



Research Progress on the Role of Inflammation in Kawasaki Disease

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

As the pathogenesis of Kawasaki disease continues to evolve, researchers have proposed a number of hypotheses, from viral infections, genetic and environmental influences, to toxin-mediated autoinflammatory responses. More and more attention has been paid to the role of inflammation in KD (Kawasaki disease) pathogenesis. Objective: To explore the role of inflammation in Kawasaki disease and to provide a new idea for the diagnosis and treatment of KD. Methods: A systematic search was conducted from PubMed and CNKI databases (last updated on March 31, 2023) for relevant and qualified articles evaluating the role of inflammation in KD. Results: The research results of the last five years were selected from these articles for meta-analysis. Conclusion: Through comprehensive analysis, we conclude that inflammatory response is the main process of vascular damage in Kawasaki disease, especially the NLRP3 inflammasome which plays an important role. However, the etiology and pathogenesis of KD are very complex, and inflammation is only one manifestation. More and more studies have shown that inflammation plays a crucial role in the pathogenesis of Kawasaki disease, which has been recognized, and we comprehensively describe some important roles and latest research perspectives of inflammation in Kawasaki disease.

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1. INTRODUCTION

Kawasaki disease (KD) is a common vasculitis that tends to occur in children under 5 years of age. It is usually acute, self-limited, and highly inflammatory in its early stages, mainly involving coronary arteries, but its pathogenesis has been unknown. In recent years, the incidence of KD has been increasing year by year, which is one of the most common causes of acquired heart disease in children [1]. The role of inflammation in Kawasaki disease is summarized from the following aspects:

2. HISTOPATHOLOGY

“The initial study of KD inflammation was a histopathological examination of the heart and coronary vessels of deceased patients. Early in the disease, stage I, a large number of mixed inflammatory infiltrates of neutrophils, eosinophils, macrophages, and lymphocytes are seen, involving the inner and outer membranes of coronary arteries” [2]. “In the second stage, coronary aneurysms may develop due to proliferative inflammation of the intima and damage to the smooth muscle cells and elastic fibers. Again, this infiltration is mixed and includes lymphocytes, monocytes, macrophages, plasma cells, and fibroblasts” [3].

“Generally, M1 macrophages are thought to be pro-inflammatory and may reflect activation of innate immune stimuli. In a study of KD coronary artery disease, a large number of immune inflammatory cells, especially M1 macrophages, were found to be the main phenotype of KD” [4]. “Abnormal activation of immunoactive cells such as macrophages, monocytes and lymphocytes is the main process of inflammatory damage in KD. These cells secrete various inflammatory cytokines and chemokines such as IL-1 β (Recombinant Human Interleukin-1 β), TNF- α (Tumor necrosis factor- α), thereby causes vasculitis in the endothelial cells” [5]. “Vasculitis endothelial cells play a vital role in maintaining the normal function of blood vessels. Studies have shown that endothelial cell injury, including inflammation and apoptosis, is the main pathological mechanism of KD” [6].

With the deepening of exploration and the support of technology, the study of KD inflammatory response has been upgraded from histopathology to the analysis of whole gene

expression profile, such as the mouse model of KD patients in the acute stage, such as LCWE (Lactobacillus casei cell wall extract) mouse model, and transcription profile analysis, which confirmed the up-regulation of multiple immune pathways. Including intracellular signal transduction, T cell activation, B cell development, etc. [7], these studies further suggest the role of immune inflammatory response in KD. Here we discuss the role of innate immunity and adaptive immune inflammation in KD.

3. CONGENITAL IMMUNE INFLAMMATORY RESPONSE

3.1 Inflammatory Factor

“High levels of IL-1 β have long been thought to be at the core of KD's acute inflammatory phase” [8]. “IL-1 β is produced by a variety of immune and non-immune cell types as part of the innate immune response. IL-1 β has a variety of pro-inflammatory effects, the most important of which is the direct activation of coronary endothelial cells, resulting in the up-regulation of cell adhesion molecules, and the production of IL-6 (Recombinant Human Interleukin-6) and IL-8 (Recombinant Human Interleukin-8), both of which are important inflammatory factors” [9].

“In addition to IL-1 β , cytokines also have TNF- α . Relevant reports have shown that the levels of TNF- α released by macrophages and monocytes in the serum of KD patients are significantly higher, which plays a facilitating role in inducing coronary artery inflammation and promoting the development of coronary artery aneurysms” [10]. However, research has confirmed that activating the inflammasomes can stimulate the production of inflammatory cytokines.

3.2 Inflammatory Bodies

Inflammatory bodies are intracellular protein complexes of the innate immune system that respond to pathogen-associated molecular patterns (PAMPS) or damage-associated molecular pattern (DAMPS).

