leading to the activation of signal 1 and the production of pro-IL-1β but how does this signal 1 occur in the sterile environment present in auto-inflammatory diseases? In pancreatic β-cells glucose metabolism causes an increase in pro-IL-1β [43]; however, this is not the case in macrophages or adipocytes [14]. Masters et al. showed a role for minimally modified LDL (mmLDL) in the priming of macrophages. mmLDL increased pro-IL-1β production and this process required TLR4 [14]. As mentioned above, FFAs have also been implicated in the priming of this system. FFA can activate the NF-κB pathway and the production of cytokines via the TLR4 pathway in macrophages and adipocytes [44].

The Role of SIRT1 and AMPK in the NLRP3 Inflammasome

SIRT1 and AMPK are key metabolic sensors and recent studies suggest AMPK and SIRT1 work together to maintain metabolic homeostasis. Emerging evidence also suggests that they play a role in the regulation of inflammation [45, 46]. SIRT1 is a NAD+-dependent deactylase, which plays a role in the maintenance of metabolic homeostasis and the prevention of obesity [47]. SIRT1 represses the expression of PPARα, a key regulator of lipid metabolism [48] and activates PGC-1β, which leads to increased fatty-acid oxidation in adipocytes [49]. SIRT1 also deacetylates the p65 subunit of NF-κB, inactivating NF-κB, limiting the expression of NF-κB-dependent genes. [50]. SIRT1 levels in adipose tissues display an inverse correlation with the levels of inflammation in these cells [51]. Adipose-specific SIRT1 knockout mice displayed increased insulin resistance as well as metabolic dysfunction [52]. SIRT1 activity levels are decreased in adipose tissues following a HFD and this is as a result of SIRT1 cleavage by caspase-1. This is most probably because of NLRP3 inflammasome activation as NLRP3 is activated in adipose tissues in response to HFD [25]. The caspase-1 inhibitor BOC-D-FMK prevented the cleavage of SIRT1. This suggests a close link between the regulation of metabolic and immune pathways.

AMPK has been implicated in the activation of NLRP3. AMPK is a protein kinase that has emerged as a key regulator of energy metabolism and glucose homeostasis through the regulation of several intracellular systems such as glucose uptake, the oxidation of fatty acids and the synthesis of the GLUT4. AMPK is a heterotrimeric complex comprising of a catalytic α-subunit and a regulatory β- and γ-subunit. The phosphorylation of AMPK on a threonine residue (Thr172 in rat) causes the activation of AMPK. Binding of adenosine nucleotides to the regulatory γ-subunit causes a conformational change that dictates the net phosphorylation of Thr172. ATP binding decreases Thr172 phosphorylation while ADP or AMP binding increases Thr172 phosphorylation [53]. Thus the AMP : ATP ratio dictates the levels of AMPK activation. Activated AMPK restores energy balance by promoting catabolic processes, such as glycolysis, while inhibiting energy-consuming processes, such as protein

synthesis, thus increasing the net ATP levels [54]. AMPK also inhibits cell growth and proliferation to limit ATP consumption [55]. AMPK responds to a wide variety of stimuli, including cellular stress, exercise and several hormones, cytokines and adipokines. AMPK can be activated via two pathways involving the AMP-dependent activation of LKB1 or the $Ca2+$-dependent activation of $CaMKK\beta$ [56]. These mechanisms of activation are reviewed in [57]. Activated AMPK is responsible for metabolic changes via the phosphorylation of multiple downstream targets. Many of its targets are transcription factors (TF) and phosphorylation of these TF can inhibit binding thus repressing transcription or promote binding thus promoting transcription. In a microarray study the expression of a dominant negative form of AMPK in skeletal muscles led to the increased expression of 234 genes and the decreased expression of 130 genes [58].

