

The NLRP3 Inflammasome

Subjects: [Cell Biology](#)

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As a critical component of the innate immune system, the nucleotide-binding and oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3 (NLRP3) inflammasome can be activated by various endogenous and exogenous danger signals. Activation of this cytosolic multiprotein complex triggers the release of the pro-inflammatory cytokines interleukin (IL)-1 β and IL-18 and initiates pyroptosis, an inflammatory form of programmed cell death. The NLRP3 inflammasome fuels both chronic and acute inflammatory conditions and is critical in the emergence of inflammaging. Recent advances have highlighted that various metabolic pathways converge as potent regulators of the NLRP3 inflammasome. This review focuses on our current understanding of the metabolic regulation of the NLRP3 inflammasome activation, and the contribution of the NLRP3 inflammasome to inflammaging.

NLRP3 inflammasome

mitochondria

metabolism

inflammation

aging

1. Definition

The NLRP3 inflammasome is composed of the sensor NLRP3, the adaptor ASC, and the effector caspase-1.

2. Introduction

Activation of the NLRP3 inflammasome in macrophages occurs in two steps, each with a different activating signal [1–6]. First, macrophages are primed through the recognition of an initial “danger” signal (Signal 1), which induces the transcription and production of inactive pro-IL-1 β and NLRP3, which is subsequently ubiquitinated. Typically, the recognition of the bacterial cell wall component lipopolysaccharide (LPS), a pathogen associated molecular patter (PAMP), by Toll-like receptor 4 (TLR4) acts as a priming signal for innate immune cells such as monocytes or macrophages and activates transcription via NF- κ B. Second, the recognition of a second activation signal initiates assembly of the inflammasome complex (Signal 2). Second signals are notably diverse, such as mitochondrial oxidative damage, lysosomal membrane rupture, and plasma membrane potassium efflux [1][2][3][4][5][6]. Currently, how macrophages assemble the inflammasome complex in response to a variety of danger signals is still not entirely clear [5], but interestingly, several cellular metabolic pathways have been implicated in both stages of NLRP3 inflammasome activation. In this review, we will focus on the current understanding of how cellular metabolism regulates the activity of the NLRP3 inflammasome, and then discuss its implications on our understanding of inflammatory diseases and “inflammaging”.

3. Mitochondria as the central metabolic organelle

Mitochondria, well known as the powerhouse of the cell, act as a critical regulator of many cellular processes such as cell death, cellular signaling, and energetic homeostasis [7]. Mitochondrial dynamics, such as number and location, profoundly influence the metabolic status of a cell [8]. Inflammasomes are highly tuned to this as well. Evidence has shown that the NLRP3 inflammasome utilizes several mitochondria centric mechanisms to assemble (Figure 1). Firstly, NLRP3 possesses an N-terminal sequence that allows for it to localize to the mitochondria. Upon activation, components of the NLRP3 inflammasome translocate to mitochondria, an event dependent by the adaptor protein mitochondrial antiviral signaling protein (MAVS) [9]. Microtubules also promote the localization of the NLRP3 inflammasome to the mitochondria in the presence of activating signals by mediating the association of apoptosis-associated speck-like protein (ASC) on the mitochondria to NLRP3 [10]. The association of ASC and NLRP3 was also shown to be facilitated by calcium flux [11]. Finally, this localization is facilitated by cardiolipin, a mitochondria specific phospholipid. Cardiolipin can translocate from the inner mitochondrial membrane to the outer mitochondrial membrane, where cardiolipin directly binds NLRP3 to promote its activation [12].

Figure 1. The role of mitochondria in regulating NLRP3 activity.

Furthermore, in eukaryotic cells, reactive oxygen species (ROS) are generated by NADPH oxidases (NOXs) as well as via mitochondrial respiration and other metabolic processes [13][14]. Mitochondrial ROS is a potent NLRP3 inflammasome activator and is one indicator of cellular stress [15]. Mitochondrial DNA (mtDNA) is also shown to promote inflammasome activation (Figure 1). Mitochondrial damage following environmental or metabolic stress induces oxidation of mtDNA. Oxidized mtDNA can be released into the cytosol, where it binds NLRP3, leading to

inflammasome activation and IL-1 β secretion [7]. More recently, it has been demonstrated that specifically, newly synthesized mtDNA is critical for the NLRP3 inflammasome activation [16].

Moreover, the production of ATP in the mitochondria via oxidative phosphorylation is a process intimately linked with the inflammasome activity. For example, acute immune activation the suppression of oxidative phosphorylation-mediated ATP production favors Warburg glycolysis, a state that is coupled with increased succinate levels [17]. Notably, both of these changes facilitate NLRP3 inflammasome activation (Figure 2).

Figure 2. Regulation of NLRP3 inflammasome activity by cellular metabolic pathways.

