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Nat Immunol. Author manuscript; available in PMC 2014 July 10.

Published in final edited form as:
Nat Immunol. ; 13(4): 352–357. doi:10.1038/ni.2228.

A role for the NLRP3 inflammasome in metabolic diseases and did Warburg miss inflammation?

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Abstract

The inflammasome is a protein complex that is comprised of an intracellular sensor that is typically an NLR protein, the pro-protein, procaspase-1 and adaptor molecule ASC. Inflammasome activation leads to caspase-1 maturation and the processing of its substrate, IL-1β and IL-18. Although initially the inflammasome was described as a complex that affects infection and inflammation, recent evidence suggests that inflammasome activation influences a host of metabolic disorders including atherosclerosis, type 2 diabetes, gout and obesity. Another aspect regarding inflammation in general and inflammasome in specific is that the activation process has a profound effect on aerobic glycolysis, or the Warburg effect. How the Warburg effect might be link to inflammation and inflammasome activation is a novel concept to contemplate.

The incidence of metabolic disorders such as obesity, type 2 diabetes (T2D) and atherosclerosis has increased dramatically during recent decades, and these diseases constitute some of the most serious threats to public health. Chronic inflammation is a key common feature of metabolic disorders. Many inflammatory mediators such as tumor necrosis factor (TNF), interleukins and cytokine-like proteins known as adipokines have been linked to the development of multiple forms of metabolic disorders [1, 2]. Interleukin (IL)-1β is a prominent pro-inflammatory cytokine since it can efficiently cause the generation of other inflammatory mediators through IL-1 receptor signaling, thus initiating a self-amplifying cytokine network [3]. As a result, IL-1β is postulated to play an important role in the pathogenesis of metabolic disorders. Indeed, studies employing the recombinant IL-1 receptor antagonist (IL-1RA) anakinra have been tested in T2D, with some encouraging results [4]. Recent clinic trials also suggest that non-inflammasome cytokines TNF contributes to impaired glucose homeostasis and insulin resistance in patients with T2D [5–7]. Therefore, it is highly possible that both IL-1β and TNF may drive chronic inflammation in a cooperative manner, which highlights the importance of combined immunotherapy against multiple inflammatory cytokines. This review will focus on the possible role of the

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inflamamsome complex which is important for the maturation of IL-1β in a variety of metabolic disorders. We will also examine how metabolic alterations in cells including the so-called "Warburg effect" of aerobic glycolysis contribute to inflammatory processes relevant for these diseases. While most of the data are based on animal models, the potential translational relevance will be underscored.

The inflammasome in diabetes and obesity

Inflammasome is a large multimeric danger-sensing platform, which promotes auto-catalytic activation of the cysteine protease, caspase-1, and mediates the cleavage of inactive pro-IL-1β and IL-18 among other proteins into their active forms [8, 9]. Several recent studies have provided strong evidence to suggest a critical role of the NLRP3 inflammasome in the development of insulin resistance using gene-deletion mice [10–14]. Genetic ablation of NLRP3 (*Nlrp3*$^{-/-}$) or the NLRP3 inflammasome-associated molecules such as ASC (also known as PYCARD; *Pycard*$^{-/-}$) and caspase-1 (*Casp1*$^{-/-}$) resulted in improved glucose tolerance and insulin sensitivity after high-fat diet (HFD) feeding, therefore linking the NLRP3 inflammasome to insulin resistance in a number of studies. Several studies have explored how a HFD in mice might contribute to T2D and the role played by inflammasome proteins. Ceramide, the specific product of long-chain saturated fatty acid metabolism, can cause caspase-1 activation and IL-1β release in macrophages from wild-type (WT) mice but not in macrophages from *Nlrp3*$^{-/-}$ mice [12]. The saturated free fatty acid (FFA) palmitate, but not unsaturated FFA, induces the activation of caspase-1 and the cleavage of IL-1β and IL-18 in an NLRP3- and ASC-dependent manner [13]. Furthermore, palmitate signals through an AMP-activated protein kinase (AMPK)-autophagy-mitochondrial reactive oxygen species (mROS) pathway to activate the NLRP3 inflammasome. An NLRP3 inflammasome-dependent process affects insulin target tissues such as liver, muscle and adipose tissues (Fig 1). Therefore, these studies explore the mechanisms of NLRP3 inflammasome activation by danger signal molecules associated with saturated FFA metabolism, and highlight the importance of NLRP3 inflammasome activation in the development of insulin resistance. Interestingly, a widely used insulin secretagogue (Glyburide) provides a linkage between insulin homeostasis and the NLRP3 inflammasome activation. For example, Glyburide can inhibit NLRP3 inflammasome-mediated caspase-1 activation and both IL-1β and IL-18 release [15].

