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Inflammasomes and Childhood Autoimmune Diseases: A Review of Current Knowledge

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Abstract
Inflammasomes are multiprotein complexes capable of sensing pathogen-associated molecular patterns (PAMPs), danger-associated molecular patterns (DAMPs), and cellular perturbations. Upon stimulation, the inflammasomes activate the production of the pro-inflammatory cytokines IL-1β and IL-18 and induce gasdermin D-mediated pyroptosis. Dysregulated inflammasome signaling could lead to hyperinflammation in response to environmental triggers, thus contributing to the pathogenesis of childhood autoimmune/autoinflammatory diseases. In this review, we group childhood rheumatic diseases into the autoinflammation to autoimmunity spectrum and discuss about the involvement of inflammasomes in disease mechanisms. Genetic mutations in inflammasome components cause monogenic autoinflammatory diseases, while inflammasome-related genetic variants have been implicated in polygenic childhood rheumatic diseases. We highlight the reported associations of inflammasome signaling-related genetic polymorphisms/protein levels with pediatric autoimmune disease susceptibility and disease course. Furthermore, we discuss about the use of IL-1 receptor antagonist as an adjunctive therapy in several childhood autoimmune diseases, including macrophage activation syndrome (MAS) and multisystem inflammatory syndrome in children (MIS-C) related to COVID-19. A comprehensive multi-cohort comparison on inflammasome gene expression profile in different pediatric rheumatic diseases is needed to identify patient subsets that might benefit from the adjunctive therapy of IL-1β inhibitors.

Keywords Inflammasome · Pathogen-associated molecular patterns · Autoinflammation · Autoimmunity · Pediatric rheumatic disease

Introduction

Dysregulated interactions between genes and environment have been suggested to result in human autoimmune diseases [1]. Inflammasomes are multi-protein complexes which play important roles in sensing pathogens and cellular perturbations, including pathogen-associated molecular patterns (PAMPs), danger-associated molecular patterns (DAMPs), and homeostasis-altering molecular processes (HAMPs) [2, 3]. Upon sensing of these molecular patterns/processes, the inflammasome complexes assemble and function to cleave the inactive IL-1 family cytokine precursors and Gasdermin D (GSDMD). The resulting active IL-1β, IL-18, and GSDMD N-terminal cleavage product (GSDMD-N) mediate inflammation and pyroptosis, a proinflammatory cell death [4]. The proinflammatory milieu can further enhance inflammasome activations and potentially perpetuate chronic inflammation in genetically susceptible individuals. Therefore, inflammasomes are at the center of genes and environment interactions, and dysregulation of inflammasome pathways could lead to autoinflammatory or autoimmune diseases.

Genetic variants in components of NOD-like receptor (NLR)-associated inflammasomes, such as NLRP1 and NLRP3, have been reported to be associated with

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susceptibility to autoimmune diseases in adults [2]. In children, mutations in inflammasome components are well-known causes of monogenic autoinflammatory diseases, including familial Mediterranean fever (FMF) and cryopyrin-associated periodic syndromes (CAPS). The onset of childhood rheumatic diseases occurs mainly before the age of 16. In some subtypes of juvenile idiopathic arthritis (JIAs), the onset ages are even younger, and disease manifestations can be more severe than adult patients in juvenile systemic lupus erythematosus (JSLE). Kawasaki disease (KD), the most common systemic vasculitis, is often diagnosed before 5 years old. The human immune system is shaped by numerous interactions of host genes with microbes (viral infections, commensal colonization) and disturbances in cellular homeostasis in childhood. In addition, innate immune immaturity in recognition of toll-like receptors (TLRs) and other pattern-recognition receptors (PRRs), which provide priming signals to inflammasome activations, have also been reported in neonates [5, 6]. Since inflammasomes are essential in sensing these environmental changes and capable of forming inflammation amplification loops, affecting T helper 1 (Th1) and T helper 17 (Th17) cell differentiations, it is conceivable that aberrant inflammasome signaling can contribute to childhood autoinflammatory/ autoimmune diseases.

Depending on the involvement of inflammasomes/innate immune responses and the presence of auto-reactive T cells or auto-antibodies in disease mechanisms, pediatric rheumatic diseases could be grouped into a spectrum of disorders with autoinflammatory properties at one end, and autoimmune pathogenesis at the other end. Understanding the roles of inflammasome dysregulations in spectrums of childhood-onset rheumatic diseases will shed light not only on the development of novel diagnostic markers but also on the application of IL-1β inhibitors as alternative treatment modalities.

Mechanisms of Inflammasome Activation in Childhood Rheumatic Diseases

The caspase-processing inflammasomes reported to be involved in childhood rheumatic diseases include NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3), NLRP1 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-1), AIM2 (absent in melanoma-2), NLRC4 (NLR Family CARD Domain Containing 4), and pyrin inflammasomes (Fig. 1).

Functional NLRP3 inflammasome forms after being primed by the first signal and activated by the second signal [7]. PAMPs, DAMPs, and S100 proteins (S100A8/A9, S100A12, which are released from activated monocytes and granulocytes) are sensed by TLRs (mainly TLR4) and activate the NF-kB pathway, enhancing the transcriptions of NLRP3 and precursors of IL-1β and IL-18. Second signals include potassium efflux, ROS (reactive oxygen species) production, lysosomal rupture, and mitochondrial damage [8]. NEK7 (NIMA-related kinase 7) has been reported to mediate NLRP3 activation downstream of potassium efflux, and NEK7-induced pyroptosis was suggested to play a role in IBD [9, 10]. FAMIN (LACC1/C13orf31)-dependent fatty acid oxidation regulates mitochondrial and NADPH oxidase-dependent ROS production, while stimulated calcium-sensing receptors produce IP3 (1,4,5-triphosphate), which mediates ER (endoplasmic reticulum) Ca^{2+} efflux and causes mitochondrial damage–related NLRP3 inflammasome activation [8, 11, 12]. The AIM2 inflammasome activates upon sensing cytosolic DNA (derived from bacteria or self) and could be primed by the first signal, such as type I interferons [13]. Furthermore, neuronal apoptosis inhibitory proteins (NAIPs) detect bacterial flagella or components of the type III secretion system (T3SS) and activate the NAIP/NLRC4 inflammasome complexes [14, 15].