4. Carbohydrates and glycolysis

To date, it is still unclear whether glycolytic flux positively or negatively regulates NLRP3 inflammasome activity. Some studies show that the inhibition of glycolytic flux attenuates the inflammasome. For example, one study showed that treatment of classically activated macrophages with aminooxyacetic acid, an inhibitor of aspartate aminotransferase, decreases glycolysis, concurrently reducing NLRP3 inflammasome activation [18]. Seemingly in conflict with these observations, a study demonstrated that the activation of the NLRP3 inflammasome in macrophages is inversely related to glycolysis such that inhibition of glycolysis activates the NLRP3 inflammasome [19]. Further investigations are needed to understand this discrepancy as to whether glycolysis promotes or attenuates NLRP3 inflammasome activation. Nonetheless, cellular conditions such as cellular redox balance and metabolite prevalence may play a broader role in this regulation.

With this discrepancy in mind, several glycolysis regulators have been implicated in controlling the activity of the NLRP3 inflammasome (Figure 2). Hexokinase, a glycolytic enzyme that adds a phosphate group onto glucose to initiate glycolysis, was shown to be essential for NLRP3 inflammasome activation by activating glycolytic flux [20]. Another well-known regulator is pyruvate kinase M2 (PKM2), which is responsible for catalyzing the final rate-limiting step of glycolysis. One study found that inflammasome activation is dependent on the activity of PKM2. IL-1 β secretion resulted from PKM2-dependent lactate production, which promoted phosphorylation of eukaryotic translation initiation factor 2 alpha kinase 2 (EIF2AK2), a protein that is known to be implicated in inflammasome activation [21].

5. NLRP3 Inflammasome and Inflammaging

Akin to the inflammation of chronic inflammatory conditions, inflammaging is the long term, low-grade immune activation from sterile sources that develops with aging. This type of inflammation contributes to the aging process [22], following a lifetime of inflammation from origins such as the NLRP3 inflammasome.

Two well-characterized conditions, in which the aberrant activity of the NLRP3 inflammasome contributes to and exacerbates pathology, leading to inflammaging, are obesity and diabetes. Obesity and specifically obesity-associated insulin resistance have been linked to the activity of the NLRP3 inflammasome [23][24]. Saturated fatty acids such as palmitate, which are enriched in high-fat diet, activate the NLRP3 inflammasome, driving insulin resistance [25]. NLRP3-dependent IL-1 β secretion has been shown to impair pancreatic beta cell function [23][24][26], adipocyte function, and insulin sensitivity [27], promoting the progression of obesity and insulin resistance. The deletion of NLRP3 or inhibition of caspase-1 in mice was shown to improve insulin sensitivity and ameliorate obesity-associated pathologies [25][27][28]. Moreover, obesity accelerates age-related thymic atrophy and decreases T cell diversity [29]. Elimination of NLRP3 or ASC attenuates this age-related thymic atrophy and promotes T cell repertoire diversity [30]. In addition to the dysregulation of T cell homeostasis, age-associated B cell expansion in adipose tissues impairs tissue metabolism and promotes visceral adiposity in the elderly, a process regulated by the NLRP3 inflammasome [31]. Together, these two studies suggest that targeting the NLRP3 inflammasome has a potential beneficial effect on the re-establishment of immune competence in the elderly. Lastly, it was reported that individuals over 85 years of age could be stratified into two groups based on their expression level of inflammasome gene modules, as either constitutive or non-constitutive. The former group was associated with measures of all-cause mortality, again supporting the concept that targeting inflammasome components may ameliorate chronic inflammation and various other age-associated conditions [32].

Atherosclerosis is another condition in which the activity of the NLRP3 inflammasome promotes pathogenesis. Atherogenic factors such as cholesterol crystals [33] and oxidized LDL [34] activate the NLRP3 inflammasome. Deletion or inhibition of the NLRP3 inflammasome complex, including NLRP3, ASC, or IL-1 β , was shown to improve lipid metabolism, and to decrease inflammation, pyroptosis, and infiltration of more immune cells into plaques, thus ameliorating inflammatory responses and atherosclerosis progression [33][34][35][36][37][38][39][40][41][42][43].

Chronic NLRP3 inflammasome activity was shown to be exacerbated by defective autophagy in aged individuals, and enhancement of autophagy improves health outcomes [44]. Importantly, healthy metabolic status, such as the maintenance of SIRT2 activity, has been shown to have beneficial impacts on aging. Aging reduces SIRT2 expression and increases mitochondrial stress, leading to activation of the NLRP3 inflammasome in hematopoietic stem cells [45]. This age-driven functionality decline of hematopoietic stem cells was countered by SIRT2 overexpression, or NLRP3 inactivation [45]. Additionally, the activity of SIRT2 can prevent NLRP3 inflammasome-induced cell death [10]. In line with these findings, increased NAD⁺ levels along with sirtuin activation have been shown to improve mitochondrial homeostasis, organ function, and lifespan [46].

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