In addition to the essential role of the NLRP3 inflammasome and IL-1β in the impairment of insulin signaling in insulin target liver, muscle and adipose tissues, IL-1β also promotes β-cell dysfunction and cell death directly [16]. Islet amyloid polypeptide (IAPP; also known as amylin) has been identified as a key inducer of NLRP3 inflammasome activation and IL-1β cleavage [17]. IAPP, a hormone that is secreted together with insulin, is deposited in the islet interstitium of patients with T2D and is considered to be a significant danger risk for T2D [18]. IAPP forms amyloid structures, and amyloid particles have previously been shown to activate the NLRP3 inflammasome [8]. Therefore, it has been proposed that IAPP oligomers activate the NLRP3 inflammasome and IL-1β cleavage in a manner similar to other crystalline activators of the NLRP3 inflammasome [17]. Other studies suggest that a high level of glucose induces β-cell production and release of IL-1β *in vitro*, which then promotes functional impairment and apoptosis of β-cell in an autocrine manner [10, 19].

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However, this effect seems to be islets specific, since high level of glucose fails to promote IL-1β release induced by IAPP in bone marrow-derived dendritic cells. Instead, sufficient glucose is required for NF-κB-dependent, but NLRP3 inflammasome-independent, pro-IL-1β and IL-6 production [17]. The molecular mechanism underlying glucose-induced IL-1β release by islets remains to be determined, and will be discussed later.

Another potential regulatory mechanism of inflammasome activation during obesity and insulin resistance is autophagy. Autophagy is a cell intrinsic mechanism for the degradation and recycling of cellular components [20]. Genetic variants of the autophagy gene *ATG16L1* have been linked to Crohn's disease [21–24]. Deletion of either the *Atg16l1* or *Atg7* autophagic gene in mouse macrophages leads to increased caspase-1 activation and IL-1β release, but not TNF and IL-6 generation. This was observed in response to treatment with either lipopolysaccharide (LPS) alone or LPS in conjunction with NLRP3 inflammasome activators such as ATP and monosodium urate (MSU) [25]. These findings have been recently confirmed and more detailed molecular mechanisms involving disrupted mitochondrial homeostasis have been explored [13, 26, 27]. Deletion of autophagy gene [18, 19] or palmitate treatment [13] inhibits autophagy, which subsequently leads to the accumulation of dysfunctional mitochondria and increased mitochondrial ROS (mROS) generation. These events activate the NLRP3 inflammasome. Nakahira *et al*. suggests that the leakage of mitochondrial DNA into cytosol upon autophagy inhibition may serve as a coactivator for inflammasome activation [26]. These studies provide evidence that autophagy negatively regulates NLRP3 inflammasome activation by maintaining mitochondrial homeostasis. Accordingly, defective autophagy has been observed in the liver of both genetic (*ob/ob*) and diet-induced (HFD feeding) obesity animal models [28]. Although the mechanism by which an obese condition leads to defective autophagy has not been characterized, AMPK and/or mTOR signaling pathways may be potential candidate of upstream modulators, since these two evolutionally conserved signaling pathways have been shown to regulate autophagy by direct phosphorylation of ATG1 [29, 30]. Therefore, a strong possibility is that defective autophagy associated with obesity and insulin resistance may promote inflammasome activation and amplify inflammatory network in insulin target tissues.