Unlike the activation mechanisms of NLRP3/NLRC4/AIM2 inflammasomes, the NLRP1 inflammasome has been proposed to be regulated by the "functional degradation" model, while the "guard hypothesis" has been suggested to underly pyrin inflammasome activation [3, 16]. NLRP1 detects its own protein stability upon diverse pathogen-encoded activities, including cleavage by toxins and modification by bacterial ubiquitin ligase [17]. The bacterial peptidoglycan component muramyl dipeptide (MDP) has been reported to stimulate NLRP1 inflammasome [18]. Pyrin guards the activity of RhoA GTPase: processes leading to RhoA GTPase inactivation and dysregulation in the actin polymerization pathway activate pyrin inflammasome [19]. Pathogens are known to modulate this pathway to suppress host phagocytosis, and RhoA inactivation stops the serine/threonine-protein kinase PKN-mediated phosphorylation-dependent pyrin inhibition, thus promoting pyrin inflammasome formation [19].

Genetic mutations in molecules of pyrin and NLRP3 inflammasome activation pathways have been reported in familial autoinflammatory diseases [20]. Dysregulations in the priming or activation of NLRP3 inflammasome have been implicated in SJIA, JSLE and Kawasaki disease, and various local inflammations of childhood rheumatic diseases [21–23]. In addition, NLRC4 mutation is associated with MAS and enterocolitis, while NLRP1 genetic variant has been linked to skin autoimmunity [24]. The associations of different inflammasome dysregulations with disease susceptibility, disease activity, and treatment responses in specific childhood rheumatic diseases are further reviewed in the following sections.

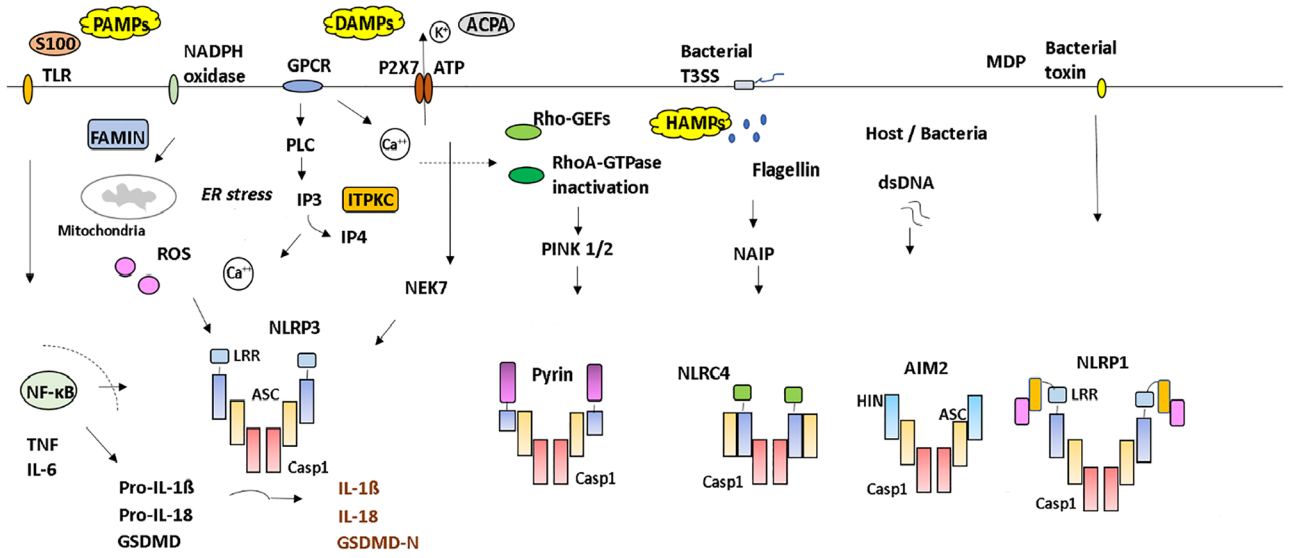

Fig. 1 Mechanisms of inflammasome activations in childhood rheumatic diseases. NLRP3, Pyrin, NLRC4, AIM2, and NLRP1 inflammasomes are multiprotein complexes, which activate caspase-1 upon stimulations, leading to the production of active proinflammatory cytokines IL-1β and IL-18, and cleavage of Gasdermin-D (GSDMD). The N-terminal domain of GSDMD (GSDMD-N) binds to membrane lipids and induces pyroptosis, an inflammatory cell death. Inflammasomes consist of sensors and several interacting domains, including caspase recruitment domains (CARDs). LRR leucine rich repeat; HIN hematopoietic expression, interferon-inducible nature, and nuclear localization domain. The NLRP3 and AIM2 inflammasomes can be primed by a first signal induced by PAMPs. S100 proteins can stimulate toll-like receptor ligands (TLRs), activating the NF-κB pathway, priming the NLRP3 inflammasome. Systemic and local S100 proteins are elevated in a variety of pediatric rheumatic diseases. DAMPs can activate the NLRP3 inflammasome via pathways involving potassium efflux and increased intracellular calcium. ACPA anti-citrullinated peptide antibody, GPCR G protein-coupled receptors. FAMIN-dependent fatty acid oxidation regulates mitochondrial and NADPH oxidase-dependent ROS production and ITPKC (inositol-trisphosphate 3-kinase C) phosphorylates IP3. Dysregulation of FMIN, ITPKC, and NEK7 (NIMA-related kinase 7) leads to NLRP3 inflammasome activation and inflammatory diseases. Pyrin inflammasome can be activated by HAMPs inactivating RhoA GTPase. PINK: PTEN-induced kinase. Genetic variants in the pyrin inflammasome activation pathway are implicated in monogenic autoinflammatory diseases and IgA vasculitis. Neuronal apoptosis inhibitory proteins (NAIPs) detect bacterial flagella or components of the type III secretion system (T3SS) and activate the NAIP/NLRC4 inflammasome complex. AIM2 detects cytosolic double-stranded DNAs (dsDNAs). NLRP1 detects its own protein stability upon diverse pathogen-encoded activities, including cleavage by toxins and modification by bacterial ubiquitin ligase. MDP: muramyl dipeptide