“Nod-like receptor protein 3 (NLRP3) activation is the key to inflammatory activation in typical inflammatories and there is a correlation between NLRP3 and tongue-associated speck-like

protein, apoptosis-associated speck-like protein(ASC), and cysteinyl aspartate-specific proteases-1 (caspase-1) containing cysteine combined to form inflammatory bodies. By regulating caspase-1 activation, promoting maturation and release of inflammatory factors such as IL-1 β and IL-18, and plays a pro-inflammatory roles” [11]. “In addition, the activation of atypical inflammasomes has been reported to be associated with caspase-4 or caspase-5-dependent pyrodeath is known to be induced by intracellular lipopolysaccharides (LPS) in Gram-negative bacteria” [12,13]. “At the same time, activation of caspase-4/5 also induces typical NLRP3 inflammasome. mRNA levels of TIFA(TRAf-interacting protein with FHA domain-containing protein A), NLRP3, CASP1(caspase-1), CASP4, CASP5 and IL1 β were significantly increased in acute and convalescent KD patients. Therefore, studies have confirmed that both NLRP3/Caspase-1 and Caspase-4/5 are involved in the pro-inflammatory immune response of KD patients at the transcriptional level” [14].

3.3 Activation of NLRP3 Inflammasome

Studies have shown that the NLRP3 inflammasome is a complex composed of three subunits, and activation of the NLRP3 inflammasome requires two signals.

The first signal causes NF κ B(Nuclear factor-B) activation, which leads to increased NLRP3 and pro-IL1 β levels. Binding of pathogen-associated

molecular patterns (PAMP) or damage-associated molecular patterns (DAMP) to pattern recognition receptors (PRRs) results in NF κ B activation. NF κ B is a transcription factor that increases NLRP3 and pro-IL1 β in cells, which is called priming.

“The second signal leads to the assembly of the named body protein, further leading to the activation of cystatin 1, which is called activation. Caspase-1 converts pro-IL1 β to IL1 β and converts pro-IL18 to IL18, respectively also leads to programmed inflammatory cell death through the formation of pores in the cell membrane, with the end resulting in being the release of inflammatory cytokines and inflammatory cell death through the formation of cell membrane pores” [15].

3.4 Regulation of NLRP3 Inflammasome

MicroRNAs (miRNAs) are endogenous non coding RNA molecules that play important roles in various cellular and metabolic pathways, including cell proliferation, differentiation and apoptosis. MiRNAs are also involved in regulating inflammatory responses and maintaining immune stability [17]. Recent studies have shown that MicroRNA-223(miR-223) limits the development of cardiovascular diseases by down-regulating “NLRP3 inflammasome activity and subsequent IL-1 β production. miR-223 may be a potential biomarker for the early diagnosis of KD in humans, and may be promising as a novel therapy for KD in the future” [18].

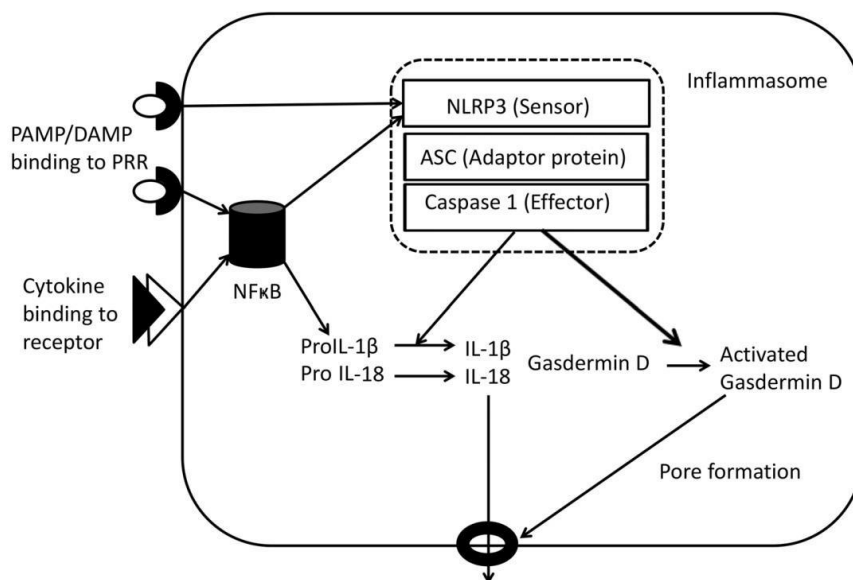


Fig. 1. NLRP3 inflammasome activation pathway [16]

Studies at different periods consistently found that ITPKC (inositol 1,4,5-trisphosphate 3-kinase C) polymorphism is associated with KD susceptibility, and ITPKC controls NLRP3 activation by regulating calcium ion mobilization. ITPKC is a gene that encodes inositol triphosphate 3-kinase, which converts inositol triphosphate (IP3) to inositol tetraphosphate and terminates the propagation of Ca²⁺ signaling pathways. Recent studies have shown that reduced function of inositol 3-kinase triphosphate leads to accumulation of IP3 [19]. "Increased IP3 leads to increased intracellular Ca²⁺ and activation of NLRP3. Increased IP3 also leads to activation of T cells through Ca²⁺/NFAT (nuclear factor that activates T cells) pathway" [20].