In addition to a direct effect of the NLRP3 inflammasome on innate immunity, recent studies show that IL-1β and IL-18 play an essential role in shaping adaptive immune responses in several animal models such as experimental autoimmune encephalomyelitis (EAE), arthritis and cytotoxic T cell (CTL)-mediated anti-tumor responses [31]. Specifically, IL-1 promotes the differentiation of T helper 17 (T_H17) lineage by increasing the expression of IRF4 and RORγt, two essential transcription factors involved in T_H17 differentiation [32], whereas IL-18, in synergy with IL-12, induces IFN-γ-producing T_H1 cells [33]. More importantly, the differentiation of human T_H17 cells requires the presence of IL-1β [34, 35]. Based on recent studies suggesting that the aberrant accumulation and activation of lymphocytes in adipose tissues (including both T and B cells) impair insulin sensitivity in obesity-induced insulin resistance [36–40], it is reasonable to argue that NLRP3 inflammasome activation might lead to lymphocyte accumulation and activation in obesity and insulin resistance. Indeed, significantly decreased numbers of both $CD4^+$ and $CD8^+$ effector memory T cells have been observed in the adipose tissue of *Nlrp3*$^{-/-}$ mice after HFD

feeding [12], suggesting that the NLRP3 inflammasome-regulated adaptive immune response may also contribute to insulin resistance.

It has been long-postulated that obesity is a strong risk factor for insulin resistance and T2D, and this is partially mediated through enhancing chronic inflammation in insulin target tissues [1]. Recently it has been proposed that the inflammasome affects adipocyte differentiation and HFD-induced obesity [11, 14]. Stienstra *et al*. demonstrated that NLRP3-dependent caspase-1 and IL-1β activation inhibits adipocyte differentiation and insulin signaling [11]. This same group also found that the genetic ablation of NLRP3 inflammasome or pharmacological inhibition of caspase-1 provides a beneficial effect in HFD-induced obesity, presumably through increasing energy expenditure [14]. However, the protective role played by NLRP3 inflammasome in HFD-induced obesity was not uniformly observed because two other studies have not confirmed these findings [12, 13]. These studies did not observe a difference in total body weight between *Nlrp3*$^{-/-}$ mice and WT mice after HFD feeding [12, 13], although NLRP3 seems to play a role in adipocyte morphology [12]. The reason for the different observations is currently unknown, but may potentially involve subtle differences such as HFD from different sources. Another important potential link to obesity is the observation that there is enhanced β-oxidation of fatty acids in *Casp1*$^{-/-}$ mice. This is likely to be due to decreased IL-1β since IL-1β limits β-oxidation and will therefore decrease adiposity. Accordingly, a caspase-1 inhibitor led to higher fat oxidation rates in obese mice [11]. NLRP3 inflammasome activation might therefore promote obesity.

The inflammasome in atherosclerosis

Atherosclerosis has components of a chronic inflammatory disease characterized by the accumulation of lipid components and recruitment of immune cells in atherosclerotic lesions [41, 42]. When low-density lipoprotein (LDL), a cholesterol-containing lipoprotein, is retained in the artery wall, it leads to vascular inflammation and cholesterol accumulation, partially as cholesterol crystals [41, 42]. Among the inflammatory mediators, IL-1β has been shown to play a significant role in promoting the development of lipid plaques and also destabilizing the plaques in mice. In *Apoe*$^{-/-}$ mice which spontaneously develop atherosclerosis due to hypercholesterolemia, IL-1β deficiency results in an attenuated development of atherosclerotic lesions [43]. The application of IL-1RA has been shown to prevent lesion development [44]. Therefore, experimental animal studies support the concept that IL-1β collaborates together with other proinflammatory cytokines such as TNF to exacerbate the pathology of metabolic disorders. The role of inflammatory cytokine IL-6 in obesity and insulin resistance remains controversial. Although it has been proposed that IL-6 plays a detrimental role in impairing glucose homeostasis and insulin sensitivity [45], a recent study points to the beneficial effect of IL-6 by promoting insulin secretion and the maintenance of glucose homeostasis in diet-induced or genetic animal models [46].

Two recent studies showed that cholesterol crystals activate the NLRP3 inflammasome and IL-1β release in mouse and human macrophages, thus highlighting a posible role of NLRP3 inflammasome in atherosclerosis [47, 48]. The accumulation of a small amount of cholesterol crystals was observed in early diet-induced atherosclerotic lesions, which was associated with the recruitment of inflammatory macrophages [47]. Cholesterol crystals generated *in vitro*