Monogenic Autoinflammatory Diseases

Monogenic autoinflammatory diseases (AIDs) are a group of disorders caused by mutations in genes controlling the inflammatory responses to environmental triggers (Table 1). In the last years, extensive genetic characterization and phenotypic classification have been done, which revealed new insights in the inflammasome regulation mechanisms [25, 26]. Mutations in *MEFV* (encoding pyrin) have been described in FMF and PAAND (Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis) [20, 27]. Theses mutations lead to poor pyrin affinity toward PKN1/PKN2, or cause defective PKN phosphorylation of pyrin, resulting in constitutive pyrin inflammasome activation [19]. Similarly, the mutation in *MVK* (encoding mevalonate kinase) in hyper IgD syndrome (HIDS) causes decreased production of geranylgeranyl pyrophosphate and RhoA inactivation, thus activating pyrin inflammasome [28]. In addition, proline serine threonine phosphatase-interacting protein 1 (PSTPIP1) and actin-interacting protein WD repeat–containing protein 1 (WDR1) also regulate pyrin inflammasome; mutations in genes encoding the two proteins have been reported in pyogenic arthritis, pyoderma gangrenosum, acne (PAPA) and autoinflammatory periodic fever, immunodeficiency, and thrombocytopenia (PFIT), respectively [19, 29].

CAPS, or cryopyrinopathies, are AIDs with gain of function mutations in NLRP3 [20]. The three clinical disorders within CAPS (familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), neonatal-onset multisystem inflammatory disease/chronic infantile neurological, cutaneous, and articular syndrome (NOMID/CINCA)) varied in disease manifestations and severities. Furthermore, other AIDs with mutations in genes involving the priming and activation signals for NLRP3 inflammasome were also reported [30, 31]. The loss of function mutation in *TNFAIP3*, an inhibitor of NF-kB activation, in HA20 increased priming of NLRP3 inflammasome [30]. The hypermorphic *PLCG2* mutation in the auto-inflammation and phospholipase Cγ2 (PLCγ2)-associated antibody deficiency and immune dysregulation (APLAID) syndrome

Table 1 Mutations in monogenic autoinflammatory diseases

Disease	Gene	Mutated protein	Functional impact on inflammasome	Ref
FMF	MEFV	pyrin	Poor pyrin affinity toward PKN, and pyrin inflammasome activation	[20]
PAAND	MEFV	pyrin	Defective PKN phosphorylation of pyrin	[27]
HIDS	MVK	MVK	Partial deficiency of MVK results in reduced geranylgeranyl pyrophosphate, reduced Rho A activation, and pyrin inflammasome activation	[28]
PAPA	PSTPIP1	pstpip1	Pyrin inflammasome dysregulation	[19]
PFIT	WDR1	wdr1	Hypomorphic mutation results in impaired F-actin depolymerization and pyrin inflammasome activation	[29]
CAPS	NLRP3	nlrp3	Gain of function in nlrp3 inflammasome	[20]
Majeed	LPIN2	lipin-2	Loss of function in lipin-2 results in increased potassium efflux and nlrp3 inflammasome activation	[32]
APLAID	PLCG2	$PLC_{\gamma}2$	Hypermorphic mutation results in increased PLCγ2 activity, ER release of calcium, and nlrp3 inflammasome activation	[31]
HA20	TNFAIP3	A20	Loss of function mutation results in impaired ubiquitination of NEMO, TRAF6, and RIPK1 proteins, and nlrp3 inflammasome activation	[30]
MAS/ Enterocolitis	NLRC4	nlrc4	Gain of function in nlrc4 inflammasome	[24, 33]
NAIAD	NLRP1	nlrp1	Gain of function in nlrp1 inflammasome	[34]
MSPC/ FKLC	NLRP1	nlrp1	Gain of function in nlrp1 inflammasome	[35]

increases Ca^{2+} release from ER, and the loss of function mutation in *LPIN2* in the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome) leads to increased potassium efflux, both activating the NLRP3 inflammasome [31, 32]. Mutations in components of other inflammasomes, such as *NLRC4* and *NLRP1*, were also implicated in AIDs like macrophage activation syndrome (MAS)/enterocolitis and NLRP1-associated autoinflammation with arthritis and dyskeratosis (NAIAD), respectively [24, 33, 34]. Interestingly, NAIAD patients were reported to show autoimmune features as well [34]. *NLRP1* mutation has also been detected in a syndrome of skin inflammation and epidermal hyperplasia [35].

Treatment for monogenic AIDs includes colchicine and IL-1 inhibitors. Since colchicine is a known RhoA activator, which leads to pyrin phosphorylation and inhibition, it is conceivable that colchicine showed favorable efficacy in treating AIDs with pyrin inflammasome hyperactivation, such as FMF [19].

