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NLRP3 Inflammasome as Therapeutic Targets in Inflammatory Diseases

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Abstract

Innate immunity is a first line defence system in the body which is for sensing signals of danger such as pathogenic microbes or host-derived signals of cellular stress. Pattern recognition receptors (PRR's), which present in the cell memebrane, are suspect the infection through pathogen-associated molecular patterns (PAMP), and activate innate immunity with response to promote inflammation via inflammatory cells such as macrophages and neutrophils, and cytokines. Inflammasome are protein complexes which are part of innate immunity in inflammation to remove pathogens and repair damaged tissues. What is the important role of inflammation in disease? In this review, we are focused on the action mechanism of NLRP3 inflammasome in inflammatory diseases such as asthma, atopic dermatitis, and sepsis.

Key Words: Asthma, Atopic dermatitis, Inflammasome, Sepsis

INTRODUCTION

Inflammation is a complex and a protective response by the immune system against physical, chemical and infective agents. However, it is frequent that inflammatory response to several stimuli leads to the damaging of normal tissues (Nathan, 2002; Rankin, 2004). Every year millions of the people are affected by chronic and acute inflammatory diseases such as asthma, atopic dermatitis and sepsis (Lambrecht and Hammad, 2003; Bel, 2013).

Atopic dermatitis (AD) is a common skin disease in children and it is multifactorial inflammatory disease (Liang *et al*., 2016). AD is an allergic disease which is mediated by T-helper 2. Th-2 initiates interleukin (IL)-4, IL-5, and IL-13 expression in AD, which stimulates B cells, mast cells, and epidermal cells to produce IgE and various cytokines and induce degranulation cytokines (Brandt and Sivaprasad, 2011; Kabashima, 2013; Weidinger and Novak, 2016). Innate immune functions and the regulations of adaptive immune responses there is Interleukins have important role. SNPs in the Nlrp3 gene are associated with atopic dermatitis (Macaluso *et al*., 2007; Bivik *et al*., 2013; Zhang *et al*., 2015). Sepsis is a harmful systemic inflammatory response to infection. IL-1family are inflammasome associated cytokines and propagates the acute inflammatory response (Luo *et al*., 2014).

The inflammasome is discovered by Martinon and colleagues in 2002, which is a protein complex known to promote inflammation (Martinon *et al*., 2002).

We are herein focused on the action mechanism of NLRP3 inflammasome in inflammatory diseases. In particular, the relationship between atopic dermatitis, asthma and sepsis and inflammasome was studied (Table 1).

INFLAMMATION AND INNATE IMMUNITY

When the body effected by some infection inflammation is an immediate response from the innate immunity and it is like a barrier and prevent the infection, allows repair of damaged tissue after the elimination of the pathogens. Introduction of pathogens or mechanical injury to cells or tissue initiates the inflammation. Pattern recognition receptors (PRR's) which are attached to the membrane of cell are toll-like receptor (TLRs) or Nod-like receptors (NLRs) for recognition of inflammatory events (dos Santos, 2012). PRRs recognize the pathogen-associated molecular patterns in an infection and when any mechanical damage is present. Damage associated molecular patterns (DAMPs) are also recognized by PRRs. Innate im-

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Table 1. Inflammatory diseases and their NLRP3 activators and cytokines which is released by NLRP3 activation to specific diseases respectively

Disease	NLRP3 Activators	Cytokines	References
Asthma	Various pathogens, toxins, bacteria, RNA and Der f1	IL-1β, IL-18	Whelan *et al*., 2004; Mariathasan and Monack, 2007; Besnard *et al*., 2011; Tsai *et al*., 2018
Atopic Dermatitis	*Staphylococcus aureus*, *S. aureus* linked α-toxins	IL-1β, IL-18, IL-5, IL-31	Marples *et al*., 1973; Tomi *et al*., 2005; Arend *et al*., 2008; Munoz-Planillo *et al*., 2009; Boguniewicz and Leung, 2010; Niebuhr *et al*., 2014
Sepsis	ROS, mtDNA,TLR4 agonist and LPS	IL-1β, IL-18, IL-33	Martin *et al*., 2003; Bauernfeind *et al*., 2009; Willingham *et al*., 2009; Yin *et al*., 2011; Kamo *et al*., 2013; Luo *et al*., 2014

munity responds with a sterile inflammatory response after the recognition of a PAMPs or DAMPs and those responses uses the innate immune cells which are macrophages, neutrophils cytokines to promote inflammation (Land, 2013).

