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Regulation of Nlrp3 inflammasome by dietary metabolites

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Abstract

The bidirectional communication between innate immune cells and energy metabolism is now widely appreciated to regulate homeostasis as well as chronic diseases that emerge from dysregulated inflammation. Macronutrients-derived from diet or endogenous pathways that generate and divert metabolites into energetic or biosynthetic pathways-regulate the initiation, duration and cessation of the inflammatory response. The NLRP3 inflammasome is an important innate sensor of structurally diverse metabolic damage-associated molecular patterns (DAMPs) that has been implicated in a wide range of inflammatory disorders associated with caloric excess, adiposity and aging. Understanding the regulators of immune-metabolic interactions and their contribution towards chronic disease mechanisms, therefore, has the potential to reduce disease pathology, improve quality of life in elderly and promote the extension of healthspan. Just as specialized subsets of immune cells dampen inflammation through the production of negative regulatory cytokines; specific immunoregulatory metabolites can deactivate inflammasome-mediated immune activation. Here, we highlight the role of energy substrates, alternative fuels and metabolic DAMPs in the regulation of the NLRP3 inflammasome and discuss potential dietary interventions that may impact sterile inflammatory disease.

(1) Inflammasomes as sensors of inflammation

1.1 Inflammasome structure and activation

Nod-like-receptors (Nlrs) are the platform for formation of inflammasomes, large multiunit complex that are instrumental for recognizing a variety of intracellular pathogens as danger signals, activating caspase-1 and controlling the maturation and secretion of interleukin (IL)-1 β and IL-18 [1]. The NLR family has several members, and each has the ability to complex and recruit caspase-1 in a manner that is distinct and dependent upon the type of danger signal. The regulation of inflammasome activation is most well-understood for Nlrp3. Similar to most NLRs, the Nlrp3 inflammasome contains three distinguishing components: a pyrin domain (PYD), nucleotide binding site (NACHT) and c-terminal

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leucine rich repeat (LRRs). The LRR is thought to play an autoinhibitory role, whereas the NACHT domain permits homotypic binding between Nlrp3 proteins. The pyrin domain is critical for interacting with the adaptor protein, apoptosis-associated speck-like protein (ASC), which contains a caspase activation and recruitment domain (CARD) that facilitates recruitment and interaction of the cysteine protease pro-caspase-1 [2].

Two signals are required for full inflammasome activation and cytokine secretion: signal 1 priming is necessary for gene transcription and signal 2 causes inflammasome complex formation, which leads to cleavage of caspase-1 into enzymatically active heterodimers [3, 4]. Canonically, TLR signaling serves as signal 1, and induces gene transcription of Nlrp3, pro-caspase-1, pro-IL-1 β and pro-IL-18, providing an abundance of protein for downstream activation. Signal 2 is delivered by sensing of a second ligand by Nlrp3 and subsequent inflammasome complex assembly (Nlrp3, Asc and Caspase-1). Complex assembly is critical for commitment to activation, as it permits autocleavage of pro-caspase-1, subsequent cleavage of pro-interleukins and release of active cytokines into extracellular space [5].

Along with caspase-1 activation and cytokine secretion, the Nlrp3 inflammasome also activates a form of cell death called pyroptosis [6]. Pyroptosis is a type of inflammatory cell death in which the cell swells and bursts, releasing cytokines and Nlrp3 activators into the environment, as a mechanism for continued inflammasome activation. All inflammasomes, including Nlrp3, are highly expressed in myeloid cells. Their mechanisms of activation and downstream effects have been predominantly examined in macrophages, although neutrophils also express the individual proteins and activate the Nlrp3 inflammasome [7, 8].

1.2 IL-1 signaling and pathogenic effects

Signal transduction of IL-1 β and IL-18 requires binding of each to their corresponding receptor and the formation of a heterotrimeric complex, consisting of the ligand, a primary receptor and an accessory receptor. Receptor/ligand complexes allow for interactions between Toll/IL-1 receptor (TIR) domains and initiates intracellular signaling through p38 MAPK, NF κ B and c-JUN. IL-1 β and IL-18 share a primary receptor (IL-1R1) but require distinct accessory receptors, IL-1RAcP or IL-18RAcP respectively, to trigger their distinct signaling pathways [9].

