Infection and autoinflammation in inborn errors of immunity: brothers in arms

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Abstract

The binary view of inborn errors of immunity classified as either autoinflammatory conditions or primary immunodeficiency in the strict sense of the meaning i.e. increased susceptibility to infection is challenged by the description of recent inborn errors of immunity (IEI). Triggers leading to cell death pathway activation and disruption of cell death pathways, play a major part in the pathophysiology of infection and autoinflammation. In addition, molecules with a double role in the extracellular versus intracellular milieu add to the complexity. In all, in-depth study of human inborn errors of immunity, will continue to instruct us on fundamental immunology and lead to novel therapeutic targets and approaches that can be used in other monogenic and polygenic/complex immune disorders.

INTRODUCTION

Human inborn errors of immunity represent a growing body of inherited disorders in which one or more flaws in host defense result in increased susceptibility to infection - the “classic” clinical presentation of IEI - in addition to various other manifestations of failing immunity: severe autoimmunity, allergy, malignancy and autoinflammation [1,2]. We will here primarily focus on IEI presenting with infection and autoinflammation. The concept of autoinflammation and autoimmunity dates back to the early 1900s with Paul Ehrlich defining “horror autotoxicus”. However, the unraveling of the molecular origin of an autosomal dominant inherited syndrome of recurrent fever and

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inflammation, TNF receptor- associated periodic syndrome (TRAPS) and the locus for the gene associated with familial Mediterranean fever (FMF) after a decade of positional-cloning efforts revived the field and led to coining the term autoinflammation [3-5]. Auto-inflammatory syndromes manifest with apparently unprovoked recurrent or continuous episodes of fever, systemic and/or organ specific inflammation that may lead to central nervous system findings in some patients. The inflammatory attacks can be triggered by stress or environmental factors (for instance infection) in some diseases. Auto-antibodies and self-reactive T cells, features of auto-immunity, are typically absent [6]. Classically, autoinflammation and auto-immunity were hypothesized to be mutually exclusive with autoinflammation resulting from monogenic defects in innate immunity as opposed to auto-immune manifestations resulting from dysregulated adaptive immune responses. The classic auto-inflammatory conditions, were also collectively seen as a distinct entity, with no associated increased susceptibility to infection. The so-called inflammasomopathies, leading to unhindered cleaving of pro-IL-1β and pro-IL-18, with cryopyrinopathies (CAPS) as a prototype fit this view perfectly. As the discovery of new IEI races forth, it becomes increasingly clear that any dichotomous classification is an oversimplification. Increased susceptibility to infection and autoinflammation coalesce in many complex IEI, including in IEI affecting adaptive immunity, via multiple cellular signaling pathways. Besides, in some cases, immunosuppressive or immunomodulatory treatment approaches may contribute to the increased susceptibility to infection. In this Review, we will provide an update on recent IEI with infection and autoinflammation as predominant phenotypes, and on novel insights in previously described IEI (Table 1).

RECENTLY DESCRIBED IEI COMBINING INFECTION AND AUTOINFLAMMATION

1. Defects of the NF-κB -pathway: recent updates and novel IEI

The NF-κB pathway is a central gateway to inflammatory responses. Countless signaling pathways converge to activate NF- κB in response to diverse stimuli: cytokines (IL-1beta, TNF), pathogens (via Toll like receptors (TLR)), and various cellular stimuli (reactive oxygen species, signals of endoplasmic reticulum stress etc.). A proinflammatory response ensues, which is tightly regulated by a series of ubiquitination, deubiquitinating, and phosphorylation events [7,8]. Several IEI affect the NF-κB pathway, most presenting with a blended phenotype of variable severity of susceptibility to infection and autoinflammation [7,9]. Ectodermal dysplasia with anhidrosis and immunodeficiency, EDA-ID, is the prototype of the IEI affecting the NF-κB pathway. X-linked recessive EDA-ID, due to NF-κB essential modulator (NEMO) deficiency, is caused by hypomorphic mutations in *IKBKG*, encoding a key regulator of the canonical NF-κB pathway [10]. Patients with X-linked EDA-ID display reduced cellular responses including IL-1β, IL-18, TNF, and TLR ligands which probably explains their susceptibility to bacterial,

mycobacterial, fungal and viral infections in the presence of grossly normal T, B and NK cell development. Most patients can be managed with antimicrobials and immunoglobulin substitution; some have undergone hematopoietic stem cell transplantation (HSCT) [11]. A similar yet more severe phenotype, usually fatal prior to age 1y without HSCT, is caused by heterozygous gain-of-function mutations in NFKB Inhibitor Alpha (NFKBIA) encoding IκB-α, resulting in impaired NF-κB activation [12,13]. The exact molecular mechanism underlying the gastrointestinal autoinflammation in EDA-ID is unclear but is potentially linked to the gut protective function of NEMO [14].