INFLAMMASOME

Inflammasome are major complexes which are involved in innate immunity activities such as infection and changes in cellular homeostasis to initiate response to remove pathogens and repair tissue damage by activates pro-caspase-1, which then proceeds to cleave the pro-inflammatory cytokines IL-1β and IL-18 (Wilson *et al*., 1994; Man and Kanneganti, 2016). There are four structural subsets in inflammasome which are include nucleotide-binding oligomerization domain receptors (NLR) family, pyrin domain containing 1 (NLRP1), NLRP3, NLR family CARD domain-containing protein 4 (NLRC4) and absent in melanoma (AIM2) (van de Veerdonk *et al*., 2011). Pyroptosis, which is inflammatory form of cell death initiated by inflammasome, is due to an activating cleavage of gasdermin D, which forms pores in the plasma membrane (Kayagaki *et al*., 2015; Shi *et al*., 2015; Kesavardhana and Kanneganti, 2017).

NARP3 INFLAMMASOME AND INFLAMMATORY DISEASES

NLRP3 is most studied and focused inflammasome by many researchers, which is present with over 90 disease associated mutations. Leucine-rich repeats, nucleotide - binding domains (NBD), and an N-terminal pyrin domain in *NLRP3* allowing recruitment of ASC activate pro caspase-1 (Hoffman *et al*., 2001; Kanneganti *et al*., 2006; Masters *et al*., 2009). An inflammasome complex containing ASC and caspase-1 which is formed by *NLRP3* inflammasome and which complex respond to a wide range of infections and stress stimuli. There is a two-step process is required for *NLRP3* activation. DAMPs and PAMPs are initiated the first step which are upregulate the pro-IL-1β, pro-IL-18 and components of inflammasome and assembly of the components into the inflammasome structure. The production of IL-1β, a pro-inflammatory cytokine, is the second step of NLRP3 activation (Bauernfeind *et al*., 2011a; Gross *et al*., 2011). Low K+ concentrations in the environment, a wide range of bacteria and viruses are triggered *NLRP3* activation (Petrilli *et al*., 2007). In the presence of ATP microbial substances such as muramy l peptide, lipopolysaccharide and bacterial RNA are activating *NLRP3* (Kanneganti *et al*., 2006), also bacterial toxin like nigericin and maitotoxin can activate NLRP3 (Mariathasan *et al*., 2004).

The activation of *NLRP3* mechanism explained by several hypotheses. One of the hypotheses proposes *NLRP3* activation requires low K^+ concentration. Some toxins can form pores in the membrane of cells allowing for K^+ efflux (Perregaux and Gabel, 1994). The extracellular ATP causes K^+ efflux which induce the activation of P2X7 receptors on pannexin 1 (Colomar *et al*., 2003). Another model proposes DAMPs leads *NLRP3* activation (Hornung *et al*., 2008). These also has been suggested that reactive oxygen species (ROS) cause the breakdown of thioredoxin and its interacting protein (dos Santos, 2012). The recruitment of ASC and pro-caspase 1 into the inflammasome structure is induced by *NLRP3* receptor when TXNIP therein binds on it.

Asthma and NLRP3

More than 300 million people affected by asthma in worldwide, which is chronic inflammatory disease that is defined as reversible airway narrowing and is characterized by episodic symptoms of dyspnea, wheezing and coughing. Bronchial epithelial cells (BEC) are physical barrier and first line of defence against inhalants such as microorganisms, gases and allergens (Lambrecht and Hammad, 2012; Bel, 2013). In the asthma pathogenesis loss of BEC integrity is a hallmark and there is strong evidence of sloughing of found in bronchial biopsy samples from patients with mild to severe asthma (Chanez, 2005; Martinez-Giron and van Woerden, 2010). Airway structural changes is leading to remodelling of the airways because of the repetitive cycles injury and repair of BECs (Holgate, 2000; Davies, 2009; Holgate *et al*., 2009).