Dysregulation of Inflammasome in Subtypes of JIA

Juvenile idiopathic arthritis (JIA) is the most common childhood chronic rheumatic disease consisting of different clinical subtypes and heterogeneous immune mechanisms. Enthesitis-related JIA (ERA) and psoriatic JIA can also be grouped into the juvenile spondyloarthritis (JSpA) category. SJIA represents 4 ~ 17% of all JIA cases, and in addition to arthritis, SJIA patients show signs of systemic inflammation, such as spiking fever, rash, lymph node enlargement, and hepato-splenomegaly [36]. Despite the clinical similarities between SJIA and AIDs, mutations in *MEFV* or *NLRP3* have not been detected in SJIA. Until now, only genetic mutations in *LACC1* causing increased ROS production and NLRP3 inflammasome activation have been linked to symptoms of SJIA (Table 2) [11]. MAS, a condition most frequently associated with SJIA, could be linked to NLRC4 inflammasome activation and will be discussed in detail in the next section [33, 36]. Gene expression studies on SJIA peripheral blood cells revealed IL-6 and TLR/IL1R pathway activations, and upregulations of *AIM2*, *NLRC4*, and *IL18RAP* were observed in neutrophils from children with both active and inactive SJIA (Table 2) [37, 38]. Furthermore, S100 proteins (S100A8/A9, S100A12), which are known to prime NLRP3 inflammasome activation, have been reported to be elevated in SJIA serum and are associated with disease activity and treatment failure (Table 3) [39–41]. The end products of inflammasomes like IL-1β and IL-18 were also significantly higher in SJIA plasma as compared with healthy controls (Table 3) [21]. While the recombinant IL-1 receptor antagonist (IL-1Ra) has achieved satisfactory therapeutic responses in new-onset SJIA, it is shown that persistently increased IL-18 level could be a hint for unsuccessful therapy withdrawal [42, 43].

Although in non-systemic type JIA, circulatory S100A8/A9 is not as high as SJIA, a high baseline level has been suggested to predict response to the standard systemic therapy

Table 2 Risk allele and gene dysregulation involving inflammasomes in pediatric rheumatic diseases

Disease	Subgroup	Genomic variant	Gene expression	Potential functional impact on inflammasome	Ref
JIA	Systemic JIA (sJIA, Leprosy, Crohn's disease)	LACC1 p.C284R, p. I254V		Increased ROS production results in NLRP3 inflammasome activation	[11]
	Systemic JIA		Upregulation of AIM2, NLRC4, IL18RAP	Activation of AIM2 and NLRC4 inflammasomes	[38]
	Oligo-/poly-articular JIA	NLRP3 rs4353135	Upregulation of NLRP3	Activation of NLRP3 inflammasome	[46]
JSpA	JSpA	TLR4 rs4986791		Increased priming for NLRP3 inflammasome activation	[49]
	JSpA		Upregulation of TLR4 and NLRP3	Activation of NLRP3 inflammasome	[50]
	Psoriatic JIA	MEFV rs224204		Change in MEFV transcript variant	[48]
	Psoriatic JIA	NLRP3 rs3806265		Activation of NLRP3 inflammasome	[48]
JSLE	JSLE	IL1B rs1143629		Increased IL-1ß production	[70]
	JSLE		Reduced AIM2 DNA methylation	upregulation of AIM2 and AIM2 inflammasome activation	[72]
	JSLE male	TNFAIP3 rs2230926		increased NFkB signaling and priming for NLRP3 inflammasome activation	[71]
	JSLE male		Upregulation of AIM2	Activation of AIM2 inflammasome	[22]
	JSLE female		Upregulation of NLRP3	Activation of NLRP3 inflammasome	[22]
JIMM	JDM	TNF rs1800629	Upregulation of TNF-alpha	Increased priming for NLRP3 inflammasome activation	[88]
	JDM	IL1B rs1143634		Increased IL-1ß production	[88]
KD		ITPKC rs28493229	Downregulation of ITPKC	Increased intracellular calcium results in NLRP3 inflammasome activation	[98, 99]
HSP		MEFV variants in exon 10		Activation of pyrin inflammasome	[94]

Table 3 Protein markers related to inflammasome activation and association with disease course

Disease	Protein marker	Association with disease course	Ref
Systemic JIA	S100A8/A9	Predicts subclinical disease activity and relapse	[39–41]
	S100A12	Disease activity	[40]
	IL-18	Disease activity, predicts MAS occurrence	[64, 128]
	IL-1ß	IL-1ß blockade has been suggested for treatment	[42, 43]
Oligo-/poly-articular JIA	S100 proteins	Joint inflammation	[129]
JIA (non-systemic)	S100A8/A9	Predicts response to anti-TNF treatment and flare at etanercept discontinuation	[45]
JIA (any subtype)	S100A8/A9	Predicts response to MTX	[44]
ERA	S100A8/A9 (fecal)	Correlates with children who needed longer NSAIDs treatment	[53, 54]
IBD	S100A8/A9 (fecal)		[52]
JSLE	IL-18		[73]
JDM	S100A8/A9	Disease activity	[92]
	TNF-α	Disease activity	[91]
KD	IL-1ß	IL-1ß blockade has been suggested for IVIG-resistant subjects	[99, 102]

with methotrexate (MTX) [44]. In addition, high levels of baseline S100A8/A9 in non-systemic JIA were reported to correlate with good response to anti-TNF treatment, whereas elevated S100A8/A9 levels at discontinuation of etanercept were found to be associated with higher chance of disease flare-up [45]. Our previous study on Taiwanese oligoarticular/polyarticular JIAs revealed the association of *NLRP3* genetic variant rs4353135 G allele with increased disease risk [46]. The G allele carriers were found to have increased macrophage IL-1β production and Th17 response [46]. The G/G genotype oligoarticular/polyarticular JIA patients were associated with the need for treatment with the tumor necrosis factor (TNF) inhibitor [46]. In addition, anti-citrullinated protein antibodies (ACPAs) are present in a small percentage of JIA patients (especially in the RF (+) polyarticular subtype) [36]. ACPAs have been shown to activate the Akt/NF-κB signaling pathway, resulting in priming [47]. Moreover, ACPAs were reported to activate pannexin channels, hence increasing ATP release and NLRP3 inflammasome activation [47].

