NLRP3 Inflammasome

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NLRP3 inflammasome sensors are activated in response to both DNA and RNA viruses. Indeed, the NLRP3 inflammasome is essential in defending against viral infections (reviewed detailed in). However, in the steady-state, inflammasome assembly is tightly regulated at a low level to prevent an aberrant pro-inflammatory response and cell death.

Keywords: NLRP3 inflammasome ; IL-1β and IL-18 ; viral infection ; inflammation ; chronic respiratory diseases ; idiopathic pulmonary fibrosis

1. Introduction

Despite less knowledge about the defined etiology and precise mechanisms, considerable advances in understanding IPF pathogenesis have been achieved in recent years. IPF is characterized by progressive extracellular matrix (ECM)-producing fibroblasts, fibroblast-myofibroblast transition, and extensive deposition of ECM by transforming growth factor-β1 (TGF-β1)-induced myofibroblasts [1][2]. Although IPF has been redefined due to repeated micro-injury of the alveolar epithelium and aberrant epithelial-mesenchymal transition (EMT) crosstalk in a genetically susceptible aging individual, chronic inflammation still plays an important role [3][4]. Inflammation also has contributions to IPF initiation and progression. Intrinsic factors, occupation, environmental influences, including exposure to microbes, particles, irritants, pollutants, allergens, and toxic molecules, genetic and epigenetic risk factors may lead to chronic inflammation that in turn leass to the development of IPF [5][6][7][8].

Innate and adaptive inflammation appears to be a prominent feature, markedly increased in the IPF group with rapid disease progression [9]. Along with previous studies, innate and adaptive immune and inflammatory cells produced heterogeneous contributions in remodeling and fibrosis processes [10]. Inflammation induced by viral infections and co-expression of virus-related proteins were firmly associated with IPF [11][12].

Upon infection with a respiratory virus, innate immune response signaling cascades start with the recognition of specific viral components, or pathogen-associated molecular patterns (PAMPs) and endogenous danger molecules that are generated and exposed from damaged or dying cells, damage-associated molecular patterns (DAMPs), by germline-encoded receptors called pattern recognition receptors (PRRs) [13][14]. PRRs are classified into four significant subfamilies: toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR)-containing receptors (NLRs), retinoic acid-inducible gene-1 (RIG-1)-like receptors (RLRs), and C-type lectin receptors (CLRs) [15]. TLRs and CLRs control the extracellular environment and endosomal compartments, while RLRs and NLRs recognize microbial patterns or danger signals within the cellular cytoplasm [16].

2. NLRP3 Inflammasome

The inflammasome is a multiprotein complex activated in response to microbial invasions or danger signals [17]. In sensing viral infection, inflammasomes will activate the innate immune response to regulate unwanted inflammasome activation and overt inflammation [18]. The classical inflammasome mainly activates caspase-1, whereas the non-classical inflammasome pathway is a caspase-1-independent inflammasome [19]. Indeed, inflammasomes regulate the secretion of pro-inflammatory cytokines, activate caspase-1, and the induction of pyroptosis as a mediator in the innate immune response [20]. When persistent inflammation occurs, activation of inflammasome complexes is initiated, leading to further activation of caspase-1, proinflammatory cytokines, and pyroptosis induction [21].

The complete structure of inflammasome is a sensor (NLRs, absent in melanoma 2 (AIM2)-like receptors (ALRs), and pyrin) that recognize a ligand, an adaptor (apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC)) and a zymogen pro-caspase-1 [22][23]. NLRs are cytosolic receptors widely identified in non-vertebrates and vertebrates, where humans express 22 NLR genes and at least 34 in mice [24][25]. NLRs are divided

based on their specific N-terminal domain: NLRAs that have an acidic activation domain, NLRBs that possess a baculovirus inhibitor of apoptosis repeat (BIR)-like domain, NLRCs that feature a caspase activation and recruitment domain (CARD) or a Death domain (DD), and the NLRP subfamily that contain a pyrin domain (PYD) [26].

The NLRP subfamily comprises C-terminus (LRR), a central nucleotide-binding and oligomerization terminus (NOD/NACHT), and N-terminus (Pyrin domain or PYD) [27]. Several NLR and non-NLR families that can form multiprotein complexes inflammasome have been described, including NLRP3, NLRP1, AIM2, NLRC4, and pyrin. [28]. The NLRP3 inflammasome is assembled upon ligand recognition, the PYD of NLR sensor associates with the PYD of ASC, then recruits and activates caspase-1, leading to the proteolytic cleavage and secretion of the pro-inflammatory cytokines, IL-1β and IL-18, as well as to gasdermin D (GSDMD)-mediated pyroptotic cell death [29]. The NLRP3 inflammasomes are widely expressed in the cytoplasm of various cells, including fibroblast [30][31]. The structure of NLRP3 is depicted in **Figure 1** .