Biallelic loss-of-function mutations in Inhibitor of Nuclear Factor Kappa B Kinase Subunit Beta (*IKBKB*) encoding IKK2, result in a complete loss of expression with a clinical phenotype of early onset bacterial, viral, fungal and mycobacterial infections. The patients mostly have normal T and B cell numbers but with a naïve phenotype. Responses to stimulation of T-cell receptors, B-cell receptors, TLRs, inflammatory cytokine receptors are impaired [15-18]. These patients need urgent HSCT, but outcome is poor due to ongoing invasive pyogenic infections, potentially because of the failure of HSCT to correct the immunological defect in non-hematopoietic cells [19]. Recently, a homozygous missense mutation in IKBKB, resulting in a milder phenotype, was reported [20]. Interestingly, a de novo heterozygous gain-of-function mutation in *IKBKB* (p.V203I) leading to enhanced NF-κB signaling was described in two unrelated kindreds. These patients presented with early-onset recurrent viral, bacterial and fungal infections due to lymphopenia and disturbed B- and T-cell signaling, and with features of autoinflammation including hidradenitis suppurativa, severe dermatitis, cataracts and dental anomalies compatible with ectodermal dysplasia [21]. The different outcomes of homozygous loss-of-function and heterozygous gain-of-function mutations in *IKBKB* present another example of the delicate balance governing NF-κB signaling.

A similar yet narrower clinical picture of invasive pyogenic infections is seen in patients with rare inherited defects of the Linear ubiquitin chain assembly complex (LUBAC). LUBAC consists of HOIL-1 interacting protein (HOIP) and the two accessory proteins HOIL-1 (Heme-Oxidized IRP2 Ubiquitin Ligase 1) and SHARPIN (or SHANK interacting protein like 1) and stabilizes NEMO and other key proteins in the NF-κB pathway by attaching linear ubiquitin chains [22]. Distorted LUBAC activity caused by biallelic deleterious / hypomorphic mutations in either HOIP or HOIL-1 lead to an infectious phenotype with impaired NF-κB signaling (as shown in fibroblasts) and autoinflammation with excessive responsiveness to IL-1 stimulation in patient derived monocytes [23,24]. Patients with HOIL-1 deficiency have chronic autoinflammation and cardiac and muscular amylopectinosis [23]. The first described patient with HOIP deficiency presented multiorgan autoinflammation. The patient's B cells show an impaired response to CD40 engagement and their fibroblast show impaired responses to IL-1β and TNFα. [24]. Recent studies in a second patient confirmed the reduced phosphorylation and

decreased degradation of I-kappa-B alpha (IκBα), and delayed phosphorylation of IκB kinase α/β (IKKα/β) with impaired activation of NF-κB. In the same study, transcriptomic analysis showed a type I IFN signature more strongly upregulated than the TNF gene expression pathway in patient-derived peripheral blood mononuclear cells [25]. However, the narrow infectious phenotype, at least in the few patients described, remains incompletely explained.

Work from mouse models suggested that receptor-interacting serine/threonine-protein kinase 1 (RIPK1) is a target for treating autoinflammation in NEMO deficiency [14]. RIPK1 inhibitors have been studied to treat various human conditions [26]. However, recently IEI associated with pathogenic variants in RIPK1 have been described. RIPK1 is a key molecule for mediating mixed lineage kinase domain-like (MLKL) dependent necroptosis and caspase-8 dependent apoptosis and governs signalling downstream of death receptors and pattern recognition receptors. RIPK1 is post-translationally regulated by deubiquitinases, including A20, phosphorylation and caspase-8-mediated cleavage. Dysregulations of these post-translational modifications switch on the pro-death function of RIPK1, and kindle inflammation [27]. Homozygous loss-of-function mutations in *RIPK1*, described in 12 patients from 9 kindreds, lead to impaired T- and B-cell development and lymphopenia and impaired NF-κB activity as well as decreased p38 mitogen-activated protein kinase activity. Enhanced propensity to TNF-induced necroptosis and increased NLRP3 inflammasome activity may explain the inflammatory features of the disease [28] [29]. The resulting phenotype is characterized by severe infections (sepsis, abscesses) and autoinflammation (including very early onset inflammatory bowel disease). In contrast, heterozygous - missense mutations p.D324N, p.D324H, p.D324Y prevent caspase cleavage of RIPK1 in humans, thereby promoting RIPK1 activation, and result in early-onset fevers and intermittent lymphadenopathy (cleavage resistant RIPK1 induced autoinflammatory (CRIA) syndrome) without infections [30,31]. These non-cleavable RIPK1 proteins promote cell death and pro-inflammatory cytokine production. While CRIA patients' PBMCs and monocytes display a strong inflammatory signature induced by TNF, their fibroblasts demonstrate compensatory mechanisms to mitigate the deleterious effects of the activated RIPK1 [31,32]. The patients are treated successfully with tocilizumab.