As for JSpA, associations of inflammasome genetic variants, *MEFV* rs224204 and NLRP3 rs3806265, with susceptibility to psoriatic JIA have been reported [48]. Furthermore, a TLR4 polymorphism, the Thr399Ile SNP, has been shown to have increased frequency in a small Croatian JSpA cohort [49]. Lamot L et al. performed microarray gene expression studies on whole blood derived from children with JSpA and revealed *TLR4* and *NLRP3* upregulations in untreated patients [50]. Like other non-systemic JIA, S100A8/A9 protein level was high in the synovial sub-lining layer of the inflamed joints in psoriatic arthritis [51]. Fecal S100A8/A9 (calprotectin) is a well-known marker for inflammatory bowel disease (IBD) and has been suggested to aid in the determination of further endoscopy for children with suspected IBD [52]. Elevated levels of fecal calprotectin have also been observed in the ERA subtype of JIA [53]. Furthermore, gastrointestinal endoscopies have been recommended in JIA patients who had high fecal calprotectin value when cutting down exposure to NSAIDs [54].

Macrophage Activation Syndrome in SJIA

Macrophage activation syndrome (MAS) is an overwhelming inflammation characterized by dysfunction of perforin-mediated natural killer (NK) cell/CD8 + T cell cytotoxicity and cytokine storm [55–57]. MAS occurs most frequently in SJIA: about 10 ~ 30% of SJIA patients are complicated with MAS [58]. Occasionally, MAS were also reported in cases of juvenile SLE (JSLE) and Kawasaki disease (KD) [57, 59, 60]. Symptoms and signs of MAS include high fever, hepatosplenomegaly, hyperferritinemia, pancytopenia, consumptive coagulopathy, elevated liver enzymes, and multi-organ dysfunction/failure [57, 61]. Mutation in nucleotide-biding domain of NLRC4 has been discovered in patients with early onset fever flares and recurrent MAS, and the same mutation has been reported to elevate systemic IL-18 levels derived from intestinal epithelium in mice [33, 62].

Furthermore, both IL-18 and IL-1β produced by NLRP3/NLRC4 inflammasomes were suggested to play important roles in MAS associated with rheumatic diseases [62, 63]. SJIA patients having higher amounts of serum IL-18 were more likely to develop MAS, and their IL-18 levels further increased at the time of MAS [64, 65]. IL-18 primed NK cells showed higher cytotoxic potential in normal circumstances [66]. However, it has been reported that subpopulations of SJIA complicated with MAS carried heterozygous

protein-altering variants affecting cytotoxic activities found in patients with familial HLH, and prolonged IL-18 and IL-6 stimulation in SJIA could also lead to NK cell dysfunction [56, 67]. It is hypothesized that upon infection, the most common trigger of MAS in SJIA, IFN-γ level increases, which further enhances macrophage IL-18 production and result in MAS [63] (Fig. 2a). Higher doses of anakinra (anti-IL-1β) has shown efficacy in treating SJIA-associated MAS [63]. Yet, MAS still could occur in SJIA cases well-controlled by biologics, including tocilizumab (anti-IL-6), anakinra, and canalimumab (anti- IL-1β) [63, 68]. Research needs to be done to test the effects of inflammasome/IL-18 inhibitors on treating MAS associated with pediatric rheumatic diseases.

Dysregulation of Inflammasome Genes in JSLE

Although SLE is a prototypical autoimmune disease, several genetic variants involving NLRP3 inflammasome activation have been reported to be associated with juvenile SLE (JSLE) (Table 2) [69]. Since *NLRP1* polymorphism has been implicated in adult SLE, Pontillo A et al. had analyzed the difference in variant allele frequencies of *NLRP1*, *NLRP3*, *CARD8*, and *IL1B* between JSLE patients and healthy controls [70]. They found that the *IL1B* rs1143629 polymorphism showed significant association with JSLE [70]. *TNFAIP3* rs2230926 variant was found to be associated with JSLE in Japanese males [71]. In our previous study, gender differences in SLE inflammasome activations were also observed [22]. We had included childhood-onset SLE in the Taiwanese study cohort, and *NLRP3* overexpression in female macrophages, together with an upregulation of *AIM2* in male macrophages, were noted [22]. At the epigenetic level, reduced *AIM2* DNA methylation causing increased *AIM2* expression has been reported in SLE patients as compared with their healthy siblings [72]. At the protein level, increased serum IL-18 level has been noted in juvenile SLE and has been suggested to correlate with active renal disease in adult SLE patients [73, 74]. The association of IL-1ß with JSLE, however, remains unclear.

Interestingly, the complement protein C1q is known to be important in clearing apoptotic cells, and in preventing excessive inflammasome-mediated inflammation [75]. C1q has been reported to inhibit procaspase-1 and pro-IL-1β cleavage, and to promote the expression of negative regulators of the inflammasome [75]. Autoantibodies against C1q has been shown to be associated with active lupus nephritis in both adult and childhood SLE patients [76, 77]. It is conceivable that neutralization of C1q by anti-C1q auto-antibodies, together with increased consumption of C1q in SLE, might weaken the prevention of potential hyper-inflammation, and lead to enhanced macrophage inflammasome activation upon other triggers (Fig. 2b).