The sensitization with OVA and alum activates the *NLRP3 inflammasome* which leads to IL-1β maturation and humoral adaptive immune response. Allergic lung inflammation with lower eosinophil influx and impaired Th2 response causes by NLRP3 deficiency (Besnard *et al*., 2011).

Microbial infections and non-infectious stimuli induces the host cell death which process is called pyroptosis and it is depending upon caspase-1 activation which mediates cell death and cleaves and secretes proinflammatory cytokines, such as interleukin (IL)-1β and IL-18 (Yeretssian *et al*., 2008; Bergsbaken *et al*., 2009). Cell death and pro-inflammatory signals cause tissue damage and which lead to permanent structural changes (Tanaka *et al*., 2001). In airway epithelia inflammatory injuries contributed by pyroptosis which act as patho-

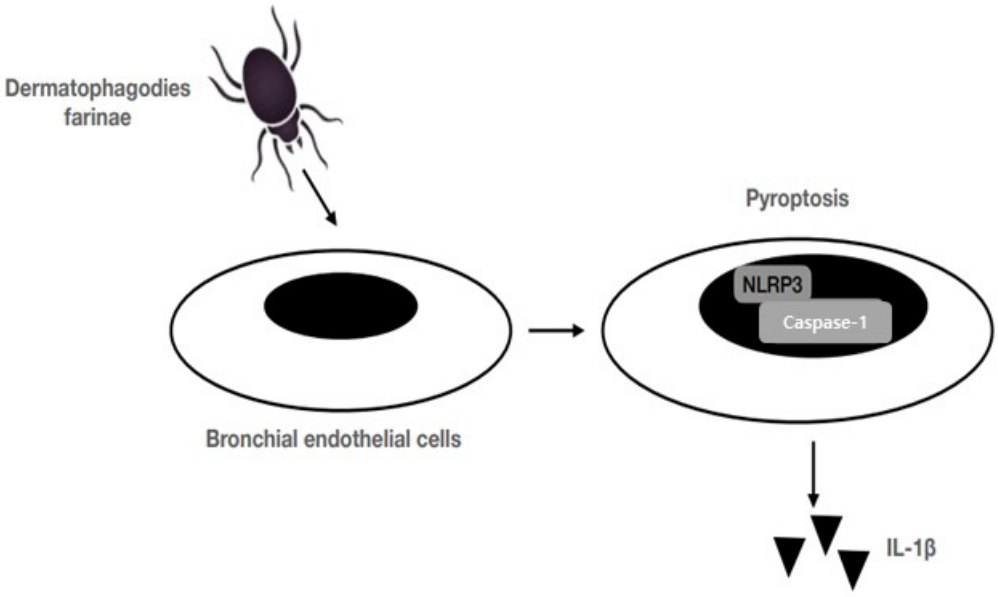

Fig. 1. Proposed scheme of Der f1-induced pyroptosis in bronchial epithelial cells (Figure modified from Tsai *et al*., 2018). The Der f1 allergen induces BEC death through the caspase-1 pathway, referred to as pyroptosis. Following pyroptosis, BECs secrete interleukin (IL)-1β, which may perpetuate asthma pathogenesis. Der f1, Dermatophagodies farina allergen 1; NLRP3, NOD-like receptor family pyrin domain-containing protein 3.

genic mechanism. Conversion of pro-IL-1β to mature IL-1β catalysed by Caspase-1 which is a key inflammatory mediator controls both local and systemic immune response (Denes *et al*., 2012). IL-1β plays an important role in the early phase of asthma pathogenesis and to modulate airway construction and relaxation responses directly on the airway smooth muscle (Whelan *et al*., 2004). Recent research demonstrated Der f 1 increased the proteolytic activation and activity caspase 1 which in turn induced the secretion of IL-1β from BECs (Tsai *et al*., 2018). For the recognition of exogenous microbial components or endogenous destructive cellular factors NLRs plays an important role in innate immunity. Various pathogens, toxins, bacterial RNA and uric acid triggered the activation of NLRP3 inflammasome via toll-like receptors and P2X7 receptors (Mariathasan and Monack, 2007). Here one evidence to the Der f1 increased the association of NLRP3 and caspase-1. The Der f1 induced activity of caspase-1 was shown to decrease in pHBECs and HBE-135 cells when NLRP3 was knockdown and IL-1β, pyroptosis also reduced (Tsai *et al*., 2018) (Fig. 1).