IL-1 β is a pleiotropic cytokine, in part, because its receptor is widely expressed. IL-1 is responsible for the pathology of a number of diseases [10–12]. Receptor binding induces a signaling pathway and gene transcription which feeds forward into the inflammatory process. Its activities include tissue destruction, fibroblast proliferation and collagen deposition. IL-1 signaling in endothelial or stromal cells induces chemokines, such as CXCL1 and IL-8, which are secreted to recruit granulocytes [13, 14]. Granulocytes further advance disease pathogenesis through release of cytokines and proteases. IL-1 also induces expression of pathogenic cytokines (GM-CSF, IFN γ , IL-17) from T cells and innate effector cells [15, 16]. Inhibition of IL-1 signaling, using an IL-1 receptor antagonist has been successful for reducing disease symptoms in type-2 diabetes and gout [17, 18].

(2) Metabolites can act as DAMPs to activate Nlrp3 inflammasome in macrophages

2.1 DAMPs and mechanisms of Nlrp3 activation

Inflammasomes are activated by a wide range of signals, which are either host or pathogen-derived. Host-derived endogenous signals are termed DAMPs (damage associated molecular patterns) and serve to alert the cell to stress or insult. Intriguingly, components of nutrition can act as DAMPs; these includes the actual metabolites (glucose and fatty acids) or byproducts of metabolites (cholesterol, ceramide, uric acid). DAMPs are commonly elevated during chronic nutrient excess as seen during obesity, which can lead to sterile inflammation that cannot be resolved.

Considering the structural diversity of DAMPs that can activate the inflammasome, it is unlikely that Nlrp3 directly interacts with all of them. Instead, investigators have focused on identifying common mechanisms of activation by DAMPs that converge on Nlrp3. While a direct mechanism for sensing is still unclear, potassium efflux is the common mechanism that causes Nlrp3 inflammasome activation [19]. Additional components of Nlrp3 inflammasome activation may include the phagocytosis of large particulate matter such as cholesterol crystals or uric acid crystals, which causes lysosome destabilization and the release of cathepsin B into the cytosol [20, 21], and the formation of reactive oxygen species (ROS) as part of oxygen metabolism carried out by the electron transport chain [22, 23].

2.2 Role of metabolic alterations in macrophage polarization

Macrophages are innate immune cells with a wide variety of roles, dependent on the environmental state. Classically activated macrophages (also called M1 macrophages) are stimulated by lipopolysaccharide (LPS) and interferon (IFN)- γ ; they secrete inflammatory cytokines and reactive oxygen species to mediate clearance of pathogens. In contrast, alternatively activated macrophages (M2 macrophages) are cultured with IL-4 and are typically found to secrete matrix metalloproteinases and growth factors; they are highly phagocytic and are characterized as wound healing, reparative cells. Metabolic state and fuel usage are also a critical element for their polarization. M1 macrophages are highly glycolytic, which permits or allows them to meet their energy requirements and clear microbial insults. Alternatively, M2 macrophages have increased oxidative phosphorylation and triglyceride uptake, which suggests a model in which energy from oxidative phosphorylation directly contributes to M2 macrophage tissue remodeling and wound repair [24]. However, a thorough examination of macrophage transcriptomics following exposure to numerous stimuli, including cytokines, fatty acids or pathogens, reveals the wide spectrum of macrophages activation rather than a binary M/M2 model [25].

Adipose tissue macrophages are “metabolic macrophages”

Adipose tissue macrophages (ATMs) are well-studied tissue resident macrophages that respond to both inflammatory and dietary insults. ATMs promote white adipose tissue (WAT) growth and homeostasis by disposing of excess lipids and producing growth factors or anti-inflammatory molecules in response to stressed adipocytes and alterations in diet

