Autoimmunity Reviews 17 (2018) 694–702

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

NLRP3: A promising therapeutic target for autoimmune diseases

Hui-Hui Shen [a], Yue-Xin Yang [b], Xiang Meng [c], Xiao-Yun Luo [a], Xiao-Mei Li [d], Zong-Wen Shuai [e], Dong-Qing Ye [f,g], Hai-Feng Pan [f,g,*]

[a] Department of Clinical Medicine, The second School of Clinical Medicine, Anhui Medical University, 81 Meishan Road, Hefei, Anhui, China
[b] Department of Radiation Oncology, The First Affiliated Hospital of Anhui Medical University, 218 Jixi Road, Hefei, Anhui, China
[c] Department of Stomatology, School of Stomatology, Anhui Medical University, 81 Meishan Road, Hefei, Anhui, China
[d] Department of Rheumatology & Immunology, Anhui Provincial Hospital, 17 Lujiang Road, Hefei, Anhui, China
[e] Department of Rheumatology & Immunology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China
[f] Department of Epidemiology & Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui, China
[g] Anhui Province Key Laboratory of Major Autoimmune Diseases, 81 Meishan Road, Hefei, Anhui, China

ARTICLE INFO

Article history:
Received 21 January 2018
Accepted 26 January 2018
Available online 3 May 2018

Keywords:
NLRP3
Inflammasomes
Autoimmune disease
Autoimmunity

ABSTRACT

NLRP3, a member of nucleotide-binding domain-(NOD) like receptor family, can be found in large varieties of immune and non-immune cells. Upon activation, the NLRP3, apoptosis-associated speck-like protein (ASC) and procaspase-1 would assemble into a multimeric protein, called the NLRP3 inflammasome. Then the inflammasome promotes inflammation (through specific cleavage and production of bioactive IL-1β and IL-18) and pyroptotic cell death. Previous studies have indicated the importance of NLRP3 in regulating innate immunity. Recently, numerous studies have revealed their significance in autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc) and inflammatory bowel disease (IBD). In this review, we will briefly discuss the biological features of NLRP3 and summarize the recent progression of the involvement of NLRP3 in the development and pathogenesis of autoimmune diseases, as well as its clinical implications and therapeutic potential.

Contents

Abbreviations: NOD, nucleotide-binding domain; ASC, apoptosis-associated speck-like protein; PRRs, sensor- pattern-recognition receptors; NLRP3, nucleotide-binding oligomerization domain and leucine rich repeat pyrin 3 domain; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; NACTH, nucleotide triphosphatase domain; ROS, reactive oxygen species; CARD, caspase activation and recruitment domain; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; SSc, systemic sclerosis; IBD, inflammatory bowel disease; LRR, leucine-rich repeat; Treg, regulatory T cells; SNPs, single nucleotide polymorphisms.

* Corresponding authors at: Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui 230032, China.
E-mail addresses: ydq@ahmu.edu.cn, (D.-Q. Ye), panhaifeng@ahmu.edu.cn (H.-F. Pan).

https://doi.org/10.1016/j.autrev.2018.01.020
1568-9972/

1. Introduction

Inflammasomes are a class of poly-protein complexes primarily composed of a sensor, an adaptor protein and an effector. Varieties of exogenous and endogenous stimuli, including microbes, nanoparticles, oxidized DNA, etc. can be recognized by the sensor- pattern-recognition receptors (PRRs), and subsequently trigger the downstream cascade reactions. Nucleotide-binding domain-(NOD) like receptors (NLRs) belong to the PRRs family [1]. To date, at least 8 subtypes of inflammasomes have been identified, among which NLR-associated ones are the most extensively studied, especially the nucleotide-binding oligomerization domain and leucine rich repeat pyrin 3 domain (NLRP3) [2]. Once activated, NLRP3 would oligomerize [3] and upregulate cellular synthesis and maturation of several pro-inflammatory cytokines or chemokines (e.g. IL-1β and IL-18) or trigger pyroptosis [4,5], thereby resulting in inflammation against environmental or host-derived antigens.

The immune system includes innate and acquired immunity, whose deficiency or inappropriate activation could lead to visceral or systemic dysfunctions. The innate immune system provides the first line of defense to recognize microbes or endogenous molecules via pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) by host pattern recognition receptors (PRRs) [6]. As a crucial component of the innate immune system, the NLRP3 inflammasome acts an important role in host defense by recognizing viral infection and triggering autoimmune responses [7–10]. Autoimmune disorders are a series of idiopathic diseases characterized by uncontrolled, chronic auto-inflammatory conditions. The most common autoimmune diseases include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), Sjögren's syndrome (SS), systemic sclerosis (SSc) [11], etc. Inflammasomes, a molecular platform activated upon signs of cellular “danger” to trigger innate immune defenses through the maturation of pro-inflammatory cytokines such as interleukin IL-1β [12], are closely knitted with autoimmune diseases [2]. Researchers expanded on the proposal via investigations into gene transcription or protein expression of the NLRP3 inflammasome signaling pathway in autoimmune diseases, and have gained remarkable findings, which strongly indicate that NLRP3 inflammasome complex may serve as a promising and novel therapeutic target for clinical treatment in inflammatory-related diseases [13].