Inflammatory stimuli, such as LPS, or nutrient-rich conditions, such as FFAs, result in decreased activation of AMPK [59]. Levels of AMPK and LKB1 expression were reduced in the fat of mice fed a HFD [59]. Activation of AMPK inhibits LPS and FFAs ability to activate NF-κB luciferase or TNFα in macrophages, showing that AMPK is a key suppressor of LPS and FFA-induced inflammation in macrophages. AMPK is therefore likely to promote a switch from a pro-inflammatory to an anti-inflammatory phenotype in cells of the immune system. AMPK has also been shown to play a role in NLRP3 activation. AMPK promotes autophagy, a catabolic process that ensures the lysosomal degradation of unwanted or dysfunctional components of the cell. The deactivation of AMPK by saturated fatty acids, such as palmitate, leads to decreased autophagy and iNOS, which results in decreased NO production, increased mitochondrial dysfunction and an increase in mitochondrial ROS production [60]. This in turn leads to the activation of the NLRP3 inflammasome. Several AMPK activators have been shown to inhibit inflammatory responses and this is reviewed in [61]. The anti-inflammatory drug salicylate activates AMPK. Salicylate binds directly to AMPK causing a conformational change that promotes activation [62]. This once again links AMPK to the regulation of the immune response.

A role for AMPK in T2D has been shown. Yuan et al. showed that treatment of obese mice with salicylate resulted in a significant decrease in blood glucose levels [63] while clinical trials with salsalate, a non-acetylated prodrug of salicylate, showed a reduction in blood glucose levels in patients with T2D [64]. The activation of AMPK is thought to benefit T2D patients in several ways. Glucose uptake stimulated by AMPK is insulin independent and still occurs in patients with T2D whose insulin-dependent glucose uptake is severely impaired [65]. As mentioned above, AMPK is known to stabilize mitochondria. Activation of AMPK can therefore overcome the mitochondrial dysfunction associated with T2D, decreasing NLRP3 activation. Obese mice models show defective autophagy and increased NLRP3 activation. This may be because of decreased AMPK activation. AICAR, an AMPK agonist, can restore autophagy and this inhibits caspase-1 activation and ROS production [12]. Leakage of mitochondrial DNA

into the cytosol, following the inhibition of autophagy, may also contribute to NLRP3 activation [66].

Glycolysis, Inflammation and NLRP3

A final intriguing aspect relating to metabolism and the IL-1β system concerns recent observations on metabolic shifts in activated macrophages. Activation of macrophages and dendritic cells by LPS induces the 'Warburg effect' leading to a switch in metabolism from oxidative phosphorylation to glycolysis [67, 68], in a manner similar to that observed in tumour cells [69]. Increased aerobic glycolysis also occurs in several pro-inflammatory cells such as M1 macrophages and T-helper 17 lymphocytes [70, 71], while oxidative metabolism predominates in anti-inflammatory cells such as M2 macrophages and CD8+ memory T cells [70, 72]. Glucose metabolism is known to increase IL-1β production in pancreatic β-cells, although the mechanism for this increase is yet unclear [43]. High concentration of glucose does not increase IL-1β in macrophages [14]; however, inhibition of glycolysis by 2-deoxy-d-glucose (2DG) following LPS stimulation reduces the levels of IL-1β mRNA produced but has no effect on TNF or IL-6 [14, 68]. Tannahill et al. recently discovered that the metabolic shift to glycolysis following LPS stimulation also results in an increase in succinate, which led to the stabilization of the transcription factor HIF1α that targets IL-1β. LPS also increased the succinylation of several proteins, including malate dehydrogenase and glyceraldehde-3-phosphate dehydrogenase. Interestingly, although succinate was produced from glutamine through anerplerosis via αKG, the GABA shunt was also a major supplier of succinate. The synthesis of fatty acid was increased, as was the products of the pentose phosphate pathway following LPS stimulation [68].

While LPS induces glycolysis, the activation of the NLR inflammasomes may in fact inhibit glycolysis. Several glycolytic enzymes, including fructose-biphosphate aldolase, glyceraldehyde-3-phosphate dehydrogenase, α-enolase and pyruvate kinase have been shown to be cleaved by caspase-1. These enzymes were cleaved in WT mice infected by Salmonella Typhimurium, an activator of the NLRC4 inflammasome, but were not cleaved in caspase-1 deficient mice [73]. The rate of glycolysis was higher in caspase-1 deficient cells once again implicating caspase-1 in the inhibition of glycolysis [73]. As glycolysis is essential for the survival of macrophages, inhibition of glycolysis should promote cell death. Glycolysis is however likely to activate NLRP3 in a feedback loop. Glycolysis increases the production of ROS, FFA and purines, such as uric acid, all of which are known to activate the NLRP3 inflammasome.