Early-onset severe multisystem autoinflammation without apparent infection susceptibility is observed in patients with biallelic loss-of-function mutations in *OTULIN*, a deubiquitinase that negatively regulates LUBAC. In contrast to OTULIN-deficient monocytes, in which TNF signaling and NF-κB activation are increased, loss of OTULIN in patient-derived fibroblasts leads to a reduction in LUBAC levels and an impaired response to TNF. Both patient-derived fibroblasts and OTULIN-deficient monocytes are more prone to TNF-induced death [33,34]. As HSCT leads to complete resolution of inflammatory symptoms, including fevers, panniculitis and diarrhea, hematopoietic system derived

cells likely play a major role in the development of autoinflammation. Several other IEI resulting from a dysregulation in the NF-κB pathway present with a blended phenotype of variable degrees of susceptibility to infection and autoinflammation. Based on the recent progress in gene discovery projects, additional monogenic defects presenting with autoinflammation and infection will likely be discovered in the near future.

2. Inborn errors of immunity with increased type I IFN signalling

The concept of type I interferonopathies was proposed by Crow in 2011 to refer to a group of novel IEI in which the homeostasis of type I interferon signaling is disturbed. Already 30 years before, Ion Gresser had deduced from experiments in rodents that excessive type interferon might be harmful to the host [35]. Type I interferons are key to antiviral defense and are induced upon detection of nucleic acids by various innate immune receptors. The trade-off to this mechanism in the context of the highly conserved structure of DNA and RNA is the risk of sensing self-nucleic acids as non-self. The tight regulation of nucleic acid sensing in the (intracellular and extracellular) environment, leading to type I IFN induction, is unavoidably subject to errors. Thus, both gain-of-function mutations in nucleic acid sensors as well as loss-of-function mutations in regulatory molecules can lead to type I interferonopathies [36], the disease prototype of which is Aicardi-Goutières syndrome. Intriguingly a direct link between the diseased status and the excessive type I IFN signaling remains to be demonstrated [36].

AR Interferon Stimulated Gene 15 (*ISG15*) deficiency was first described in the context of Mendelian Susceptibility to Mycobacterial disease [37]. Follow-up reports described the presence of intracranial calcifications and central nervous system inflammation, reminiscent of Aicardi-Goutières syndrome, the prototypical type I interferonopathy [38]. More recently, necrotizing skin lesions, ulcerations, lupus and inflammatory myositis have expanded the phenotype [39]. The dual and diverse roles of extracellular versus intracellular ISG15 explain the distinct manifestations. ISG15 is an ubiquitin-like protein the expression and conjugation to target proteins (so-called ISGylation) is induced by infection, IFN- α/β, but also DNA damage and ageing [40]. Initial work mainly focused on its role in antiviral immunity in mice. However, the initial reports on AR ISG15 deficiency revealed a picture of mycobacterial disease, without overt susceptibility to severe viral disease, owing to the non-redundant role of ISG15 as an extracellular IFN- γ-inducing molecule. The ultimate effect of absent intracellular ISG15 lies in impaired accumulation of USP18, a critical negative regulator of cellular type I IFN signaling, which is stabilized by ISG15 in an ISGylation independent way [41,42]. Initial studies ascribing an antiviral role to ISG15 in human cells focused on the initial phases of infection and failed to recognize the role of ISG15 in regulating type I IFN response [41]. In vitro work contrasted findings in ISG15-deficient mice and humans: levels of viral replication were significantly lower in human ISG15-

deficient fibroblasts upon priming with IFN- α/β, in line with the clinically observed lack of susceptibility to viral infection. This species-specific gain-of-function in antiviral immunity observed in ISG15 deficiency is explained by the role of ISG15 to sustain USP18 levels in humans, a mechanism not operating in mice [41].

