Seminars in Immunology 27 (2015) 334–342

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Review

Regulation of Nlrp3 inflammasome by dietary metabolites

Christina Camell[a,b], Emily Goldberg[a,b], Vishwa Deep Dixit[a,b,*]

[a] Section of Comparative Medicine and Program on Integrative Cell Signaling and Neurobiology of Metabolism, Yale School of Medicine, New Haven, CT 06520, United States
[b] Department of Immunobiology, Yale School of Medicine, New Haven, CT 06520, United States

ARTICLE INFO

Article history:
Received 26 September 2015
Received in revised form 14 October 2015
Accepted 19 October 2015
Available online 20 November 2015

Keywords:
Nlrp3 inflammasome
DAMP
Metabolite
Sterile inflammation
Dietary intervention
Fatty acids
Ketones
Macrophage

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)-1β 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 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-1β 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

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.

* Corresponding author at: Section of Comparative Medicine and Department of Immunobiology, Yale School of Medicine, 310 Cedar St, New Haven, CT 06520, United States. Tel.: +1 203 785 2525; fax: +1 203 785 7499.
E-mail address: Vishwa.Dixit@yale.edu (V.D. Dixit).

http://dx.doi.org/10.1016/j.smim.2015.10.004
1044-5323/

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-1β 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, NFκB and c-JUN. IL-1β 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-1β 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, IFNγ, 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 include 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].

2.2.1. 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 IFNγ 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 (Fig. 1).

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