One of the known triggers of NLRP3 inflammasome activation in SLE is neutrophil extracellular trap (NET)-associated proteins [78]. For example, LL-37 (cathelicidin) activates NLRP3 inflammasome via P2X7

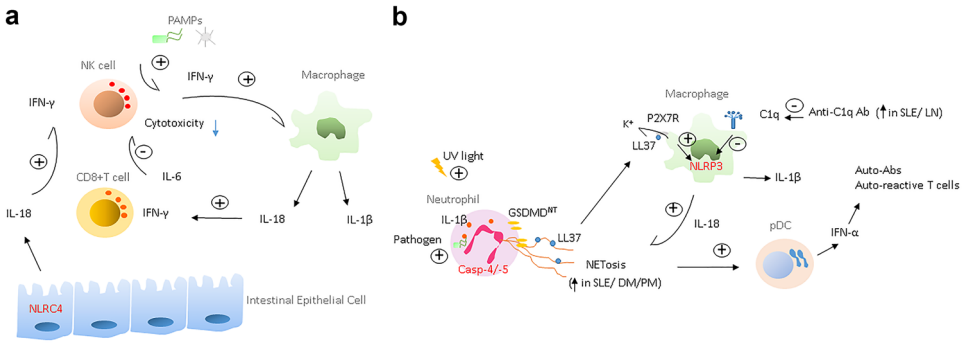

Fig. 2 Involvement of inflammasomes in MAS and JSLE. **a** Model of hyper-inflammation in MAS: IL-18 produced by NLRC4 inflammasome enhances T cell/ NK cell IFN-Y production upon pathogen trigger, and then activates inflammasome in the macrophage. Prolonged IL-6 and IL-18 secretion in active rheumatic diseases such as JIA could lead to NK cell dysfunction, impaired cytotoxicity, and increased levels of inflammation. **b** Model of hyper-inflammation in JSLE: NETosis is increased in lupus neutrophils/ low-density granulocytes. NET-associated proteins (i.e., LL37) activate NLRP3 inflammasome in lupus macrophages, resulting in increased IL-18 production, which further stimulates NET formation. NETosis via caspase 4/5 non-canonical inflammasome activation and GSDMD-dependent mechanisms form pores on neutrophil plasma membranes. NETosis facilitates the generation of autoantibodies, and induction of type I interferons in pDCs. C1q prevents excessive inflammation via inhibition of pro-caspase-1 and pro-IL-1ß cleavage, and via promoting the expression of negative regulators of inflammasome. In lupus patients, C1q could be neutralized by anti-C1q auto-antibodies. LN lupus nephritis, DM dermatomyositis, PM polymyositis

receptor-mediated potassium efflux [79, 80]. It has been reported that in lupus macrophages, inflammasome activation triggered by NET/ LL-37 is augmented [78]. The inflammasome-derived IL-18 further stimulates NETosis, a special form of cell death in neutrophils releasing decondensed chromatin, granules, and bactericidal components (NETs) [81]. In addition, the non-canonical (caspase-4/11) inflammasome could mediate GSDMD-dependent NET formation in neutrophils [82]. Increased NETosis and impaired NET degradation have been found in systemic autoimmune diseases, including SLE, dermatomyositis, and polymyositis [83–85]. Furthermore, both pathogens and ultraviolet light, a frequent trigger of autoimmune diseases, could enhance NET formation [82, 86]. In a review written by Giaglis S et al., increased NET formation was suggested to be a biomarker for monitoring disease activity in JSLE [83]. These findings implicate essential roles of cross-talks between inflammasome activation and NETosis in JSLE pathogenesis. It is proposed that enhanced lupus macrophage NLRP3 inflammasome activation induces IL-18, which forms a feed-forward loop with neutrophil NETosis, thus stimulating plasmacytoid dendritic cell (pDC) to produce IFN-α and augment the formation of auto-antibodies/ auto-reactive T cells [83] (Fig. 2b).

Dysregulation of Inflammasome Genes in JDM

Juvenile idiopathic inflammatory myopathies (JIMM) are classified as a group of autoimmune diseases affecting muscles, and to a lesser extent, skin [87]. The group includes juvenile dermatomyositis (JDM), juvenile polymyositis (JPM), immune-mediated necrotizing myositis, and myositis associated with another connective tissue disease. JDM is the most commonly occurring JIMM, and compared with the adult counterpart, JDM patients are more likely to develop calcinosis, have different pattern of myositis-specific autoantibodies, and are not associated with malignancy [87]. In a research article, Mamyrova G et al. studied the TNF-alpha and IL-1 cytokine polymorphisms in 221 Caucasian JDM patients and found that TNF-alpha − 308A is a risk factor for JDM and the development of calcinosis (TNF-alpha − 308AA genotype) [88]. Furthermore, IL-1beta + 3953T was also reported as a JDM susceptibility allele [88]. Although the authors did not find associations of TNF or IL-1 genetic polymorphisms with the JDM disease course, it has been suggested by others that TNF alpha-308A was associated with prolonged JDM symptoms requiring more than 36 months of immunosuppressive therapy and a more severe disease [89]. Increased IL-1 receptor expression has been observed in muscle biopsies of adult dermatomyositis (DM) and polymyositis (PM) patients [90]. In mixed JDM and DM cohorts, circulating TNF-alpha level has been shown to be moderately correlated with disease activity [91]. Of note, the serum TLR4 ligand S100A8/A9 level was found to be associated with global and muscle activities of JDM [92]. Therefore, priming of inflammasomes might be a potential disease mechanism in JDM.