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activate caspase-1 and both IL-1β and IL-18 cleavage in LPS-primed human peripheral blood mononuclear cells and mouse macrophages, which is dependent on NLRP3 and ASC [47, 48]. Moreover, cholesterol crystal-induced NLRP3 inflammasome activation was sensitive to cytochalasin D and bafilomycin treatment, suggesting the requirement of phagocytosis and lysosome acidification for inflammasome activation, which is consistent with NLRP3 inflammasome activation induced by other crystals such as MSU, silica, asbestos and alum [49–52]. In line with the *in vitro* data, hypercholesterolemic LDL receptor deficient (*Ldlr*$^{-/-}$) mice reconstituted with bone marrow from *Nlrp3*$^{-/-}$, *Pycard*$^{-/-}$ or *Il1b*$^{-/-}$ mice developed significantly less atherosclerotic plaques than those reconstituted with WT bone marrow [30]. These findings suggest critical roles of hematopoietic cell-derived NLRP3, ASC and IL-1β in the development of atherosclerotic lesions. However, the crucial role of the NLRP3 inflammasome in atheroscleosis was challenged by another study using a double-mutant crossing *Apoe*$^{-/-}$ mice with *Nlrp3*$^{-/-}$, *Pycard*$^{-/-}$ or *Casp1*$^{-/-}$ mice [53]. This study failed to find any differences in atherosclerosis progression, infiltration of plaques by macrophages, or plaque stability in the presence or absence of the NLPR3 inflammasome. The obvious difference between these two studies is the investigation of hematopoietic-derived versus whole body-derived NLRP3 inflammasome in the development of atherosclerosis. It is quite clear that the NLRP3 inflammasome may also function in the stromal compartment to regulate disease progression in addition to the hematopoietic compartment, especially in the colitis and colitis-associated cancer [54, 55]. Therefore, further investigations are required to clarify these differences.

The inflammasome in gout

Gout is historically known as a disease of Kings since it is believed to result from a rich diet and in particular those high in purines. It is associated with elevated levels of uric acid (hyperuricemia) in the blood which forms crystals and are then deposited in joints. Uric acid can be released from dying cells which activates cells as a danger signal [56]. It is generally accepted that IL-1β plays an important role in the promotion of inflammatory responses in joints, supported by several recent clinical trials where the treatment of gout with anakinra or other drugs that inhibit IL-1β showed amelioration of symptoms [57–60].

The mechanisms by which urate crystals cause inflammatory arthritis and IL-1β is generated remain largely unknown until the NLRP3 inflammasome was identified as the link between urate crystals and gout [49]. MSU and calcium pyrophosphate dihydrate (CPPD) induce the cleavage of caspase-1 and IL-1β or IL-18 in LPS-primed macrophages that is dependent on NLRP3 and ASC. *In vivo*, NLRP3 inflammasome-mediated IL-1β generation promotes neutrophil recruitment and peritoneal inflammation induced by MSU. A question that remains is the mechanism whereby MSU or other crystal structure activates the NLRP3 inflammasome. Unlike other germline-encoded pathogen recognition receptors, there is no evidence to suggest a direct recognition of danger signals by NLRP3. Therefore it is reasonable to argue that the NLRP3 inflammasome detects some forms of alterations in cellular homeostasis induced by danger signals. One such proposed signal has been increased ROS generation [8]. One study suggests that the thioredoxin-interacting protein (TXNIP), a protein upregulated by glucose and linked to insulin resistance, interacts with NLRP3, leading to IL-1β release [10]. Inflammasome activators induce the transfer of TXNIP

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from thioredoxin to NLRP3 in a process involving ROS. However, this finding has been challenged by a recent study, particularly in macrophages [17]. A very recent study identified caspase-1 interacting proteins including cellular inhibitors of apoptosis protein 1 (cIAP1), cIAP2 and an adaptor protein TRAF2, which are required for spontaneous and agonist-induced caspase-1 cleavage [61]. The cIAP E3 ligase activity mediates lysine 63-linked polyubiquitination of caspase-1, although its functional relevance to caspase-1 maturation remains to be explored. Other potential mechanisms of the inflammasome activation involve the participation of additional effector molecules such as other NLR molecules or pathogen recognition receptors (PRR) such as Toll-like receptor (TLR) and RIG-I-like receptor (RLR). For example, NAIP (NLR family, apoptosis inhibitory protein) proteins mediate the NLRC4 inflammasome activation through a direct ligand-binding mechanism [62]. Prokaryotic messenger RNA promotes the NLRP3 inflammasome activation through a TRIF (TIR domain-containing adaptor protein inducing IFN-β)-dependent manner, which is an adaptor protein downstream of TLR3 and TLR4 [63]. RNA virus-induced activation of RIG-I signaling leads to inflammasome activation [64]. However, earlier studies have noted the transcriptional induction of NLRP3 by microbes [65, 66], while a recent study suggests that ROS induces the expression of NLRP3 [67]. Hence the transcriptional effects on components of the inflammasome in addition to post-translational effects have to be taken into consideration.