[26]. ATMs are maintained through the coordinated efforts of other AT tissue residents, including, innate lymphoid cells (ILCs), that produce IL-5, which, in turn causes eosinophils to produce M2-driving cytokines, IL-4 and IL-13 [27–29]. Other work indicates that lipids and metabolites in WAT are important for maintaining the M2-like state, more recently referred to as metabolic macrophages [30, 31]. In line with this argument, ATMs and T regulatory cells, both of which are abundant in lean adipose tissue, preferentially use fatty acid oxidation rather than glycolysis [32–35]. Toll-like receptor stimuli, such as saturated fatty acids, S100A8 and endotoxin, increase with high-fat feeding [36, 37], thus shifting the balance of stimuli that macrophages experience. Additionally, a HFD-driven increase in IFN γ helps promote a shift towards M1-like macrophages [38, 39]. Both proliferation of ATMs and recruitment of inflammatory CCR2⁺ monocytes serve as sources for increased macrophage numbers when the adipose tissue is stressed [40, 41]. Intriguingly, ATMs are recruited by adipose tissue lipolysis, as well as, the lipogenic state induced by HFD [42]. Lipolysis-recruited ATMs express higher levels of M2-like markers and contain large numbers of lipid droplets [43]. The differences between the two metabolic states, fasting and obesity, in controlling the adipose macrophage response are not completely clear.

(3) Metabolites as DAMPs

3.1 Cellular role of nutrients and metabolites

The metabolic state of the cell is dependent on nutrient availability and cellular demands; nutrient sensing is tightly regulated with master regulators, such as AMPK, acting to incorporate signals that guide the cellular response to pathogens. Common immediate responses to pathogens include protein production to produce secretory factors or allow intracellular signaling and lipid synthesis for the generation of new organelles. Production of cellular organelles is one component of proliferation, a highly demanding process that requires careful regulation of gene transcription and translation. Nutrients are not only used as substrates in metabolic pathways (Figure 2), but can directly regulate the fate of a cell through non-oxidative means, such as acting as substrates for downstream products (eg. sphingolipids) or second messengers. These activities cause alterations in gene and protein expression, thus modifying their response to inflammatory insults or interaction with other cell types. Nutrients require transport to cross cellular membranes; the expression of membrane transporters is one mechanism for regulating a cell's access to nutrients and altering its ability to appropriately respond to metabolites. Other mechanisms include the ability to regulate enzymatic expression or activity during specific environmental states and shuttling metabolites into alternative pathways. Some nutrients and metabolites have a regulatory or anti-inflammatory effect (addressed further in section 5).

3.2 Glycolysis, fatty acid oxidation and ketogenesis review

Glucose

TRANSPORT & METABOLISM: Glucose uptake catalyzes the pentose phosphate pathway, which is necessary for nucleotide synthesis as well as glycolysis. During glycolysis, glucose is converted into pyruvate, which, in oxygen-sufficient conditions, is metabolized to acetyl-CoA and oxidized in the TCA cycle. During oxygen-deficient conditions, pyruvate is reduced to lactate and NAD⁺; lactate is secreted extracellularly and, NAD⁺, which is

required for the conversion of glucose to pyruvate, feeds back into the TCA cycle. Classically activated macrophages have Warburg-like metabolism, with preferential reliance on glycolysis and glutaminolysis [44]. Increased glucose uptake is used to generate lactate and NAD⁺ to sustain both glycolysis and the TCA cycle. Glycolysis and glutaminolysis support the synthesis of NADPH, which is necessary for generation of ROS and macrophage microbicidal activity. The importance of these pathways is evident during inhibition of glycolysis or glutaminolysis, which impairs ROS production and microbicidal activity of classically activated macrophages and has been thoroughly reviewed elsewhere [44–46].

Fatty acids

TRANSPORT: Fatty acids are complexed with lipoproteins as they require a carrier protein for transport, with release from the lipoprotein occurring via lipoprotein lipase (LPL) immediately prior to entry into the cell. Macrophage expression of LPL has been implicated in the development of atherosclerotic lesions in the Apoe^{−/−} mice [47]. Furthermore, silencing of LPL in adipose tissue macrophages resulted in decreased expression of genes involved in lipid metabolism, reduced lipid uptake and elevated circulating free fatty acids (FFA), indicating that macrophage uptake of fatty acids may provide systemic benefits and ease the lipid load [48]. Fatty acid transporters, including CD36, G-protein coupled receptors (GPRs), and lipid chaperones (fatty acid binding proteins; FABP), transport fatty acids into the cell, which allows transport to the mitochondria for β -oxidation or to the endoplasmic reticulum where they are used to generate sphingolipids. Inhibition or deletion of CD36 alters macrophage utilization of fuel and improves disease pathology associated with metabolic syndrome [49–52].