The role of ITPKC, NLRP3 and cytokines such as IL1 β and IL18 in children with acute KD has been investigated. They found that ITPKC was down-regulated and NLRP3 was up-regulated in the children. IL18 levels are elevated and associated with inflammatory markers. IL1 β levels were not significantly elevated in children with KD compared to controls, but were higher in IVig-resistant children in their cohort. These studies may indicate that NLRP3 inflammasome-driven IL-1 β plays an important role in disease development in children with IVig-resistant KD, and also suggest that in addition to IL-1 β , it is also a therapeutic target for KD through the regulation of NLRP3 inflammasome-resistant [21]. Management of the water-soluble portion of *Candida albicans* (CAWS) is a mouse model that causes KD coronary arteritis. This model was used to show that damage to KD vascular inflammation is mediated by NLRP3 activation and IL-1 β production, as the control group suggested that NLRP3 deficient mice did not develop vasculitis [22]. In both studies, NLRP3 bodies were found to be involved in KD pathogenesis.

Based on the above studies, it can be seen that the action process of inflammatories in KD is that when the body is subjected to invasion by exogenous pathogenic toxins or stimulation by endogenous danger signals, inflammatories are self-activated and form active substances (caspase-1), which further promote maturation of more downstream pro-inflammatory factors (such as IL-1 β and IL-18), thus promoting cellular inflammatory response. Even apoptosis. The production of inflammatory factors can further cause the activation of immune cells such as T cells and NK cells, and the release of interferon- γ

(IFN- γ), tumor necrosis factor- α (TNF- α) and other inflammatory factors. Such recurrent and even diffuse inflammation leads to the damage of vascular endothelium, which may play a role in KD systemic vascular inflammation and CAL. Although a single mechanism such as inflammasome may not fully explain the pathogenesis of KD, such research will certainly promote the development of new diagnostic markers and therapeutic targets in KD.

4. ADAPTIVE IMMUNE INFLAMMATORY RESPONSE

In addition to the role of innate immune response in generating inflammation in KD, relevant studies have shown that antigen-specific adaptive immune response also occurs in KD patients. For example, both B cells and CD8+T cells have been reported to have oligoclonal amplification in acute KD. Autoantibodies against various myocardial, endothelial, and extracellular matrix proteins have been documented in many studies. The clinical significance of these autoantibodies is unclear.

"In a long-term follow-up study, 22% of patients detected autoantibodies several years after diagnosis of KD" [23]. However, there is no convincing evidence that KD patients are at higher risk of developing autoimmune diseases later in life.

4.1 B Cell Activating Factor (BAFF) and IgA Reactions

1. "B cell activating factor is an important cytokine for B cell activation and differentiation. In autoimmune diseases characterized by autoantibody production, BAFF is usually highly expressed and is a target for therapeutic intervention" [24,25]. "Children with KD also showed high levels of BAFF and returned to normal after IVIG treatment" [26,27]. "The increase in BAFF may be related to the increase in the percentage of antibody-secreting cells in acute KD, which decreased after treatment" [28].

2. "In KD patients, IgA producing plasma cells infiltrate the coronary wall. The frequency of IgA plasma cells is also higher in the upper respiratory tract of KD patients. A recent study has suggested that IgA response in KD may be

an important factor in vascular injury. LCWE mouse model is an example of PAMP-induced coronary arteritis, and LCWE-induced KD model was used to demonstrate that adaptive immune response is involved in vascular injury in KD patients. Foreign scholars have proved that vascular inflammation is related to the increase of serum IgA level and IgA+B cells in lymphoid tissue" [29]. "Deposition of the IgA-C3 immune complex was also noted in the heart and aorta of LCWE-treated mice. In this model, vascular inflammation and damage were IgA dependent, because IgA deficient mice did not develop coronary vasculitis" [29].

4.2 CD8+ T Cells

"LCWE mouse model experiments suggest that CD8+T cells promote vascular inflammation and injury" [30]. The coronary arteries of LCWE-treated mice showed infiltration of CD4+ and CD8+T cells as well as regulatory T cells, dendritic cells, neutrophils, and macrophages. Elimination of CD8+T cells with monoclonal antibody significantly alleviated vasculitis and myocarditis in LCWE-treated mice. The clearance of CD4+T cells and other cells did not have the same effect [30], indicating that CD8+T cells played a role in KD vasculitis injury.

5. CONCLUSION

KD inflammation mainly involves innate immune inflammatory response and adaptive immune inflammatory response, including the involvement of inflammatory cells, inflammatory factors and inflammatory bodies, among which inflammatory bodies play an important role. Early detection of the expression of NLRP3 inflammatory bodies in peripheral blood and intervention therapy may provide new ideas for the diagnosis and treatment of KD. However, how specific inflammatory bodies cause damage to blood vessels in KD patients still needs further study. By exploring the specific pathogenesis of inflammation in Kawasaki disease, we hope to provide new guidance for clinical diagnosis and treatment, so as to reduce the incidence of Kawasaki disease, especially the coronary artery injury.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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