Another IEI combining increased susceptibility to infection and autoinflammation is human adenosine deaminase type 2 deficiency (DADA2). Initially described in 2014 as a condition with predominant severe vasculitis (polyarteritis nodosa, lacunar strokes and intracranial hemorrhages) [43,44], additional descriptions have demonstrated the various clinical presentations of this condition, including bone marrow failure, hematologic malignancy, auto-immunity and common variable immunodeficiency like conditions with bronchopulmonary infections and an unexpected increased susceptibility to infections with herpes viruses - cytomegalovirus (CMV), Epstein Barr virus (EBV), herpes simplex virus 1, human herpes virus 6 (HHV6) - as well as human papillomavirus (HPV) and Molluscum contagiosum virus [45]. Although the pathophysiology of the condition is incompletely unraveled, the central role of ADA2-deficient monocytes in fueling autoinflammation has been robustly demonstrated [46]. However, in addition to increased TNF signaling, a type I IFN signature is present [47]. A disputed hypothesis states that ADA2-deficient endothelium is key to the increased type I IFN signaling, due to decreased methylation of multiple endogenous retroviruses (i.e. reactivation of retroelements) fueling type I IFN expression [48,49]. DADA2 results in impaired B cell development and differentiation, accounting for the humoral immunodeficiency phenotype and the recurrent sinopulmonary infections. Moreover, T cell exhaustion and altered unconventional T cell generation may serve as an initial explanation for the increased susceptibility to viral infection [50]. However, additional research is needed to reconcile the increased type I IFN expression and the viral infection phenotype [50]. Potentially, the study of cell death mechanisms in this condition can shed additional light into this matter.

3. IEI causing autoinflammation through endoplasmic reticulum stress

In conditions of decreased protein folding capacity of the endoplasmic reticulum (ER), un-or misfolded proteins accumulate to cause ER stress. This triggers the unfolded protein response, a set of reactions aimed at maintaining homeostasis, by transiently reducing protein translation, by increasing ER folding capacity and ER-associated protein degradation and by initiation of programmed cell death, if ER stress fails to resolve. Unsolved ER stress can lead to inadequate cytokine secretion with strong induction of Interferon Stimulated Genes (ISGs) [51]. The prototypic condition in which protein misfolding plays an important role is Tumor Necrosis Factor Receptor-associated periodic syndrome (TRAPS), in which missense mutations in the ectodomain of the TNF receptor superfamily 1A gene (*TNFRSF1A)* lead to the protein misfolding and ER retention [3,52,53]. TRAPS is the most prevalent autosomal dominant

autoinflammatory disorder characterized by prolonged attacks of fevers, peritonitis, and soft tissue inflammation. Patients with TRAPS do not experience increased susceptibility to infections. Dysfunction of the proteasome, which serves to maintain protein homeostasis by degrading polyubiquitinated proteins, can also lead to ER stress. A typical example is CANDLE (Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature), caused by biallelic loss-of-function variants in some of the proteasome components, and resulting in type I interferon induction [54-56]. Recently, heterozygous mutations in the proteasome maturation protein (*POMP*), a chaperone for proteasome assembly, were described in two unrelated patients with early onset combined immunodeficiency, inflammatory neutrophilic dermatosis and auto-immunity (thrombocytopenia and auto-antibodies) [57]. The truncated protein escaped nonsense mediated decay and inhibited assembly of the proteasome, in a dominant negative manner. The patients' predominantly naïve T cells showed impaired effector cytokine production, explaining the combined immunodeficiency phenotype. Both hematopoietic and non-hematopoietic cells displayed a type I IFN signature. However, the patients never experienced fever in the absence of demonstrable infection, in contrast to CANDLE [57]. Two patients received HSCT and are alive and well without infection and inflammation, highlighting that the proteasome dysfunction in hematopoietic cells, played the major part in the pathogenesis of the disease [58].