In the present review, we will briefly discuss the immunological functions of NLRP3 and its role in autoimmune diseases, as well as their potential as therapeutic target for these diseases.

2. NLRP3 and its immunological functions

NLRP3 belongs to the NOD-like receptor family, which is the most extensively studied inflammasome. It is a protein of 1016 amino acids transcribed from the gene Cias1, which is located on the human chromosome 1q44 and contains 9 coding exons [14]. The architecture of NLRP3 is pyrin domain at the N-terminus (PYD), an array of 12 leucine-rich repeat domain (LRR) at the C-terminus and the intermediate nucleotide triphosphatase domain (NACTH) mediated oligomerization [14]. PYD allows homotypic interactions with the bipartite adaptor protein called apoptosis-associated speck-like protein (ASC), which containing a CARD. LRR gets involved in modulating NLRP3 activity and sensing microbial ligands and endogenous alarmins [15].

By responding to a wide range of PAMPs and DAMPs, including fungi, ATP, etc., the NLRP3 scaffold, ASC and pro-caspase-1 assemble into a multimeric protein, called the NLRP3 inflammasome [16], which then regulates the maturation of pro-inflammatory cytokines IL-1β and IL-18 [17]. Expression of the NLRP3 inflammasome can be found in large varieties of immune and non-immune cells, including monocytes/macrophages [18], osteoblasts [19], T and B cells [20], epithelial cells [21], myofibroblasts/fibroblasts [4], keratinocytes [22,23] and hepatic stellate cells [24].

Due to the fact that many nonhomologous molecules can induce NLRP3 activation, the process is widely believed to involve the generation/activation of a secondary messenger. Though the exact activation mechanism is not yet clear, quantities of mechanisms have been put forward. The well-established include k^+ efflux [25–27], the generation of mitochondrial reactive oxygen species (ROS) [28] and oxidized mitochondrial DNA (mtDNA) [29], an increase in intracellular calcium and a decrease in cellular cyclic AMP [30,31], phagosomal destabilization [32], etc.

The central role of the NLRP3 inflammasome is to activate caspase-1, which could convert pro-inflammatory cytokines IL-1β and IL-18 from their precursors to biologically active forms [33]. Cytokines exert key roles in host defense and inflammation by inducing innate immune inflammatory responses. Among them, IL-1β and IL-18 are two of the mostly studied cytokines known to be cleaved by active caspase-1. IL-1β, whose secretion is tightly regulated, needs two signals for its activation. The first one is mediated by a receptor complex consisting of the type I IL-1 receptor (IL-1R) and the IL-1R accessory protein (IL-1RACP). The second signal refers to inflammasome activation, where caspase-1 induces the maturation of IL-1β for secretion [34]. Sharing some common maturation and secretory mechanism with IL-1β, IL-18 (formerly known as interferon-γ inducing factor) is constitutively expressed in its precursor pro-form in general and can be rapidly cleaved upon inflammasome activation [35]. Furthermore, Th17 is a newly identified subpopulation of $CD4^+$ T cells [34]. Regulatory T cells (Treg) inhibit the inflammatory Th17/Th1 response and are critically involved in the limitation of chronic inflammation and the development of tolerance [34–36]. The imbalance between Th17 cells and Treg cells has been considered as a new paradigm in the pathogenesis of autoimmune diseases, such as SLE [37–39], RA [40,41], SSc [42], IBD [43], etc. Previous study showed that the activation of NLRP3 inflammasome promoted the differentiation of Th17 cells [44]. Additionally, several studies have demonstrated that inflammasomes inhibitors decreased Treg cells activity. For example, epigallocatechin-3-gallate (EGCG) has been reported to have anti-inflammatory effects via increasing the number and promoting the function of human Treg cells [45]. IL-1β can act on lymphocytes by several means including upregulating IL-2 receptor expression, prolonging survival of T cells, and enhancing antibody production by B cell proliferation [37]. IL-18 enhances Th1 cell proliferation and production of IFN-γ. Both of them play a critical role in driving the differentiation and amplification of Th17 and Th1 cells [46].

In conclusion, IL-1β and IL-18, as the products of inflammasome activations, contribute to pro-inflammatory T cells differentiation and target organ damage [38,40], further amplify T and B cells responses and might serve as a crucial link translating NLR activation into adaptive immune responses [41]. Given that the wide variety of endogenous danger signals that active NLRs [12] and the role that inflammasome products play in shaping adaptive immunity, a role for the NLRP3 inflammasome in some autoimmune diseases is probable though now it is unclear. Besides, genetic polymorphisms have been shown in components of NLRP3 which proved to have associations with autoimmune diseases [42,47], such as Muckle–Wells syndrome (MWS), chronic infantile neurological cutaneous and articular syndrome (CINCA), and familial cold auto-inflammatory syndrome (FCAS) [43]. In brief, NLRP3 is involved in the identification of pathogens and inflammation-related cytokines production, and plays a significant role in the human body's immune system (Fig. 1).

3. NLRP3 in autoimmune diseases

Autoimmune diseases are characterized by inappropriate immune response against the body's own cells, tissues or organs, which comprise of SLE, RA, SSc, IBD and other related diseases. Although the pathogenesis and etiology research on these diseases advancing, as well as continuous progress on treatment, the long-term prognoses are unsatisfactory for most patients [44,45]. Thus, there is an urgent need