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EDITORIAL COMMENTARY

Role of Inflammasomes in Kawasaki Disease

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Kawasaki disease (KD) is an acute systemic vasculitis with a potential to cause coronary artery lesions (CAL) [1]. Various environmental and genetic factors have been implicated in causation. Intravenous immunoglobulin (IVIg) therapy is the standard of care. Family-based studies and genome-wide association studies have identified several genetic factors that have been associated with susceptibility to KD, resistance to IVIg therapy, and the development of CAL [2].

Histopathology of coronary vessels in the acute phase shows neutrophilic infiltration with destruction of media and intima [1]. Cytotoxic T cells, plasma cells, monocytes, and macrophages replace neutrophils in the subacute phase. Mouse models and transcriptome analysis of patients in the acute phase of KD have suggested a role of innate immune cells and inflammasome activation [1].

Inflammasomes are cytoplasmic multiprotein complexes, which act in a cascade fashion after getting signals from pattern recognition receptors [3]. NLRP3 is one such inflammasome, found predominantly in macrophages. At rest, levels of NLRP3 and pro-IL1β are undetectable. Activation of the inflammasome (Fig. 1) requires two signals [4]. The first signal (priming) results in activation of NFκB, which causes increased levels of NLRP3 and pro-IL1β. The second signal (activation) results in the assembly of inflammasome proteins, leading to the activation of caspase-1. The end result is the release of inflammatory cytokines and inflammatory cell death by formation of pores in cell membrane.

ITPKC is a gene that encodes for inositol triphosphate 3-kinase. This enzyme converts inositol triphosphate (IP3) to inositol tetraphosphate and terminates the propagation of the Ca^{2+} signalling pathway. Alphonse et al. have shown that decreased functioning of inositol triphosphate 3-kinase results in an accumulation of IP3 [5]. Increased IP3 leads to increased intracellular Ca^{2+} and activation of NLRP3 inflammasome [5]. Increased IP3 also results in the activation of T cells through Ca^{2+}/NFAT (nuclear factor of activated T cells) pathway [5].

DNA methylation is a type of epigenetic modification that can change the activity of a gene without causing a mutation in the gene itself. Such modification in the promoter region has been found to result in decreased gene expression. If this modification occurs in the promoter region of *ITPKC*, it can result in decreased activity of the gene and could potentially cause inflammation by activation of the NLRP3 inflammasome and T cells.

In this issue of the Journal, Ji et al. have looked at ITPKC, NLRP3, and cytokines such as IL1β and IL18 in 25 children with acute KD [6]. They found that ITPKC and NLRP3 were down- and upregulated, respectively, in these children. IL18 levels were raised and correlated with inflammatory markers. IL1β levels were not significantly raised in children with KD compared with controls, but higher IL1β levels were seen in IVIg-resistant KD in their cohort. DNA methylation was observed in the promoter region of ITPKC in children with KD.

Even though one single mechanism such as activation of NLRP3 inflammasome may not be able to explain the complete pathophysiology of KD, such studies would definitely lead to the development of newer diagnostic markers and therapeutic targets in KD.

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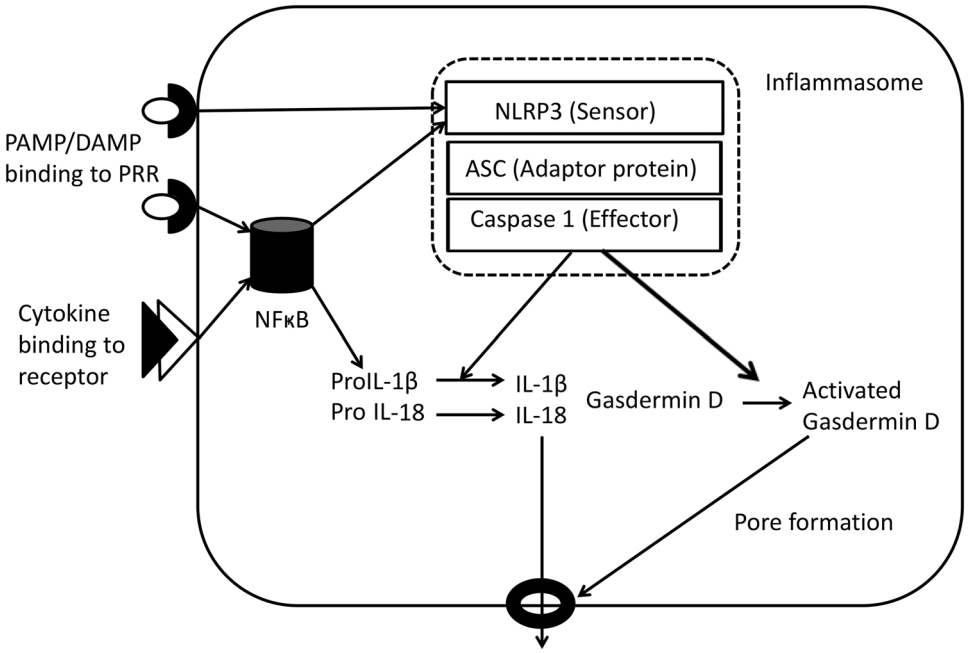

Fig. 1 NLRP3 inflammasome pathway (Activation of NLRP3 inflammasome pathway requires two signals: priming and activation. Binding of pathogen-associated molecular patterns (PAMP) or damage-associated molecular patterns (DAMP) to pattern-recognition receptors (PRR) results in activation of NFκB. NFκB is a transcription factor, which results in increased production of NLRP3 and pro-IL1β in the cell. This is called priming. Another signal results in the NLRP3 inflammasome assembly. This is called activation and leads to activation of caspase-1. Caspase-1 converts pro-IL1β and pro-IL18 to IL1β and IL18, respectively. It also results in programmed inflammatory cell death by forming pores in the cell membrane through gasdermin)

Declarations

Conflict of Interest None.

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