A role for GPRs or FABPs in altering macrophage fuel usage and inflammatory responses is not entirely understood. GPR 120 and GPR40 are activated by long chain fatty acids, are required for the anti-inflammatory activation and inhibition of the Nlrp3 inflammasome by omega-3 fatty acids [53, 54]. GPR84, a receptor for medium chain fatty acids, is highly expressed on macrophages, but investigated [55]. GPR43 is also expressed on macrophages and neutrophils, but recognizes short chain fatty acids and has been proposed to have a protective role in intestinal inflammation and arthritis [56]. Lysosomal lipolysis, via lysosomal acid lipase, is critical for the oxidative state and polarization of anti-inflammatory macrophages [49].

B-OXIDATIVE PATHWAY: Long-chain fatty acids require carnitine palmitoyltransferase (CPT) to cross the mitochondrial membrane, whereas short chain fatty acids can diffuse across. CPT1a knockdown or inhibition in macrophages results in less fatty acid oxidation (FAO) and more fatty acid-induced proinflammatory signaling and ER stress, in agreement with the paradigm that FAO is more prevalent in M2 macrophages. Direct inhibition of FAO promotes an exaggerated inflammatory response to lipotoxic insult [57, 58]. During β -oxidation, fatty acids are broken down to generate acetyl-CoA, NADH and FADH₂. Acetyl-CoA enters the citric acid cycle (TCA) where it is oxidized to CO₂ and NADH for downstream fueling of the electron transport chain during oxidative phosphorylation. The TCA cycle also generates substrates for synthesis of isoprenoids, cholesterol, and flavonoids. There are a number of enzymatic reactions in the TCA cycle for which little is

known regarding their potential influence on macrophage fuel utilization or inflammatory status.

Acetyl-CoA can also serve as a precursor for cholesterol or ketone bodies (see section 5) via HMG-CoA Reductase (HMGR). Cholesterol synthesis occurs when acetyl-CoA is transported from the mitochondria to the cytosol and is regulated by HMGR and through low density lipoprotein (LDL) receptor-mediated uptake and high density lipoprotein (HDL)-reverse transport [59]. Cholesterol uptake and the receptors involved have been implicated in macrophage polarization and metabolic disease pathogenesis [60].

NON-OXIDATIVE PATHWAY: Alternatively, fatty acids can enter a non-oxidative pathway, in which they are converted into substrates for sphingolipid synthesis or stored as triglycerides; the exact mechanisms for choosing a pathway are not known, but are at least partially dictated by the saturation and carbon-chain length of fatty acids [61]. Ceramides are most commonly synthesized through the *de novo* pathway and are the central molecule used for the production of sphingolipids [62]. The first step is irreversible and requires the condensation of serine and palmitoyl CoA by serine palmitoyltransferase [62]. *De novo* ceramide synthesis occurs in the endoplasmic reticulum, but ceramide is then transported to the golgi where it can serve as a substrate for more complex sphingolipids, sphingomyelin and ceramide-1-phosphate [62]. Ceramide can also be generated through the hydrolysis of sphingomyelin (salvage pathway) or synthesis from sphingosine and more complex sphingolipids (recycling pathway) [62, 63]. Lipids and ceramides are not only key structural components of the cell, but also have the potential to activate the Nlrp3 inflammasome [64].

