The Role of NLRP3 Inflammasome in IgA Nephropathy

Subjects: Health Care Sciences & Services

Contributor: Xiaofang Wu, Lei Zhao, Kailong Li, Jurong Yang

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular disease worldwide today. The NLRP3 inflammasome is a polyprotein complex and an important participant in inflammation. The NLRP3 inflammasome participates in a variety of kidney diseases, including IgAN.

Keywords: autophagy ; exosomes ; IgA nephropathy ; NF-κB

1. Introduction

Immunoglobulin A nephropathy (IgAN) is the most common variety of primary glomerular disease worldwide today, and the deposition of IgA immune complexes (IgA-ICs) within glomeruli is the most outstanding characteristic [1][2][3]. The deposition of immune complexes can activate mesangial cell proliferation and induce cytokine secretion, resulting in inflammation and ultimately leading to kidney damage [3][4].

The nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) compose a group of pattern recognition receptors (PRRs) and participate in inducing host innate immune responses to cellular injury [5]. The NLR family pyrin domain-containing 3 (NLRP3) is one of the best understood members and the core protein of the NLRP3 inflammasome [5][6]. The NLRP3 inflammasome is an approximately 700 kD polyprotein complex and an important participant in inflammation, which consists of NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and the protease caspase-1 [5][6][7]. Active caspase-1 cleaves the cytokines pro-interleukin-1β (pro-IL-1β) and pro-interleukin-18 (pro-IL-18) into their mature and biologically active forms IL-1β and IL-18, inducing inflammation and tissue damage [8].

NLRP3 inflammasome activation is a two-step process, consisting of priming and activation. A priming signal is required for its activation, such as ligands for Toll-like receptors (TLRs), NLRs or cytokine receptors, which trigger the transcription of nuclear factor-kappa B (NF-κB) [8][9]. NF-κB promotes the expression of NLRP3 and pro-IL-1β, but does not upregulate pro-IL-18, ASC or pro-caspase-1 [8][10]. Inflammasome can be activated via both exogenous pathogen-associated molecular patterns (PAMPs) and endogenous damage-associated molecular patterns (DAMPs) [9]. It happens when exposed to stimulus such as reactive oxygen species (ROS), mitochondrial dysfunction, lysosomal damage, ionic flux, pathogen-associated RNA and bacterial or fungal toxins [8][9][11]. NLRP3 inflammasome activation happens not only in immune cells, such as macrophages and dendritic cells, but also in kidney cells, such as podocytes, mesangial cells, renal tubular epithelium, etc. [6][7][12].

2. The NLRP3 Inflammasome and Related Pathways

2.1. The NLRP3 Inflammasome and NF-κB Pathway

NF-κB plays a pivotal role in the pathogenesis of inflammation, and NF-κB expression is correlated with the poor prognosis of IgAN patients [13][14]. Varieties of endogenous or exogenous stimuli could trigger the transcription of NF-κB, which is the main signal inducing the activation of the NLRP3 inflammasome [9][15].

Activation of the NF-κB/NLRP3 pathway might participate in the pathogenesis of inflammation in IgAN, and inhibiting NLRP3 activation can alleviate the inflammation [4][16][17][18][19][20][21]. For example, He L. et al. found that triptolide could down-regulate serum levels of IL-1β and IL-18 and may exert an anti-inflammatory effect by suppressing NLRP3 and TLR4 expression on IgAN rats [21]. Another study on rats found that artemisinin and hydroxychloroquine combination therapy exert protective effects on IgAN by inhibiting NF-κB signaling and NLRP3 inflammasome activation [19].

2.2. The NLRP3 Inflammasome and Autophagy

Autophagy, a vital intracellular process that degrades dysfunctional proteins and organelles (e.g., mitochondria) via lysosome-mediated degradation, clears damaged intracellular pathogens and regulates the diverse immune system such as antigen presentation [22][23][24]. Autophagy has now been identified as an important regulator of the NLRP3 inflammasome [24][25][26][27]. Previous studies have shown that inflammatory signals lead to an induction of autophagy, which plays a negative role in the activation of the NLRP3 inflammasome and promotes cell survival and restores tissue homeostasis after damage in autoimmune diseases, including IgAN [20][22][28].