Although it has been well documented that crystal structure such as MSU, silica, asbestos and alum induce NLRP3 inflammasome-dependent caspase-1 and IL-1β or IL-18 cleavage, particularly *in vitro* [49–52], recent studies have observed NLRP3 inflammasome-independent effects of uric acid, silica and alum in the development of T_H2 immune response and T_H2-associated IgE antibody response 68, 69. One study shows that uric acid is released in the airways of asthmatic patients and allergen-challenged mice and promotes T_H2 immune response by activating dendritic cells via spleen tyrosine kinase (Syk) and PI3-kinase δ signaling pathways [54]. Another study reports that silica and alum promote prostaglandin E_2 (PGE_2) production in macrophages through the Syk-p38 pathway, which enhances T_H2 response-associated IgE production [68, 69]. Both of these studies found that NLRP3 had no effect. Therefore, crystals including alum adjuvant are found to induce both NLRP3 inflammasome-dependent and -independent immune effects. Further investigation is warranted to clarify the role of the inflamamsome in these responses in physiologic settings.

Metabolic changes in inflammatory signaling

Another interesting aspect regarding IL-1β concerns the role of glucose metabolism in IL-1β gene transcription. As mentioned above, in pancreatic β cells, glucose was shown to boost production of IL-1β, although no mechanism was provided [19]. This is less evident in macrophages, where although glucose is required, high levels (mM) do not boost the response. However, treating macrophages with 2-deoxyglucose (2-DG) was found to inhibit transcription of IL-1β induced by LPS, but had no effect on TNF gene transcription [17]. 2-DG inhibits glycolysis by acting as a competitive substrate for hexokinase, thereby limiting glucose metabolism. Why would this affect IL-1β gene transcription?

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LPS has been shown to have a profound effect on the metabolic profile of target cells. In dendritic cells LPS promotes aerobic glycolysis – a process termed the Warburg effect [70, 71]. Warburg had originally defined this process in tumor cells, whereby respiration and the Kreb's cycle (also known as the tricarboxylic acid (TCA) cycle) in mitochondria is limited, and glycolysis is enhanced. Several reasons for this metabolic shift have been proposed, notably increased ATP production to meet the energy demands of the tumor cells. Glycolysis, although less able to generate ATP, can be greatly enhanced via induction of the enzymes involved [72]. A second reason is for biosynthesis since intermediates for biosynthesis of amino acids, lipids and nucleotides are made from glycolysis [73]. This could in fact be a mechanism for increased production of uric acid in inflammation, in the case of the pentose phosphate pathway. The mechanism of the Warburg effect in tumors has recently been shown to involve induction of the embryonic pyruvate kinase M2 (PKM2) isoform [74], which strongly promotes hypoxia-inducible factor (HIF)-1α induction [75]. PKM2 occurs in a complex with HIF-1α and prolyl hydroxylase 3 (PHD3) on the HIF-1α promoter. HIF-1α induces glycolytic enzymes, promoting the glycolytic flux [76]. This same process could be happening in response to LPS, since LPS stabilizes HIF-1α via an as yet ill-defined mechanism, and HIF-1a-deficient (*Hif1a*$^{-/-}$) macrophages are defective in their responses to LPS [77]. LPS has also been shown to induce the ubiquitous isoform of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (uPFK2), which strongly promotes glycolysis [78]. Attenuation of uPFK2 thus limits macrophage responses to LPS [78]. Another mechanism might involve decreased expression of PHD2 and PHD3 which would stabilize HIF-1α [79]. 2-DG will block the flux through glycolysis and has been shown to inhibit various LPS responses, including induction of IL-1β transcription and other gene products such as CD40, CD80 and CD86 [70].