Atopic dermatitis and NLRP3

Atopic dermatitis is a common skin disease which is mediated by Th2 through the inflammasomes. The host protects itself from pathogens by innate immune system, which initiates the repair process of injury or trauma. Almost 80-100% of AD patients are colonized with *Staphylococcus aureus* (*S. aureus*) and strong correlation between disease severity and *S. aureus* colonization of lesional and nonlesional skin (Marples *et al*., 1973; Tomi *et al*., 2005; Boguniewicz and Leung, 2010). Innate immunity is activated by pathogen-recognition receptors such as Toll-like receptors and nucleotide-binding oligomerization domain receptors (NLRs) (Soumelis *et al*., 2002; Jiao *et al*., 2016). The most well-known inflammasome NLRP3 links to staphylococcal α-toxin to caspase-1 activation through the formation of a multiprotein platform called the inflammasome and secrets IL-1β, and NLRP3 also recruits apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC). And then pro-caspase-1 is activated to caspase-1 when assembled of inflammasome and leads to release of IL-1β and IL-18 (Arend *et al*., 2008; Munoz-Planillo *et al*., 2009). Normal NLRP3 activation contributes host defence but excessive activation leads to inflammatory diseases.

There are several mechanisms initiated by *S. aureus* and its toxins that result in AD. Super antigens of *S. aureus* have the ability to induce cutaneous lymphocyte-associated antigen (CLA) expression as a skin-homing receptor on circulating T cells. Keratinocyte-derived chemokines and thymic stromal lymphopoietin (TSLP) induce the recruitment of T cells, Th2 cell differentiation, and the induction of T cells to secrete IL-5 and IL-31. Mast cell degranulation induced by α-toxin and which is activates the nucleotide-binding oligomerization domain receptor protein 3 (NLRP3) inflammasome that eventually (Fig. 2).

It is reported that Nlrp3 gene polymorphism activates the inflammasome to induce the allergic inflammatory response and increase the risk of atopic dermatitis (Macaluso *et al*., 2007; Zhang *et al*., 2015). 2,4 dinitrochlorobenzene (DNCB) and House dust mite (HDM) initiates the NLRP3 inflammasome signalling pathways and increase of NLRP3 and ASC expression, which enhanced the maturation of caspase-1 and IL-1β and induction of pyroptosis (Bivik *et al*., 2013). NLRP3 inflammasome activation by house dust mites are present in higher frequencies in the surroundings of patients with AD and induce caspase-1 dependent release of IL-1β and IL-18 from human keratinocytes (Jang *et al*., 2018).