Inflammasomes in Childhood Systemic Vasculitis

Pediatric vasculitis is classified according to the size of the affected vessels and the presence or absence of granuloma. Among childhood primary vasculitis, Henoch Schönlein purpura (HSP/IgA vasculitis) and Kawasaki disease (KD) are the most common [93]. It is reported that FMF might predispose a child to HSP, and HSP carriers of *MEFV* gene variants in exon 10 are more likely to present with abdominal pain and intussusception (Table 2) [94]. Furthermore, various microbes, such as *Group A streptococcus*, *Staphylococcus aureus*, influenza virus, adenovirus, parvovirus, and mycoplasma have been suggested as triggers for HSP [93]. Both *Group A streptococcus* M1 protein and parvovirus B19 nonstructural protein-1 (NS1) have been reported to upregulate *NLRP3* expression [95, 96]. Whether activation of pyrin or NLRP3 inflammasome plays a role in HSP pathogenesis requires further investigations.

KD is a multi-system vasculitis that frequently targets the coronary arteries in young children. It is hypothesized that infectious or other environmental triggers contribute to KD and disease severity in genetically susceptible children [97]. Global gene expression profiling in blood of acute KD patients revealed a prominent innate immune signature, including upregulation in genes of the IL-1 signaling pathway [23]. In addition, genetic variant of inositol 1,4,5-triphosphate kinase C (*ITPKC*) has been shown to confer susceptibility to KD and related coronary artery lesions (Table 2) [98]. It is proposed that upon stimulation, children with the *ITPKC* rs28493229 risk genotype had lower ITPKC levels, resulting in defective phosphorylation of IP3, increased calcium release from intracellular stores, and subsequent NLRP3 inflammasome activation [99]. Alphonse MP et al. used Itpkc-deficient mice in a disease model and showed compatible cellular and clinical findings with KD children [99]. The same authors also genotyped a KD cohort and found *ITPKC* rs28493229 CC genotype to be associated with higher circulating IL-1ß and IL-18 in acute phase, and with non-responsiveness to IVIG therapy (Table 3) [99]. Based on the inflammasome activation mechanism in KD pathogenesis, clinical trials

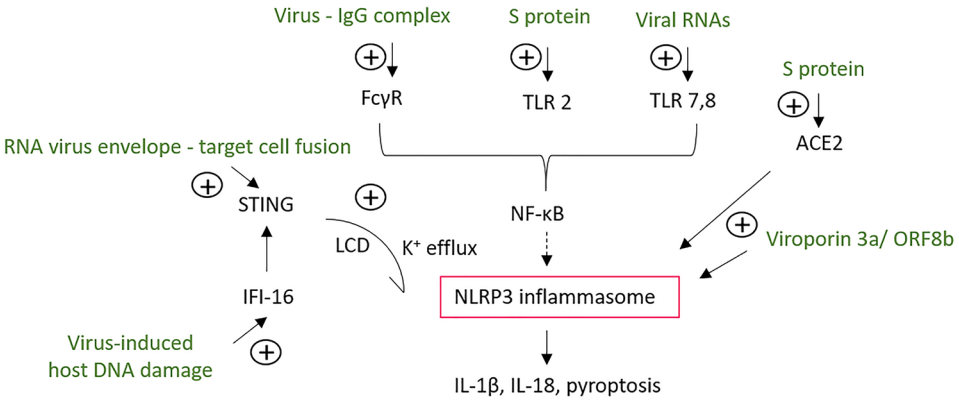

Fig. 3 NLRP3 inflammasome activation in COVID-19. Components of SARS-CoV-2 can activate NLRP3 inflammasome directly (Viroporin 3a and ORF8b) or indirectly. S protein: spike protein; LCD: lysosomal cell death

using anakinra, a recombinant human IL-1R1 antagonist, to treat KD have been conducted [100, 101]. Anakinra has been shown to be effective as an adjunctive therapy in controlling KD [102].

Inflammasome Activation in COVID-19 and MIS-C

This year, the coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a widespread global health threat. Most infected adults showed mild symptoms, while a subpopulation of patients progressed to severe COVID-19, including acute respiratory distress syndrome (ARDS), and multi-organ failure [103]. Dysregulation of NLRP3 inflammasome, together with increased frequency of activated granulocytes and cytokine storm, were implicated in the pathogenesis of severe COVID-19 [104–107].

Several components of SARS-CoV-2 could activate the NLRP3 inflammasome (Fig. 3). While the viral spike (S) protein could stimulate TLR2, the viral RNAs could stimulate TLR7 and TLR8, leading to NF-κB activation and priming of NLRP3 inflammasome [108, 109]. The viral antigen-antibody complex has been reported to stimulate the activating Fc gamma receptor (Fc_YR), which also activates NF-κB via phospholipase C gamma (PLC_Y) and protein kinase C (PKC) pathways [110, 111]. Furthermore, the S protein has been proposed to bind to the SARS-CoV-2 viral entry receptor, angiotensin-converting enzyme 2 (ACE2), resulting in NLRP3 inflammasome activation [112]. Importantly, the SARS-CoV-2 viral proteins Viroporin 3a and ORF8b were suggested to directly activate NLRP3, and genetic diversification on these viral proteins was associated with differential severity of clinical phenotypes [107, 113, 114]. In addition, it has been reported that both viral envelope-target cell fusion product and virus-induced host cell damage could stimulate stimulator of interferon genes (STING), which further activates the NLRP3

