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Research Progress on Nox/ROS Signaling Pathway Inducing Pyroptosis of Bone Marrow Hematopoietic Progenitor Cells via NLRP3 Inflammasome

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ABSTRACT
The inflammasome is a critical component of the innate and adaptive immune systems. One of its main biochemical functions is the activation of Caspase-1, which promotes the maturation of IL-18 and IL-1β, ultimately inducing pyroptosis. Compared to other inflammasomes, NLRP3 inflammasome is activated by a wider variety of stimuli. The activation of NLRP3 involves two steps: priming (which includes transcriptional and post-translational modifications) and activation, which is significantly associated with lysosomes, ion flux, and mitochondria. This review focuses on the mechanisms by which the Nox/ROS signaling pathway induces pyroptosis of bone marrow hematopoietic progenitor cells via the NLRP3 inflammasome.

KEYWORDS
Nox/ROS signaling pathway; NLRP3 inflammasome; pyroptosis of bone marrow hematopoietic progenitor cells

1 Introduction

The inflammasome is a protein complex capable of recognizing intracellular DAMPs or PAMPs. It mediates the secretion, maturation, and processing of IL-18 and IL-1β, regulates the expression of relevant inflammatory genes, and induces biological effects such as cell apoptosis [1]. As a major component of the body's innate and adaptive immunity, the activated inflammasome mediates host immune responses to cellular stress, tissue damage, and pathogen infection [2]. While there have been extensive reports on NLRP3 inflammasome-mediated pyroptosis, the mechanism by which the Nox/ROS signaling pathway induces pyroptosis in bone marrow hematopoietic progenitor cells via the NLRP3 inflammasome remains unclear [3]. This article primarily analyzes and investigates the mechanism underlying Nox/ROS signaling pathway-induced pyroptosis in bone marrow hematopoietic progenitor cells through the NLRP3 inflammasome and provides the following review.

2 Functions and structure of the NLRP3 inflammasome

Various inflammasomes share a similar structure, formed by connecting the inflammasome sensor molecule to Caspase-1 via ASC. ASC, an adaptor protein encoded by the *PYCARD* gene, contains a CARD domain, a caspase activation domain, and a PYD domain [4]. ASC binds to upstream inflammasome sensor molecules through its PYD domain, facilitating the assembly of ASC dimers. Subsequently, ASC recruits pro-Caspase-1 via its CARD domain and cleaves pro-Caspase-1 using its caspase activation domain, thereby activating Caspase-1 [5]. Following activation, Caspase-1 cleaves proteins such as Gasdermin D, pro-IL-1β, and pro-IL-18, leading to the release of mature IL-1β and IL-18 extracellularly [6]. Tissue injury or infection induces elevated IL-1β levels, which recruit and activate immune cells like neutrophils, thereby mediating a cascade of immune effects [7]. Gasdermin D promotes the formation of pores in the cell membrane, causing water influx and disruption of ion gradients across the membrane. This results in cell swelling and eventual rupture, a form of cell death known as pyroptosis [8]. Current research indicates that, apart from AIM2 and IFI16 which possess a PYHIN domain, many inflammasomes incorporate IPAF or Nod-like receptors [9]. Additionally, studies have found that RIG-I can form an inflammasome complex with Caspase-1 and ASC [10]. NLRP3 is currently the most extensively studied inflammasome. It can be activated by diverse stimuli and has been strongly implicated in the pathogenesis of numerous diseases.

The assembly of the NLRP3 inflammasome involves Caspase-1, ASC, and Nod-like receptor 3 (NLRP3). Upon activation, the NLRP3 inflammasome utilizes Caspase-1 to enzymatically cleave Gasdermin D, pro-IL-18, and pro-IL-1β, generating the N-terminal fragments of Gasdermin D and the mature cytokines IL-18 and IL-1β, all of which possess biological activity necessary for their effects [11]. Research shows that the NLRP3 inflammasome enables the host immune system to effectively combat pathogens like influenza A virus, *Staphylococcus aureus*, and *Candida albicans*. However, dysregulated activation of the NLRP3 inflammasome can lead to various acquired and hereditary inflammatory diseases.