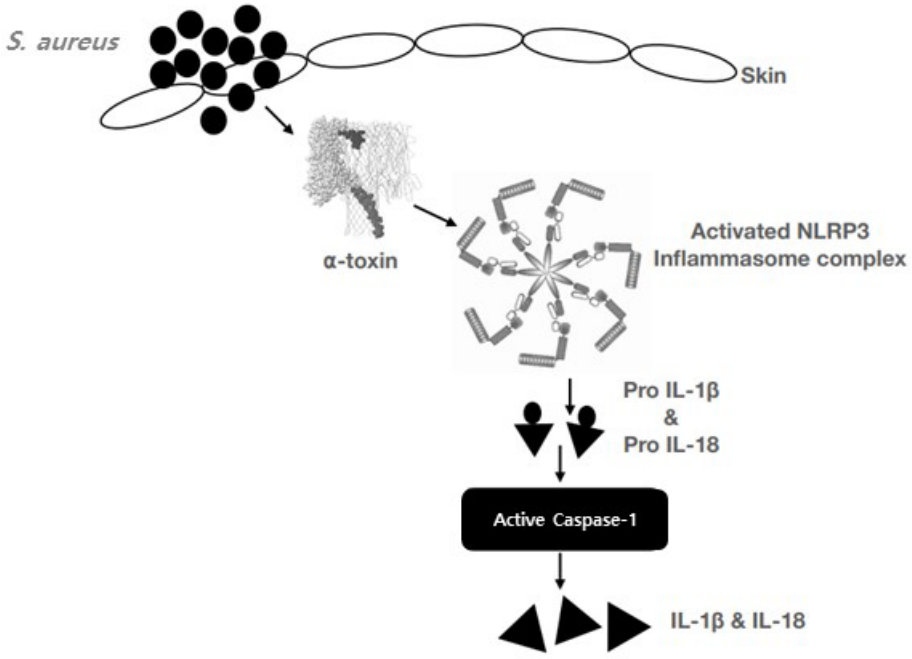

Fig. 2. The mechanism of NLRP3 activation in atopic dermatitis. *S. aureus* induce the super antigens TSST-1, which release the chemokines, TSLP from keratinocytes and recruit the T cells. α-toxin is link with *S. aureus*, activates the NLRP3 inflammasome which activates the caspase-1 and it cleavage the pro-IL-1β and pro-IL-18 to IL-1β and IL-18 (Niebuhr *et al*., 2014).

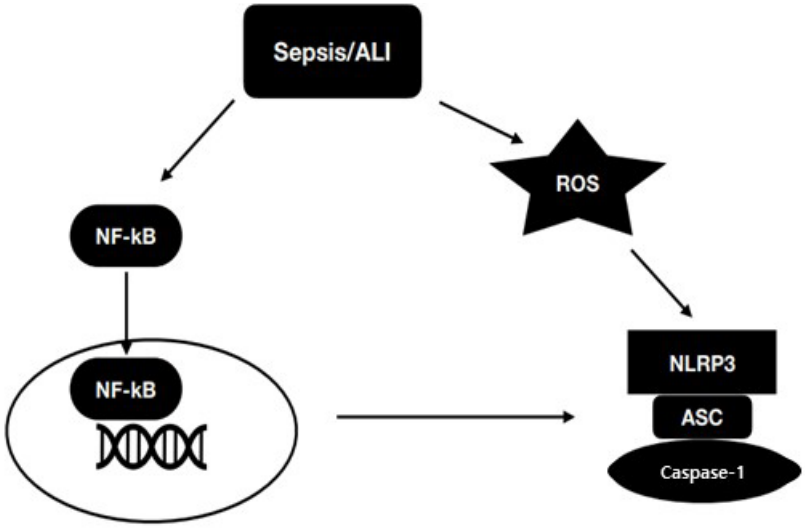

Fig. 3. Mechanism of NLRP3 activation in sepsis and ALI. ROS and NF-kB activates the NLRP3 inflammasome.

Sepsis and NLRP3

A harmful systematic inflammatory response to an infection is called sepsis (Luo *et al*., 2014). The patient with end-organ dysfunction lead by sepsis are particularly at risk of developing acute lung injury (ALI). Mostly 10-15% people affected by ALI are hospitalized in ICU. NLRP3 inflammasome dysregulation lead to sepsis and ALI (Martin *et al*., 2003). NLRP3 inflammasome activation initiate the filtration of inflammatory cells in the lung and lead to lung injury (Luo *et al*., 2014). IL-33 and HMGB1 which are depend on NLRP3 inflammasome plays an important role in sepsis-induced ALI (Luo *et al*., 2014). IL-33 belongs to IL-1 cytokine family and it is increases inflammatory response in the lung (Yin *et al*., 2011). In sepsis high mobility group box 1 (HMGB1) induces a late lethal systemic inflammation and NLRP3 and ASC/caspase-1/IL-1β signalling promotes HMGB1 induction and release (Willingham *et al*., 2009; Kamo *et al*., 2013). TLR4 agonist induces NLRP3, pro-caspase 1, pro-IL-1β and pro-IL-18 expressions through NF-kB pathway. Gram-negative bacteria are most common