Inhibition of *de novo* ceramide synthesis, using a serine palmitoyltransferase-specific inhibitor, to reduce ceramide build-up and increase fatty acid oxidation, thus reducing fatty acid-induced inflammation, has promise in a number of publications [65–67]. Macrophage-specific *Sptlc2* promotes atherosclerotic lesions [68], and sphingolipids downstream of ceramide synthesis, including plasminogen activator inhibitor (PAI)-1, sphingosine-1-phosphate and ceramide-1-phosphate, have been identified as possible mediators driving metabolic-induced inflammation [69–71]. Furthermore, adipocyte-specific overexpression of ceramidase, which increases the degradation of ceramides, improves diet-induced inflammation and insulin resistance, although the role of ceramidase in macrophages is not yet clear [72]. Other publications as well as our own unpublished data suggest that enzymes controlling the synthesis of ceramide are not critical for the induction of fatty acid induced inflammation [73]; however ceramide accumulation via phagocytosis of cellular material and dysregulated degradation may contribute to lipid-induced inflammasome activation in macrophages. The relative contribution of each pathway is a hot topic of current research; manipulating the fate of palmitate or other specific fatty acids is an attractive approach to alter immune outcome.

SIGNALING MEDIATORS: Diacylglycerides (DAGs), from stored triacylglycerides (TAGs) or phospholipids, are first converted into arachidonic acid (ARA), eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) and then into their downstream signaling products, such as leukotrienes, lipoxins, eoxins, resolvins and protectins, through the activity of lipoxygenase [74, 75]. Given that lipid signaling mediators are involved in inducing and

resolving inflammation, it is likely that some lipid mediators cause the activation of Nlrp3, whereas others may inhibit it. For example, lipoxygenase is required for monosodium urate recruitment and activation of neutrophils in a mouse model of gout, in part through the activation of Nlrp3 [76]. In humans, increased levels of leukotriene synthesis correlates with increased plaque instability, suggesting that atherosclerotic lesions may be exacerbated by the presence of these lipid mediators [77]. On the other hand, mediators generated from the omega-3 PUFAs are anti-inflammatory and are thought to mediate their effects by either directly antagonizing the activities of arachidonic acid-induced prostaglandin E₂ or inhibiting signal 1 or signal 2 of the Nlrp3 inflammasome. Lipoxygenase may also alter Nlrp3 signaling through its ability to regulate the intracellular redox state, although this has not been formally tested. The roles of lipoxygenase and individual signaling mediators and their interactions with the Nlrp3 inflammasome requires further investigation.

3.2 The inability to properly to use and excess metabolite buildup both serve as inflammatory signals

Metabolites can be produced by cells and used as signals or provided through dietary intake and used as energy. The source of dietary metabolites may impact cellular responses, although this has not been extensively studied. A cell's inability to properly metabolize lipids or glucose can result in accumulation of excess metabolites and dysregulated immune activation. Inhibition or deletion of enzymes and metabolic sensors, which leads to inappropriate metabolite usage, skews macrophage polarization and increases the risk of dysregulated and inappropriate responses [49, 78–80] as discussed in the previous section.

(4) Metabolic changes in sterile inflammation

4.1 Metabolic diseases

Diet-induced obesity, atherosclerosis, cardiovascular disease and gout are commonly associated metabolic diseases with distinguishing clinical phenotypes, including insulin resistance, high blood pressure, irregular cholesterol levels and high levels of inflammatory proteins or free fatty acids. Lifestyle choices, for example diets high in fat or cholesterol, are major risk factors that contribute to metabolic disease development (Figure 2). Chronic insult from metabolites has been implicated in causing these diseases and disease pathology has been attributed to Nlrp3 activation and IL-1 β production instigated by metabolites.

Type-2 Diabetes—Overweight or obese individuals have a markedly increased risk for type-2 diabetes, which is characterized by hyperglycemia and insulin resistance [81]. Obesity and diabetes are also associated with increased complications from other types of metabolic diseases. It is well accepted that insulin resistance can be driven by inflammatory responses resulting in inhibition of insulin signaling and hyperinsulinemia in an attempt to restore signaling [82]. Furthermore, chronic elevation of fatty acids contributes to the development of inflammation and insulin resistance [83]. Fatty acids may antagonize insulin signaling by acting as ligands for TLRs or NLRs and through the subsequent oxidative or ER stress that develops [82]. Saturated fatty acids and ceramide, which are elevated in obesity, activate Nlrp3 inflammasome aggregation and caspase-1-induced secretion of IL1 β [64, 83]. IL1 β inhibits insulin signaling in adipocytes, pancreatic cells and hepatocytes [83,

84]. In agreement with the role of IL1 β , Nlrp3 $^{-/-}$ mice on high fat diet have improved insulin sensitivity as well as reduced inflammation in adipose tissue, liver and pancreas [64, 85, 86].