Accumulating evidence has indicated that the regulation of inflammasomes and autophagy may be the key for the treatment of multiple diseases, including kidney disease [24][25][26][27]. Qu et al. showed that cisplatin may induce kidney injury by inhibiting autophagy and activating NLRP3 inflammasomes [29].

The relation between NLRP3 and autophagy also plays a vital role in the development of IgAN. In mouse models of progressive IgAN, researchers showed that resveratrol inhibits the NLRP3 inflammasome activation by augmenting autophagy and preserving mitochondrial integrity [30]. Additionally, in cultured macrophages, Tris dibenzylideneacetone dipalladium (Tris DBA), a small-molecule palladium complex, was found to inhibit the activation of the NLRP3 inflammasome and regulate the autophagy/NLRP3 inflammasome axis through SIRT1 and SIRT3 [28].

2.3. The NLRP3 Inflammasome and Mitochondrial Reactive Oxygen Species

Previous studies have indicated that the most typical mechanism for activating the NLRP3 inflammasome is the production of ROS, especially mitochondrial ROS (mtROS) [9][31][32][33]. A growing number of studies have revealed the role of blocking mtROS in kidney diseases, such as ischemic and cisplatin-induced AKI, DN, etc. [31][34][35][36][37][38]. A previous study found that Mito TEMPO, a mitochondria-targeted antioxidant, can inhibit mtROS overproduction and NLRP3 inflammasome activation, and it verified that the NLRP3 inflammasome can be activated via the mROS-TXNIP-NLRP3 signal pathway, providing a potential therapeutic target for ischemic AKI [34].

The ROS signaling pathway has also been shown to be involved in IgAN [17][39]. It has been well-recognized that albuminuria is a risk factor of IgAN, and albuminuria triggers mitochondrial dysfunction and mtROS generation, resulting in renal tubular inflammation through mtROS-meditated activation of the NLRP3 inflammasome [18][40]. A previous study found that IgA ICs could induce the activation of the NLRP3 inflammasome through ROS in macrophages [39]. Yang et al. found in induced accelerated progressive IgAN mice that antroquinonol (a pure active compound from Antrodia camphorata mycelium) promoted the Nrf2 antioxidant pathway, inhibited NLRP3 inflammasome activation and significantly improved renal function [41]. Additionally, in IgA-IC-primed macrophages, they discovered that antroquinonol inhibited NLRP3 inflammasome activation by reducing ROS production [41]. Hua et al. also found that osthole inhibited ROS production, activation of NF-κB and the NLRP3 inflammasome, exerting its reno-protective effects on the progression of IgAN both in vitro and in vivo [17]. Based on these findings, ROS inhibition may be a potential choice to inhibit NLRP3 activation and reduce inflammation in IgAN.

2.4. The NLRP3 Inflammasome and Exosomes

Exosomes are small extracellular vesicles (30–150 nm) secreted by all healthy and abnormal cells and are abundant in all bodily fluids [42][43]. Emerging evidence has revealed the relationship between exosomes and the NLRP3 inflammasome [44][45][46][47]. Recent studies have shown that exosomes can influence the course of NLRP3 inflammasome-associated diseases by secreting different substances that affect key molecules in the canonical pathway [44][45]. Dai et al. discovered that exosomes relieve myocardial ischemia/reperfusion injury by inactivating the TLR4/NF-κB/NLRP3 inflammasome signaling pathway in a neonatal rat model induced by ischemia/reperfusion [46]. In another rat model, Tang et al. found that exosomal miR-320b can directly target NLRP3 and inhibit pyroptosis, thereby protecting the myocardium from ischemia/reperfusion injury by inhibiting pyroptosis [48].

Recent research also focused on the mechanism by which exosomes mediate inflammation in IgAN [4][19]. Bai et al. found that artemisinin and hydroxychloroquine combination therapy could significantly promote the secretion of exosomes in the renal tissue of IgAN rats and inhibit the expressions of NF-κB signal and NLRP3 inflammasome-related protein [19]. Subsequently, Li et al. found that Zhen-wu-tang (a well-known traditional Chinese formula) regulated exosome secretion, which influenced the NF-KB/NLRP3 signaling pathway in the human mesangial cell proliferation model, and it could also reinforce the secretion of exosomes in an IgAN rat model [4]. These results have provided new evidence that enhancing the secretion of exosomes to inhibit the NF-κB/NLRP3 signaling pathway is a promising approach for IgAN treatment.

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