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3 Activation mechanism of the NLRP3 inflammasome

3.1 Activating stimuli

(1) Pathogens and their secreted toxins. Besides *Staphylococcus aureus* and *Listeria* spp., research indicates that bacteria such as *Burkholderia* spp., *Proteus* spp., *Salmonella enterica*, and *Cutibacterium acnes* (*Propionibacterium acnes*) can release various types of RNA, thereby activating the NLRP3 inflammasome [12]. Viruses including respiratory syncytial virus (RSV), dengue virus, and herpes simplex virus (HSV), as well as intracellular protozoan parasites like *Plasmodium* spp. (malaria), *Schistosoma* spp. (schistosomiasis), *Toxoplasma gondii* (toxoplasmosis), *Leishmania* spp. (leishmaniasis), and *Trypanosoma cruzi* (Chagas disease), can also effectively activate the NLRP3 inflammasome [13].

(2) Crystalline substances. Endogenous and exogenous crystalline structures, such as aluminum, asbestos, silica, urate crystals, and calcium oxalate crystals, can activate the NLRP3 inflammasome.

(3) Endogenous danger signals. Metabolic products (e.g., fatty acids, aldosterone, hyperglycemia) and cellular stress products like oxidized mitochondrial DNA (mtDNA) can induce NLRP3 inflammasome activation and are closely associated with the development of numerous diseases. During renal tubular injury, uromodulin (Tamm-Horsfall protein) accumulates and forms irregular, crystalloid-like structures, leading to NLRP3 inflammasome activation and subsequent tubulointerstitial inflammation [14].

3.2 Activation pathways

The NLRP3 inflammasome can be activated by stimuli such as microorganisms and endogenous molecules or their products. As clinical research deepens, increasing evidence indicates that most microbe-associated stimuli, such as muramyl dipeptide (MDP) and Toll-like receptor (TLR) agonists, do not directly activate NLRP3 . Instead, they primarily promote NLRP3 expression , thereby priming NLRP3 for activation. This process constitutes the priming step of the activation mechanism [15].

When activators like microbe-derived particles, pore-forming toxins (e.g., bacterial exotoxins), or ATP trigger activation of the NLRP3 inflammasome, the priming step requires pre-treatment of the cells. Therefore, the signal model for NLRP3 inflammasome activation consists of two distinct steps:

(1)Priming Signal: Endogenous molecules or microbial components activate NF-κB , leading to the upregulation of pro-IL-1β and NLRP3 expression.

(2) Activation Signal: Particles, pore-forming toxins, viral RNA, ATP, etc., induce the assembly and activation of the NLRP3 inflammasome complex.

4 Negative regulation of the NLRP3 inflammasome

4.1 Negative regulation of activation

Due to the diverse activation mechanisms exhibited by the NLRP3 inflammasome, its negative regulation is equally diverse and complex. During cellular stress, the autophagy pathway is activated. This promotes the clearance of intracellular components like reactive oxygen species (ROS) and damaged mitochondria, thereby negatively regulating NLRP3 inflammasome activity [16]. Substances such as β-hydroxybutyrate inhibit potassium efflux, significantly reducing ASC speck formation and oligomerization , thus negatively regulating the NLRP3 inflammasome. Conversely, clinical research has found that in some patients with autoimmune diseases, gain-of-function mutations in the *PLCG2* gene (encoding phospholipase Cγ2) lead to markedly enhanced PLCγ2 activity. This results in increased release of intracellular calcium ions (Ca^{2+}), thereby activating the NLRP3 inflammasome [17].