3. The Activation of NLRP3 Inflammasome

In general, fully activating the NLRP3 inflammasome (canonical activation) requires two steps: a priming signal (signal 1) and an activation step (signal 2). The binding of viral membrane components to PRRs, such as TLRs, NLRs, RLRs, or cytokine receptors initiates priming signals then activating the transcription factor nucleus factor-κβ (NF-κβ). NF-κβ upregulates the expression and translocation of NLRP3, pro-IL-1β, and -IL-18 from the nucleus to the cytosol, which remains inactive until stimulated by the second signal [32][33]. These priming signals also regulate post-translational modifications of inflammasome components, such as NLRP3 deubiquitination, ubiquitination, and ASC phosphorylation, which is needed for further activation of inflammasome complex assembly [34].

In case of deficient signaling molecules of the NF-κβ pathway, both IL-1R–associated kinase (IRAK)1 and IRAK4 bypass priming and directly link to TLR for rapid activation of NLRP3 through the MyD88 pathway [35][36]. The priming signals regulate NLRP3 inflammasome activation via both transcription-dependent and -independent pathways [37].

An additional stimulus (signal 2), induced by a wide range of stimuli following the priming step, is usually required to promote NLRP3 inflammasome assembly, leading to the oligomerization and activation of the inflammasome complex. The NLRP3 inflammasome complex triggers the cleavage of pro-caspase-1 into caspase-1, and subsequent maturation of pro-inflammatory cytokines IL-1β and IL-18, and pyroptosis induction [33]. Several molecular and cellular events have been proposed to trigger NLRP3 inflammasome activation, including K + efflux, Ca 2+ signaling, reactive organ species (ROS), mitochondrial dysfunction, ATP release, and lysosomal damage [27].

Apart from canonical activation, the NLRP3 inflammasome is switched on via non-canonical and alternative pathways. Unlike canonical NLRP3 inflammasome activation, non-canonical activation is critical for defense against intracellular Gram-negative bacteria [38][39] and requires a receptor, such as caspases 4/5 in humans [40][41] and caspase-11 in mice [42][43], rather than caspase-1. These caspases initiate non-canonical inflammasome activation through the direct recognition of intracellular LPS independently of TLR4 [38].

4. Viral Infection Triggered The Activation of NLRP3 Inflammasome

Numerous studies demonstrated that RNA viruses could activate the NLRP3 inflammasome. Double-stranded RNA (dsRNA), such as influenza virus, induced IL-1β; release and caspase-1 activation via both NLRP3-dependent and NLRP3-independent mechanisms [44]. Influenza virus is the most common viral activator, and components of specific viruses can activate the NLRP3 inflammasome, including influenza virus proton-specific ion channel M2 protein, nonstructural protein PB1-F2, and vRNA [25]. Recent studies showed the roles of Z-DNA binding protein-1 (ZBP1) and IFN regulatory factor 1 (IRF1) transcription factor to promote NLRP3 inflammasome activation after influenza virus infection [45].

On a molecular level, viral RNA triggers NLRP3 inflammasome activation through RNA-modulating proteins, including DHX33, RNase L, RIG-1, and ROS production [45]. DDX19A, a member of the DEAD/H-box protein family, bridged viral RNA and NLRP3 to activate the NLRP3 inflammasome [46]. A study revealed that mitochondrial mitofusin protein 2 (MFN2), involved in cytoprotection, was required for NLRP3 inflammasome activation in response to RNA viruses [47].

Ad virus, Flaviviridae family, influenza virus, and myxoma virus activate the NLRP3 inflammasome via mtROS and cathepsin B induction [44]. Dengue virus and other RNA viruses mediate mitochondria aberrations and ROS production leads to NLRP3 inflammasome activation through the RIP1-RIP3-DRP1 pathway [48].

Metabolic activity and redox state are all intricately linked to each other and connect mitochondrial network dynamics during infection and NLRP3 inflammasome activity [49]. All this evidence supports mitochondria as central regulators of NLRP3 inflammasome activation induced by ER stress, virus infections and the NLRP3 activators accompanying mitochondrial dysfunction to promote the activation of NLRP3 inflammasome [50].

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