Atherosclerosis—Cardiovascular disease (CVD) is a leading cause of death globally, accounting for 17.5 million people annually, largely due to the development of coronary disease and different types of atherosclerosis [87]. Cholesterol crystal deposits and oxidized LDL in atherosclerotic lesions indicate advanced disease pathology and have been identified as the driving cause of unresolved inflammation. Macrophage uptake of oxidized LDL and cholesterol crystals leads to formation of cholesterol-laden macrophage foam cells that are present in atherosclerotic lesions [60]. Macrophages and other cells that are recruited to the plaque produce inflammatory cytokines, including IL-1 β , pro-thrombotic molecules and vasoactive substances. In an atherosclerotic mouse model, Nlrp3-deficient mice had reduced plaque formation and less systemic inflammation [88]. The fatty acid receptor, CD36, is a critical regulator of oxidized LDL and cholesterol crystal driven Nlrp3 inflammasome activation in atherosclerosis. Oxidized LDL requires CD36 to induce IL1 β production from macrophages; however, CD36 $^{-/-}$ macrophages can still produce IL1 β in response to other activators [20, 88–90].

Gout—Gout is a severe inflammatory arthritis associated with elevated blood urate concentrations and comorbidities including obesity and cardiovascular disease [91]. An estimated 8 million adults are affected by gout in the United States [92]. The hallmark characteristic of gout is deposition of monosodium urate (MSU) crystals in the joints and synovial fluid. MSU crystals initiate a massive inflammatory response, resulting in the recurrent intense pain known as gouty flares. Neutrophil accumulation and activation are the primary culprits of acute inflammation in gout [93]. Although the precise etiology of immune activation during gouty flares is not clear, MSU crystals have been shown to activate neutrophils, monocytes, and macrophages, all of which can perpetuate neutrophil activation and accumulation in the afflicted joints [94, 95]. Importantly, mice lacking components of the NLRP3 inflammasome are protected from MSU-induced inflammation [95], and the IL-1 β inhibitor anakinra has been reported to prevent neutrophil infiltration in mice and relieve pain in patients during gouty flares [17]. This highlights the importance of the NLRP3 inflammasome in sensing metabolic products and how it contributes to inflammatory disease.

(5) Therapeutic strategies for inflammasome deactivation

Nlrp3 is a critical receptor for recognizing DAMPs and initiating recognition inflammation; it is also clear that Nlrp3 is required for appropriate viral clearance, and therefore, complete inhibition or removal of Nlrp3 activity may be ultimately harmful. Instead, targeted therapeutic treatment may more safely impair metabolite-induced Nlrp3 activation, while allowing Nlrp3 to appropriately respond to pathogens.

5.1 Calorie restriction

Calorie restriction (CR) is among the most robust metabolic interventions that extends healthspan and lifespan [96]. CR is a consistent intake of relatively few calories, but enough

to maintain weight without malnutrition. There is initial weight loss, but with metabolic adaptation to CR, global changes occur in transcriptional and cellular activities, including activation of AMPK-stimulated fatty acid oxidation, which leads to fat mobilization and glycolytic inhibition. CR also enhances autophagy and reduces oxidative stress, both of which are implicated in the activation of the inflammasome. Prior studies suggest that CR reduces adipose tissue inflammasome activation in mice and humans with type-2 diabetes [64]. In fact, a 2-year intervention in humans designed to attain 25% calorie reduction resulted in significant decreases in CRP and TNF α as compared to controls eating a diet *ad lib* [97]. Calorie restriction upregulates pathways that inhibit Nlrp3 activation, indicating that using calorie restriction to moderate the inflammation caused by metabolite-driven Nlrp3 activation may be beneficial.