bacteria for sepsis and LPS mediated inflammatory cytokines release, which is most common agonist in polymicrobial sepsis (Bauernfeind *et al*., 2009). Monocytes and macrophages in the lung are activated and release inflammatory cytokines when binding the LPS with TLR4. MyD88-dependent and independent pathways are activated by LPS through NF-kB resulting in the induction of NLRP3 protein expression. NF-kB plays a vital role in NLRP3 in LPS induced NLRP3 expression and associated pro-mediators (Bauernfeind *et al*., 2009). Reactive oxygen species (ROS), mitochondrial DNA (mtDNA) also activates the NLRP3 and promote NLRP3 expression at the transcriptional level (Zhou *et al*., 2010; Bauernfeind *et al*., 2011b; Shimada *et al*., 2012). Mitochondrial damage is also involved in Sepsis and overproduction of ROS and mtDNA released from mitochondria participate in the pathogenesis of sepsis (Fig. 3).

Drug Development of inflammatory diseases

Usually drugs are developed for diseases to target the receptors, enzymes, protein and gene etc. The process of drug development for inflammatory diseases mainly targeting on inflammasomes. Cytokine release inhibitory drugs targets the NLRP3 and AIM2 inflammasomes (Coll *et al*., 2011). The NLRP3 inflammasome complex is a potential target for the development of therapeutics for patients with inflammatory bowel diseases (Bauer *et al*., 2010). Fc11a-2 has an ability to inhibit the activation of NLRP3 inflammasome (Liu *et al*., 2013). Fc11a-2 mechanism of action in colitis is inhibition of NLRP3 inflammasome functions as it suppressed the activation of caspase-1 and reduced the production of IL-1β/IL-18 in macrophages. Resveratrol inhibit the secretion of IL-1β by down-regulating the protein and mRNA levels of IL-1β (Liu *et al*., 2013). Resveratrol mainly elevates the Siert1 and inhibit the NLRP3 inflammasome to prevent the inflammation (Fu *et al*., 2013). For the attenuation of Sepsis Resveratrol targets the inhibition of the NLRP3 inflammasome which prevents the over-release of pro-inflammatory cytokines and inflammatory cell infiltration and tissue impairment (Fu *et al*., 2013). Tranilast (TR) directly targets NLRP3 inflammasome to suppress the inflammation. TR blocks the assembly of NLRP3 inflammasome (Huang *et al*., 2018). TR improve the dysfunction of both glucose and lipid metabolism through inhibiting the NLRP3 inflammasome.

CONCLUSION

The inflammasomes play a prominent role in inflammatory diseases. Endogenous danger signals such as ATP or uric acid crystals released form dying cells are activated the inflammasomes. NLRP3 inflammasome is crucial to inflammatory diseases such as Asthma, Atopic dermatitis and Sepsis. NLRP3 inflammasome activation leads the inflammatory diseases through different pathways, which associate to ASC and caspase-1 and initiates release of the inflammatory cytokines such as IL-1β and IL-18 and also involves in pyroptosis. Actually infection recognized by PAMPs or DAMPs in the host then innate immunity is respond and promote the inflammation through immune cells such as macrophages, neutrophils, and release of proinflammatory cytokines. Usually bacteria, viruses and low K^+ concentration environments are can activate the NLRP3. Pyroptosis is depends upon caspase-1 which is activated by NLRP3 and lead to permanent changes in airways and airway epithelial inflammatory injuries in asthma pathogenic mechanism. IL-1β also responsible for early phase of asthma which is initiated by NLRP3 inflammasome through caspase-1. Mostly Atopic dermatitis is caused by Staphylococcus aureus, which α-toxin links to NLRP3 inflammasome to activate caspase-1 and release IL-1β, IL-18. NLRP3 dependent IL-33 and HMB1 release, which plays a crucial role in Sepsis induced by TLR4 agonist and the associate with caspase-1 induces release IL-1β and IL-18 through NF-kB pathway. It is suggested that NLRP3 inflammasome is a target for drugs which will cure the inflammatory diseases such as Asthma, Atopic dermatitis and Sepsis.

CONFLICT OF INTEREST

The authors confirm that they have no conflicts of interest.

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