4.2 Negative regulation of assembly

Intracellular cAMP binds to the nucleotide-binding domain (NBD) of the NLRP3 inflammasome, thereby preventing its oligomerization and inhibiting NLRP3 inflammasome activation . Additionally, γ-interferon (IFN-γ) activates inducible nitric oxide synthase (iNOS), increasing intracellular nitric oxide (NO) synthesis. NO subsequently induces S-nitrosylation of NLRP3, specifically modifying cysteine residues, which blocks ASC recruitment and inhibits NLRP3 inflammasome assembly [18]. Furthermore, proteins containing pyrin domains (PYD) —such as POPs (Pyrin-only proteins) or PAADs (pyrin, AIM, ASC death-domain-like proteins) —interact with ASC or NLRP3 via homotypic PYD-PYD interactions, thereby competitively suppressing inflammasome complex assembly .

4.3 Negative regulation of expression

Proteins including zinc finger protein A20 * and estrogen suppress NF-κB activity , thereby inhibiting *NLRP3* gene transcription. Additionally, regulators such as the aryl hydrocarbon receptor (AhR) and zinc finger protein A20 bind to xenobiotic response elements (XREs) within the *NLRP3* promoter, directly repressing its transcriptional activation.

During Epstein-Barr virus (EBV) infection, B cells secrete miR-BART15 , while myeloid cells express elevated levels of endogenous miR-223 . These microRNAs recognize and bind the 3' untranslated region (3'UTR) of NLRP3 mRNA, marking it for rapid degradation through the RNA-induced silencing complex (RISC). This mechanism achieves negative regulation of the NLRP3 inflammasome at the translational level [19].

4.4 Other inhibitory mechanisms

Research indicates that diverse molecular regulators can modulate NLRP3 inflammasome activity by targeting IL-1β and Caspase-1 [20]. Type I interferons (IFNs) trigger IL-10 secretion through STAT1-dependent signaling . Subsequently, IL-10 binds to its cognate IL-10 receptor (IL-10R) , activating the transcription factor STAT3 . This cascade ultimately suppresses transcription of pro-IL-1β and pro-IL-1α .

5 The NOX/ROS signaling pathway

The NOX/ROS signaling pathway centers on the production of reactive oxygen species (ROS) by NADPH oxidases (NOX), which serve as key secondary messengers in intracellular signal transduction. The NOX enzyme family catalyzes the oxidation of NADPH to generate ROS, which in turn regulate various physiological and pathological processes, including cell proliferation, differentiation, inflammatory responses, and cell death. One of the primary mechanisms of this pathway is the induction of oxidative stress. ROS generated by NOX enzymes can activate downstream pathways such as MAPK and PI3K/Akt, thereby modulating cellular responses. In the context of inflammation, ROS activate transcription factors like NF-κB, promoting the expression of pro-inflammatory cytokines. However, excessive activation of the NOX/ROS signaling pathway may lead to apoptosis or necrosis.

Importantly, this pathway plays a critical role in the activation of the NLRP3 inflammasome, especially in bone marrow hematopoietic progenitor cells. When ROS levels exceed the antioxidant capacity of the cell, oxidative stress ensues, acting as a primary signal to initiate NLRP3 transcription via NF-κB. Additionally, ROS can trigger secondary activation signals for the NLRP3 inflammasome through mechanisms such as mitochondrial damage and the release of mitochondrial DNA, or lysosomal rupture that liberates cathepsin B (CTSB). In hematopoietic progenitor cells, the activation of the NOX/ROS pathway can induce pyroptosis through the NLRP3 inflammasome, disrupting cell survival and function. This process is particularly relevant under pathological conditions associated with oxidative stress in the bone marrow microenvironment, such as ischemia-reperfusion injury or chronic inflammation.

6 Conclusion

The Nox/ROS signaling pathway can induce pyroptosis in bone marrow hematopoietic progenitor cells via the NLRP3 inflammasome, with its specific mechanism likely involving NLRP3 inflammasome activation. By modulating the NLRP3 inflammasome, disease progression can be effectively attenuated or even halted, highlighting its potential as a novel therapeutic target for various related conditions. While current clinical research on the NLRP3 inflammasome has shown significant advances, several mechanistic aspects require deeper exploration. These include the controversial role of ROS as either an *effector* or *direct activator* during NLRP3 inflammasome assembly and the molecular mechanisms governing endoplasmic reticulum-mitochondria signal crosstalk

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