4. Actinopathies

The actin cytoskeleton is involved in countless cellular remodeling processes, such as cell migration, phagocytosis, immune synapse formation, cell division, endo- and exocytosis, vesicular trafficking and autophagy [59]. In the context of autoinflammatory disease, actin is indispensable to the assembly and activation of NOD-like receptor (NRL) family, pyrin domain containing 3 (NLRP3) inflammasome, which is located at sites rich in polymerizing actin [11]. Besides dysregulated inflammasome function, there is a role for disturbed autophagy in actin cytoskeleton diseases [60]. To date more than twenty monogenic IEI affecting the actin-cytoskeleton have been described with variable degrees of autoinflammation [1,61]. The phenotypic spectrum of these immuno-actinopathies ranges from predominant immunodeficiency phenotype (for instance DOCK8 deficiency) to a blended phenotype of immunodeficiency and autoinflammation (for instance ARPC1B deficiency) to predominant autoinflammation (heterozygous C-terminal variants in *CDC42*) [59,62,63]. The gene product of cell division cycle 42 (*CDC42*), an intracellular member of the Ras-homologous (Rho) family of GTPases, plays a crucial role in spatiotemporal organization of actin cytoskeleton dynamics. Patients with Takenouchi-Kosaki syndrome harbor a heterozygous missense mutation in *CDC42* (p.Y64C) and display developmental delay, dysmorphic features, macrothrombocytopenia and immunodeficiency [64-66]. The phenotype of additional patients harboring heterozygous missense mutations in *CDC42* is by and

large similar [67]. More recently, four patients with the recurrent de-novo heterozygous missense mutation in the C-terminal domain of *CDC42*, p.R186C, were described to suffer from a neonatal-onset cytopenia with dyshematopoiesis, autoinflammation, rash, and hemophagocytic lymphohistiocytosis (HLH) (NOCARH syndrome)[68]. The patients had defective NK cell cytotoxicity, migration, and immunological synapse formation, as well as excessive production of proinflammatory cytokines. Treatment with IL-1 and/or IFN-γ antagonists was efficacious in some patients, while one patient underwent successful HSCT [68]. Subsequently, additional patients harboring either p.R186C,p.Y64C, or other mutations were reported with a phenotype resembling NOCARH and new features such as myelofibrosis and malignancy [69][69-72]. Although the precise mechanism of autoinflammation is yet to be solved, the p.R186C variant has been shown to lead to aberrant palmitoylation and inadequate protein retention at the Golgi, with increased NF-κB signaling [68,71].

Recently, seven patients from 5 kindreds with neonatal onset of fever episodes in the absence or presence of infection, skin rashes, skin abscesses, upper and lower respiratory tract infections were found to harbor homozygous missense mutations in Nck-associated protein 1–like (*NCKAP1L*) [73,74]. These mutations give rise to a loss-of-function of hematopoietic protein 1 (HEM1), an essential component in the actin cytoskeleton dynamics of hematopoietic cells [73,74]. HEM1 is an element of the WASP-family verprolin homologous protein (WAVE) regulatory complex (WRC) and a loss-of-function results in destabilization of the WRC or impaired binding and activation of ADP-ribosylation factor 1 (ARF1). Patient T-cells demonstrate reduced cortical F-actin, with ensuing impaired T cell lamellipodia formation, cell spreading and excessive granule release by T cells resulting in hyperinflammation. T-cell receptor induced mTORC2 dependent AKT phosphorylation is also impaired in patient cells. However, T cell and NK cell cytotoxicity was normal under the conditions studied [73-75]. The B cells show decreased lamellipodia formation and reduced membrane bound IgM in the immunological synapse, leading to reduced extracellular signaling. Hypothetically this can promote auto-antigen signaling and a BCR skewing towards autoantigens with selection of autoreactive B cells [75]. The autoinflammation likely results from the excessive cytokine release due to decreased cortical F actin accumulation and defective WRC formation [74].

CONCLUSION

The description of recently identified monogenic IEI revealed several examples of clinical phenotypes in which the presence of concurrent inflammation and infection refutes the deep-rooted strictu senso dogma that immunodeficiency and autoinflammation are mutually exclusive features of human disease [76]. Moreover, autoinflammation can no longer be solely attributed to IEI of innate immunity and the same is true for auto-immune reactions and IEI of adaptive immune response. A blended and