The signal coming from glycolysis for these responses is not known but could also involve a signal from mitochondria, since LPS also affects mitochondrial metabolism. LPS can limit mitochondrial metabolism and oxidative phosphorylation although again the mechanism is unknown [80]. There is a decrease in the expression of genes encoding multiple proteins involved in mitochondrial function [27]. This could lead to a build-up of intermediates such as succinate, which is a known inhibitor of PHD2, the enzyme that hydroxylates HIF-1α leading to its degradation [81]. Succinate would therefore increase HIF-1α levels. Also, a build-up of ROS in response to LPS can play a role in the induction of HIF-1α [82]. 2-DG has been shown to lower ROS and succinate production providing a possible explanation for how it blocks induction of IL-1β by LPS [83]. It has also been shown that the ATP produced from glycolysis is required for maintenance of the mitochondrial membrane potential in the face of mitochondrial shut-down [84].

In essence therefore, LPS signaling via TLR4 involves an alteration in intracellular metabolism which is determining for LPS responses. The shift to aerobic glycolysis is required for induction of IL-1β mRNA. The inflammasome is activated by hyperlipidemia leading to increased IL-1β production. The IL-1β then causes insulin resistance and decreased fatty acid oxidation in the mitochondria. These events promote obesity, producing a vicious cycle which is further enhanced by the increased IAPP production in the pancreas, IAPP being synthesized in concert with insulin, and having the biochemical trait of forming

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amyloid. IAPP promotes further IL-1β production, which ultimately is toxic to β cells in the pancreas. It should be noted however that a causal link between IAPP and the pathogenesis of T2D, although intriguing as an hypothesis, has yet to be proven. A similar scenario could be occurring in atherosclerosis, where cholesterol crystals exacerbate the inflammatory process via NLRP3, with this process promoting plaque formation. TLR4 could be a key driver in these events since it responds to fatty acids and also minimally oxidized LDL, providing for pro-IL-1β and priming the inflammasome. The shift to the Warburg effect could therefore be determining for inflammation (events summarized in Fig 2).

Another example of the Warburg effect being important for inflammation was highlighted by a report on T_H17 cells. HIF-1α enhances T_H17 development via activation of RORγt and p300 recruitment to the IL-17 promoter [85]. HIF-1α also attenuates regulatory T (T_{reg}) cell development by binding to their lineage-specifying transcription factor Foxp3 and targeting it for proteosomal degradation. *Hif1a*$^{-/-}$ mice could not generate T_H17 cells and were resistant to EAE 85. Similar results were obtained in another study and even more strikingly, it was shown that HIF-1α dependent glycolysis was acting as a metabolic checkpoint for the differentiation of T_H17 cells [86]. Importantly, 2-DG could convert a T_H17 cell into a T_{reg} cell [86]. Since T_H17 are the more pro-inflammatory cell type, this further emphasizes how the Warburg effect is determining for inflammation, being important for both inflammatory cytokine production from macrophages and dendritic cells and the generation of T_H17 cells.

Why would IL-1β cause insulin resistance? There are two possible options. Insulin resistance mainly occurs in liver and smooth muscle cells, and is though to involve induction of SOCS2 and SOCS3 [87], as well as activation of Jun N-terminal kinase and IκB kinase [88], to limit insulin signaling. This could spare glucose for macrophages, which require the glucose for energy demands and biosynthesis, both of these involve the switch to aerobic glycolysis, probably via HIF-1α (Fig 2). A second possibility is to limit glucose uptake in a negative feedback loop, since this could impair further IL-1β transcription and would also limit production of ROS from mitochondria. In T2D however, the on-going induction of IL-1β in response to the various stimuli including IAPP suggests any negative feedback effect is over-whelmed, and IL-1β then becomes pathogenic.

Conclusions

A wealth of evidence therefore points to an intimate relationship between IL-1β, the NLRP3 inflammasome and lipid and carbohydrate metabolism. This occurs at the level of enhanced NLRP3 inflammasome activation and IL-1β processing to the mature cytokine in response to saturated fatty acids, and also glucose metabolism via glycolysis being required for induction of mRNA encoding IL-1β. Glycolysis and HIF-1α have also been shown to be key for T_H17 cell differentiation. The pathogenic role played by IL-1β in plaque formation in atherosclerosis, and in insulin resistance and β cell loss in T2D attests to the importance of these processes in these metabolic diseases. The exacerbation of NLRP3 inflammasome activation by cholesterol crystals in atherosclerosis, and IAPP in T2D provides positive feedback loops to promote disease pathogenesis. Uric acid crystals, which are another consequence of metabolic disorder, are also NLRP3 inflammasome activators which lead to

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IL-1β production in gout. The hope is that the recent insights into the molecular basis of these diseases will help in the design of new therapies.