5.2 Small molecule supplementation

Small molecule supplementation may be an alternative way to manipulate the activity of the Nlrp3 inflammasome. MCC950 is a water soluble compound that directly inhibits a wide range of Nlrp3 activators, without altering signal 1 activation [98]; its efficacy in sterile inflammation has yet to be tested. Additionally, glyburide, a currently used sulfonylurea drug for the treatment of type 2 diabetes that works by inhibiting ATP-sensitive potassium channels, has been identified as an inhibitor of Nlrp3 inflammasome activation [99].

5.3 Anti-inflammatory supplementation to inhibit inflammasome activation

Omega-3 polyunsaturated fatty acids—Dietary supplementation may be a simpler and more reliable method for reducing metabolite-driven inflammation than calorie reduction. Supplementation with PUFAs and with the omega-3 fatty acids in particular show promise for dampening the pathogenic effects of metabolite-stimulated Nlrp3. Importantly, in human monocytes, PUFAs inhibit a wide-range of Nlrp3 activators demonstrating that their potential is not limited to only blocking saturated fatty acids [100]. Furthermore, DHA supplementation improves insulin sensitivity and alleviates inflammation in mouse models of diet-induced obesity in a GPR and Nlrp3-dependent manner [54]. In short term human trials, diet supplementation with PUFAs has also shown promise in reducing inflammatory markers and liver lipids, and modest improvements in insulin sensitivity [101, 102].

Ketones

SYNTHESIS & METABOLISM: Ketone bodies are produced during fatty acid β -oxidation and are used as an alternative energy source by the brain and heart during starvation. Ketogenesis is strongly suppressed by insulin-stimulation and glucose release [103]. In the post-prandial state, ketones levels are low, but can increase two to ten-fold during fasting. During ketogenesis, two acetyl-CoA molecules combine to produce acetoacetyl-CoA (AcAc-CoA). HMGCoA synthase (HMGCS) then catalyzes a reaction with AcAc-CoA + Acetyl-CoA + H₂O to generate 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). HMG-CoA lyase (HMGCL) then catalyzes the cleavage of acetyl-CoA from HMG-CoA to generate the ketone body acetoacetate. From acetoacetate, beta-hydroxybutyrate (BHB) and acetone can be generated. Of the three primary ketones are produced during ketogenesis, BHB is the most abundant in the body. Ketogenic amino acids (branched chain

amino acids, primarily leucine) can also be converted into 3-hydroxy-3-methylglutaryl (HMG)-CoA, the precursor to acetoacetate. In contrast, ketolysis is a relatively simple process in which BHB is reconverted to acetoacetate by the enzyme BHB dehydrogenase (BDH). AcAc is then reconverted into AcAc-CoA in a rate-limited step by the enzyme AcAc-CoA succinyl-CoA transferase (SCOT). AcAc-CoA is then cleaved to produce 2 molecules of acetyl-CoA to be oxidized in the Krebs's cycle to generate 24 molecules of ATP. Ultimately, ketones serve as a substrate to generate ATP when glucose is limited or unavailable.

TRANSPORT: BHB is a highly soluble, small polar molecule that is easily transported systemically in the body. Monocarboxylic acid transporters (MCTs) have been identified as transporters for ketones bodies in neurons and are expressed in most cell types, including macrophages [104, 105]. There are fourteen MCTs, most of which are not well understood; confounding the role of MCTs is the fact that they also transport lactate and pyruvate. GPR109a has also been proposed to be receptor on macrophages for BHB, as it mediates neuroprotective effects in mice fed a ketogenic diet [106]. However, our lab has identified functions of BHB in macrophages that are independent of GPR109a [107].

ANTI-INFLAMMATORY PROPERTIES: Although the current dogma is that hepatocytes generate ketones for use by cardiomyocytes and neurons, we recently discovered that macrophages also express the enzymes required for synthesizing and oxidizing ketones [107]. In this study, we reported that BHB blocks physical assembly of the NLRP3 inflammasome, resulting in decreased IL-1 β secretion in vitro and reduced inflammation in vivo in murine cryopyrinopathy models of constitutive NLRP3 inflammasome activation. Intriguingly, metabolic oxidation of BHB was not required for its anti-inflammatory effects in macrophages, suggesting that BHB can be used by many cell types for either energetic or signaling purposes, or perhaps both. These findings are paradigm shifting, as they reveal novel properties of ketones, and identify a class of regulatory metabolites whose functions are to regulate activation of the immune system during certain metabolic conditions. As other inflammatory diseases are linked to aberrant activation of the NLRP3 inflammasome, including type 2-diabetes, atherosclerosis, and gout (as discussed above) it will be interesting to determine whether BHB can improve health outcomes for any of these conditions.