subtle phenotype of immunodeficiency, autoinflammation is at play in the conditions described in this review. Another pattern emerges: diverse cellular mechanisms contribute to autoinflammation, ranging from dysregulated cell death, ER stress, to disturbed negative inhibition of tonic and induced type I IFN signalling, to disorganised cellular skeletal architecture. Although intrinsically oversimplifying, such pathway-based conceptualization will improve recognition of monogenic IEI and create new therapeutic targets or approaches [76]. As an example the combined immunodeficiency phenotype in POMP deficiency prompted clinicians to transplant the patients – an option less easily considered in the context of autoinflammation - with resolution of the immunodeficiency and autoinflammation demonstrating the crucial role of the hematopoietic derived cells in the generation and control of autoinflammation. It is clear that the study of IEI in patient derived cells is essential, as in many of the described conditions, the mouse phenotype is different from the human phenotype, as shown convincingly for ISG15 deficiency. The unravelling of robust autoinflammatory phenotypes will also aid in deciphering the more subtle but troublesome presentations of autoinflammation in IEI presenting predominantly with increased susceptibility to infection. Studying the effect of different mutations in the same gene or the effect of pathogenic variants that affect various genes of a signaling pathway will inform about the subtilities of balancing the level of required inflammation to meet the needs of host defense. Furthermore, these studies will shed light on the opportunities and risks of targeting the pathways that are disrupted in IEI.

CONFLICT OF INTEREST

IM holds a CSL Behring Chair, Paid to Institution. All of the other authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

SD and IM drafted and edited the work. Both SD and IM provided funding.

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Table 1. Selected recent inborn errors of immunity with autoinflammation and infection as predominant phenotypes

Condition	Gene defect	Inheritance	Infections	Autoinflammation	References
XR anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) OMIM *300291	Hypomorphic *IKBKG* mutation	XR	Viral, fungal, bacterial, mycobacterial infections	Inflammatory bowel disease	[10]
EDA-ID OMIM *164008	Gain-of-function mutation in *NFKBIA*	AD	Viral, fungal, bacterial (recurrent and invasive Klebsiella, *Pseudomonas aeruginosa*, *Haemophilus influenzae*), mycobacterial infections	Recurrent diarrhea / colitis – systemic inflammation	[12]
	Gain-of-function mutation in *IKK2* (V203I)	AD	Viral, fungal, bacterial infections	Hidradenitis suppurativa, severe dermatitis and cataracts; ectodermal dysplasia	[21]

HOIL-1 deficiency OMIMI *610924	Loss-of-function mutation in *RBCK1*	AR	Viral infections, recurrent invasive pyogenic infection	Systemic autoinflammation, amylopectinosis	[24]
HOIP deficiency OMIM *612487	Loss-of-function mutations in *HOIP*	AR	Recurrent invasive pyogenic infection	Systemic autoinflammation, amylopectinosis	[24]
RIKP1 deficiency OMIM *603453	Loss-of-function mutation in *RIPK1*	AR	Recurrent viral, bacterial, fungal and mycobacterial infection	Early onset IBD with perianal abscesses, progressive polyarthritis	[28,29]
ISG15 deficiency OMIM *616126	Loss-of-function mutation in *ISG15*	AR	Mendelian susceptibility to mycobacterial disease	Intracranial calcifications and necrotic skin diseases	[39,41]
ADA2 deficiency OMIM * 607575	Loss-of-function mutations in *ADA2*	AR	Increased susceptibility to infection with herpes viruses, Human Papillomavirus and Molluscum contagiosum virus infection	Vasculitis, polyarteritis nodosa, stroke	[43,44]
POMP deficiency OMIM * 613386	Heterozygous truncating, dominant- negative	AD	Increased susceptibility to diverse viral infections resulting in bronchopneumonia (adenovirus, RSV, and parainfluenza, rhinovirus) and diarrhea (Norovirus,	Neutrophilic dermatosis, no lipodystrophy	[57]

	mutation in *POMP*		astrovirus), Pneumocystis jiroveci pneumonia; invasive pyogenic infections (MRSA, K. pneumoniae, Pseudomonas, gram-negative rods) recurrent Salmonella and C. difficile diarrhea, Mycobacterial infection		
NOCARH syndrome	Heterozygous variants in *CDC42* (mainly Arg186Cys)	AD	Immunodeficiency with infection and sepsis mostly associated with mutations outside the C-terminal domain	Hemophagocytic lymphohistiocytosis, neonatal onset of cytopenia, fever and rashes	
HEM1 deficiency OMIM *141180	Loss- of-function mutation in *NCKAP1L*	AR	Increased susceptibility to infection (upper and lower respiratory tract infection, skin abscesses), lymphadenopathy and splenomegaly, allergy, auto-immunity	Oral ulcerations, hemophagocytic lymphohistiocytosis	[73-75]

XR: X-linked recessive, AR: Autosomal Recessive, AD: autosomal dominant