Nitric oxide (NO) also switches on glycolysis via a pathway involving AMPK and 6-phosphofructo-2-kinase [74]. iNOS, which results in the generation of NO, is induced by LPS [75]. NO results in a decrease in NLRP3 inflammasome activation via stabilization of mitochondria and decreased NLRP3 activation.

Conclusion

Recent evidence suggests that metabolic shifts associated with such disorders as T2D and obesity directly impact on the immune response and similarly the immune response impacts directly on metabolism in the cell (figure 1). It is now clear that cytokines such as IL-1β play a central role in the development of these conditions. Several of the key treatments for these metabolic disorders involve the inhibition of IL-1β production. As mentioned above, the IL-1Ra, anakinara, has shown very encouraging results from clinical trials of patients with T2D [22]. Glyceride, a drug used to treat T2D, has recently been shown to suppress IAPP-mediated NLRP3 activation and IL-1β production [14]. Metformin, an antidiabetic drug, inhibits mitochondrial function, resulting in increased AMP and ADP levels, promoting the activation of AMPK. This in turn inhibits iNOS production and promotes autophagy [60], which results in a decrease in NLRP3 activation and a decrease in IL-1β production. NLRP3 is emerging as a key component of the chronic inflammation associated with metabolic disorders. This review has highlighted the many DAMPs, generated during metabolic disorders, such as palmitate, ceramide, IAPP and MSU, which activate the NLRP3 inflammasome. Thus, a greater understanding of the method of activation of the NLRP3 pathway by these DAMPs will give us valuable insight and provide us with new targets for the treatment of these diseases.

Figure 1.
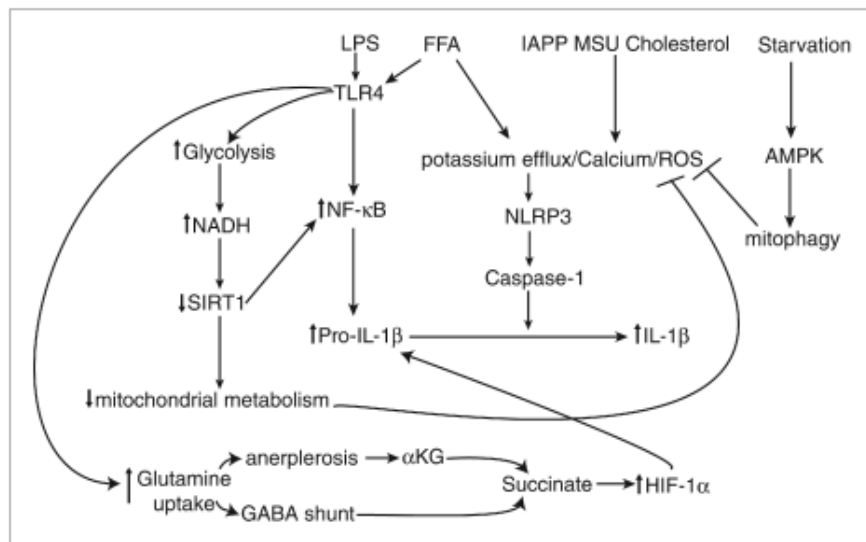
A model for the alterations in metabolism and inflammation following stimulation with LPS and various metabolic stimuli. LPS induces the production of pro-IL-1β via several different pathways. The classical pathway involves the activation of NF-κB. An increase in glycolysis leads to an increase in NADH, which will limit SIRT1 activity promoting deacylation of p65 in NF-κB, enhancing its activity. SIRT1 inhibition also limits mitochondrial metabolism. LPS increases

glutamine uptake and this is converted to succinate via two distinct pathways as shown. Increased succinate leads to the stabilization of HIF1α, which increases pro-IL-1β production. The activation of the NLRP3 inflammasome by metabolic DAMPs involves potassium efflux, mitochondrial ROS and probably calcium influx. This results in activation of caspase-1, which cleaves pro-IL-1β to active IL-1β. Starvation will activate AMPK, which promotes mitophagy. This probably acts to limit ROS, negatively regulating the inflammasome.

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Conflict of Interest

The authors declare no conflict of interest in this work.

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