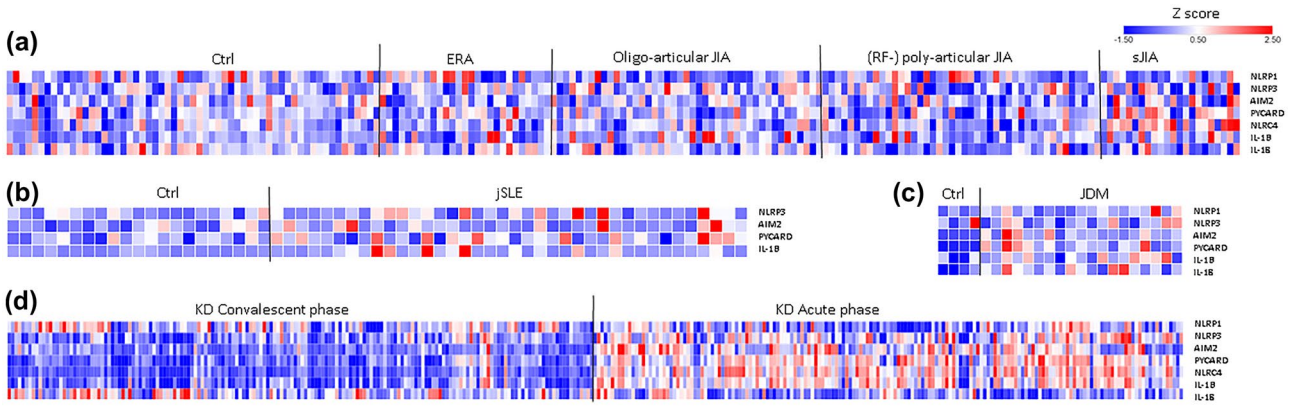

Fig. 4 Inflammasome gene expression patterns in childhood autoimmune diseases. Transcriptome data of the following cohorts were downloaded from the Gene Expression Omnibus: **a** GSE13501, JIA blood; **b** GSE8650, JSLE blood; **c** GSE11971, JDM muscle; **d** GSE63881, KD blood. Heatmap analysis was performed using GENE-E (http://www.broadinstitute.org/cancer/software/GENE-E). The expression values of genes in the inflammasome pathways are shown in *z* scores [(each value- mean value)/standard deviation]; colors represent the level of *z* scores as explained by the scale bar at the upper right corner. Each column represents one sample, while each row shows the expression levels (*z* score) of one gene. Ctrl control

inflammasome via lysosomal cell death (LCD) and associated potassium efflux [115, 116].

Children were rarely diagnosed with COVID-19 and usually showed milder symptoms than adult patients when infected [117]. Although pediatric cases of severe pulmonary complications were infrequent, a Kawasaki-like disease named multisystem inflammatory syndrome in children (MIS-C) related to COVID-19 has emerged in Europe and the USA since late April, following the peak of the pandemic [118–120]. MIS-C is reported as a post-infectious hyperinflammatory syndrome, which shares similarities with KD, toxic shock syndrome, and MAS [121]. Compared with KD, children of MIS-C were older, had gastrointestinal symptoms, elevated markers for myocardial damage, elevated ferritin, and were more frequently associated with shock [121]. Similar to KD and COVID-19-related ARDS in adults, there were evidence of inflammasome hyper-activation in MIS-C. Increased levels of both IL-6 and IL-18 were found in MIS-C [121–123]. Furthermore, treatment of MIS-C frequently required IVIG with adjuvant high dose steroid, and in some cases, the IL-1 receptor antagonist, anakinra [121].

Of note, while KD is a prevalent disease in East Asia, MIS-C were reported exclusively in other parts of the world [121]. The development of MIS-C could be the result of aberrant host-pathogen interactions. We propose that viral strains with specific ORF8 mutations might be able to induce higher levels of NLRP3 and might result in MIS-C in genetically susceptible children. Genetic polymorphisms associated with KD, such as variants in *FCGR2A*, *PELI1*, and *ITPKC*, could affect NF-κB signaling and NLRP3 inflammasome activation [99, 124–127]. It remains to be understood whether these genetic variants also play a role in the susceptibility to MIS-C associated with COVID-19.

Conclusion

Taken together, evidence of inflammasome activations could be found in polygenic childhood autoimmune diseases. Of these polygenic diseases, SJIA and KD were shown to have the strongest IL-1 signaling signature, and anti-IL-1 receptor therapy has been suggested in subgroups of these patients. We have reviewed hints of inflammasome activation at the genetic and protein levels of pathogenesis in other childhood autoimmune diseases. It is known that the activation of inflammasomes could lead to Th1 and Th17 differentiation, thus shaping the adaptive immune response toward the formation of autoimmune/chronic inflammatory diseases. However, due to the small cohort size and high degree of clinical heterogeneity encountered in most pediatric rheumatic studies, it is hard to draw conclusions on the roles of inflammasome in the prototypical childhood autoimmune diseases. A comprehensive multi-cohort comparison on inflammasome gene expression profile in different pediatric rheumatic diseases is needed to identify patient subsets that might benefit from the adjunctive therapy of IL-1β inhibitors.

Using a list of genes related to inflammasome activations (*NLRP1*, *NLRP3*, *AIM2*, *PYCARD (ASC)*, *NLRC4*, *IL-1β*, *IL-18*), we have re-analyzed the transcriptome data derived from blood leukocytes of untreated JIA (GSE13501), untreated JSLE (GSE8650), and different disease phases of KD (GSE 63,881) cohorts (downloaded from ArrayExpress Archive of Functional Genomics Data). Furthermore, we also re-analyzed the gene expression profile derived from muscle biopsies of female active JDM patients (GSE11971). Consistently, extensive inflammasome gene upregulations were noted in SJIA, acute KD, and in the inflamed muscles of JDM (Fig. 4). Increased expression of *NLRP1* was noted in subsets of the ERA and of the polyarticular group (Fig. 4a). In the small JSLE cohort, increased expression levels of *NLRP3*, *AIM2*, *PYCARD*, and *IL-1β* were detected in several patients (Fig. 4b). Furthermore, higher levels of *IL-1β* and *IL-18* were noted in active JDM muscles, and evidence of NLRP3, AIM2, and NLRC4 inflammasome activations were detected in acute phase KD blood (Fig. 4c, d). We are currently collecting more cohorts for comprehensive analyses.

Compliance with Ethical Standard

Conflict of Interests The authors declare that they have no conflict of interest.

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