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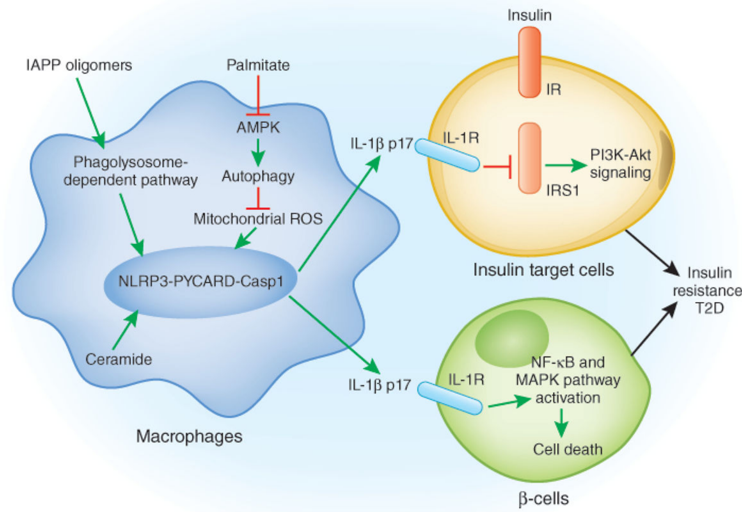

Fig 1.

A model for the pathogenesis of T2D: adipose tissue, the pancreas, NLRP3 and T2D. In adipose tissue, elevated levels of saturated free fatty acids decrease the activity of AMPK, a central regulator of energy biosynthesis and lipid metabolism, leading to defective autophagy of mitochondria (Mitophagy). The accumulation of dysfunctional mitochondria then enhances mitochondrial ROS generation and the release of mitochondrial DNA into cytosol, both of which promotes NLRP3 inflammasome activation and IL-1β release. The active IL-1β induces the activation of JNK and IKK through IL-1 receptor, which impair the insulin-insulin receptor (IR), insulin receptor substrate-1 (IRS-1), and PI3K-Akt signaling pathway. In the pancreas, the accumulation of IAPP activates the NLRP3 inflammasome and promotes IL-1β release from macrophages, which causes β-cell dysfunction and death.

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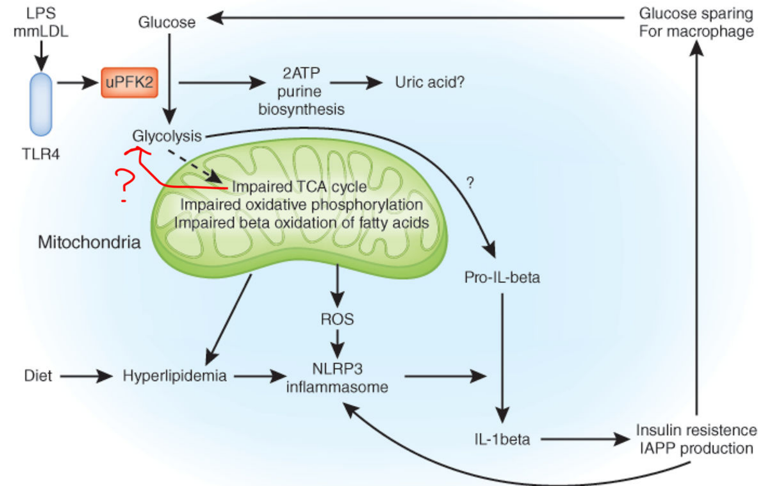

Fig 2.

Metabolic fluxes, NLRP3 and IL-1β. Hyperlipidemia in the form of saturated fatty acids such as palmitate, has been shown to activate the NLRP3 inflammasome leading to caspase-1 activation and the processing of pro- IL-1β. Impaired mitochondrial metabolism, including decreased β-oxidation of fatty acids, could promote this process, as will production of reactive oxygen species. Activation of TLR4 by LPS or minimally modified oxidized LDL promotes glycolysis via induction of enzymes such as uPFK2 leading to enhanced ATP production and nucleotide biosynthesis via the pentose phosphate pathway. Purines including uric acid, could be over-produced via this process leading to NLRP3 inflammasome activation. IL-1β will give rise to insulin resistance, causing enhanced IAPP production, which in turn will further activate NLRP3. Insulin resistance in liver and muscle could spare glucose for macrophages. See text for details.