Conclusions

In this review, we focused on immune-metabolic interactions by reviewing the role of metabolites in regulating the activation of the canonical Nlrp3 inflammasome and discussing potential dietary measures that can be used as therapeutic means to inhibit Nlrp3 activation. The Nlrp3 inflammasome is a well-recognized and understood sensor of a diverse range of metabolic DAMPs that are elevated in type 2-diabetes, atherosclerosis and gout. The exact mechanisms by which metabolites activate the inflammasome not yet completely understood. The metabolic DAMPs driving sterile inflammation can be augmented as a result of lifestyle factors, primarily dietary intake. Here, we have discussed methods for altering the diet, thus allowing for prevention or reversal of sterile inflammation driven by the Nlrp3 inflammasome.

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Abbreviations

TCA	The citric acid cycle
ETC	Electron transport chain
BHB	Beta-hydroxybutyrate
DAG	Diacylglycerides
TAG	Triacylglycerides
TLR	Toll like receptor
ROS	Reactive Oxygen Species
NEFA	Non-esterified fatty acids
ER	Endoplasmic reticulum
CVD	Cardiovascular disease
AT	Adipose tissue
LDL	Low density lipoprotein
HDL	High density lipoprotein
HMGCR	HMG-CoA Reductase
Sptlc	Serine palmitoyltransferase
CPT	Carnitine palmitoyltransferase
FAO	Fatty acid oxidation
FABP	Fatty acid binding proteins
GPRs	G-protein coupled receptors
LPL	Lipoprotein lipase
DAMPS	Damage associated molecular patterns
NLRs	Nod like receptors

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Highlights

- Immune-metabolic interactions regulate tissue homeostasis and inflammation
- The Nlrp3 inflammasome is activated by damage associated molecular patterns (DAMPS)
- DAMPS are implicated in metabolic dysregulation and inflammation
- Alternative fuels and dietary intervention may moderate Nlrp3-driven inflammation

Figure 1. Interaction of metabolic pathways with Nlrp3 inflammasome activation

Fatty- acids, glucose and ketone bodies are internalized through surface receptors and can be metabolized into acetyl-CoA through β -oxidation, glycolysis or ketolysis, respectively. In the mitochondria, acetyl-CoA enters the citric acid cycle (TCA) and generates energy in the form of ATP, through the electron transport chain (ETC) during oxidative phosphorylation. Acetyl-CoA also acts as a precursor for production of the anti-inflammatory ketone body, BHB. Alternatively, fatty-acids can enter the non-oxidative pathway to generate lipid byproducts by providing fatty-acid (FA)-CoA as a precursor for ceramides and downstream sphingolipids, or for the synthesis of diacylglycerides (DAG) to generate triglycerides (TAG) and lipid mediators such as arachidonic, eicosapentaenoic or docosahexaenoic acid. Nlrp3 activation requires two signals; signal 1 is TLR stimulation that triggers transcription of pro-IL1 β for caspase-1 cleavage. Signal 2 is a damage associated molecular pattern (DAMP) such as uric acid or ceramide which causes inflammasome aggregation. Increases in reactive oxygen species (ROS) and phagocytosis with lysosomal disruption are known to mediate the activation of Nlrp3. Inflammasome aggregation causes the release of active IL-1 β , which drives sterile inflammation and metabolic dysregulation. NEFA: Non-esterified fatty acid; TLR: toll like receptor;

Figure 2. Therapeutic potential of dampening Nlrp3 through metabolite manipulation
Schematic showing that dietary intake is one of the major risk factors in driving disease pathology through the activation of Nlrp3 inflammasome and some potential metabolite manipulations that may inhibit Nlrp3 activation.