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Monogenic Auto-inflammatory Syndromes: A Review of the Literature

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ABSTRACT

Auto-inflammatory syndromes are a new group of distinct hereditable disorders characterized by episodes of seemingly unprovoked inflammation (most commonly in skin, joints, gut, and eye), the absence of a high titer of auto-antibodies or auto-reactive T cells, and an inborn error of innate immunity.

A narrative literature review was carried out of studies related to auto-inflammatory syndromes to discuss the pathogenesis and clinical manifestation of these syndromes.

This review showed that the main monogenic auto-inflammatory syndromes are familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD), Blau syndrome, TNF receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS), and pyogenic arthritis with pyoderma gangrenosum and acne (PAPA).

The data suggest that correct diagnosis and treatment of monogenic auto-inflammatory diseases relies on the physicians' awareness. Therefore, understanding of the underlying pathogenic mechanisms of auto-inflammatory syndromes, and especially the fact that these disorders are mediated by IL-1 secretion stimulated by monocytes and macrophages, facilitated significant progress in patient management.

Keywords: Auto-inflammatory syndrome; Fever; Inflammation; Innate immune response

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INTRODUCTION

Auto-inflammatory diseases, also called periodic fever syndromes, are a group of distinct hereditable disorders characterized by unexplained, recurrent

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episodes of fever and severe inflammation, most commonly in skin, joints, gut and eyes.[1] Increased inflammation in auto-inflammatory diseases is mediated predominantly by the cells and molecules of the innate immune system, usually in a person with a significant genetic predisposition.[2,3] It should be noted that this new category of diseases are different from autoimmune diseases. However, both disorders share common characteristics including abnormal immune response against body tissues, and also increased inflammation.[4] These are monogenic or polygenic diseases, frequently involving musculoskeletal system. Nevertheless, the major agent of the damage is different in these two groups of diseases: in auto-inflammatory diseases the innate immune system directly causes tissue inflammation, whereas in autoimmune diseases the innate immune system activates the adaptive immunity which, in turn, is responsible for the inflammatory process.[5,6]

Historically, auto-inflammatory diseases are a group of genetically different but clinically similar disorders characterized by recurrent fever associated with rash, serositis, lymphadenopath, and musculoskeletal involvement.[7] Originally, the name of auto-inflammatory disease referred to the hereditary recurrent fever syndromes, like familial Mediterranean fever (FMF) and TNF receptor-associated periodic syndrome (TRAPS). Over the time other auto-inflammatory syndromes including the inherited hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) and cryopyrin-associated periodic syndrome (CAPS), which are a spectrum of three illnesses with variable severity, have been added to this list.[8] Subsequently, this category of disorders has been extended to a number of clinical entities beyond the confines of the hereditary recurrent fever syndromes, including many Mendelian inheritance diseases, such as Majeed syndrome, Blau's syndrome, deficiency of interleukin-1 receptor antagonist (DIRA), deficiency of IL-36 receptor antagonist, and pyogenic arthritis, pyodermagangrenosum and acne syndrome (PAPA). In addition, disorders of uncertain genetic etiology including periodic fever, aphtous stomatitis, pharyngitis and adenitis syndrome (PFAPA), Crohn's disease, Behçet's disease, Still's disease, and acquired auto-inflammatory syndromes like Schnitzler's syndrome are also classified as multifactorial auto-inflammatory diseases.[2]

In this review we provide brief descriptions of more common monogenic auto-inflammatory diseases in two separate categories of inflammasome and non-inflammasome related conditions.

Inflammasome-related Syndromes

Receptors of innate immune system detect pathogenic microorganisms and sterile stressors, and activate the highly pro-inflammatory cytokines.[9] Inflammasome is the key signaling platform in this system, which has critical role in the onset of a pro-inflammatory state.[10] Infammasomes are a group of cytoplasmatic protein complexes that consist of an inflammasome sensor molecule, the adaptor protein ASC and caspase 1, which are assembled after the recognition of intracellular danger associated molecular patterns (DAMPs) by NOD-like receptors (NLR), especially the NLRP3. Once the protein complexes were formed, the inflammasomes activate caspase 1, which activates the pro-inflammatory cytokines IL-1β and IL-18 by proteolysis.[11] Commonly the expression level of NLRP3 is low and existence of the nuclear factor kappa B (NF-kβ) signaling is crucial for its expression. In addition, it is proposed that the aging process can stimulate NF-kβ signaling and probably enhances the priming and potential of the inflammasome activity.[2,9,11] Interestingly, activation of inflammasome causes a rapid, pro-inflammatory form of cell death called pyroptosis.[12] Induction of inflammation in the following monogenic disorders (Table 1), is triggered by inflammasome pathway.[13,14]

Familial Mediterranean Fever

Familial Mediterranean fever (FMF), the most frequent hereditary inflammatory disease, is characterized by self-limited recurrent episodes of fever and serositis. FMF is caused by mutations in MEFV (a gene that encodes a protein variously called pyrin or marenostrin),[15,16] which is expressed in early leukocyte development and is regulated in response to inflammatory mediators.[16,17] Although FMF was originally explained as an autosomal recessive disorder, approximately 10-20% of FMF patients do not carry any MEFV mutations.[18] FMF has two phenotypes. FMF type 1 is characterized by recurrent short episodes of inflammation that leads to presentations such as serositis, fever, peritonitis, synovitis, pleuritis, and rarely pericarditis. However, the most severe complication is amyloidosis, which can lead to renal failure. FMF type 2 is also characterized by amyloidosis as the first clinical manifestation.[17]

Table 1. Auto-inflammatory disorders following inflammasome defects

Disease	Gene Mutations	Inheritance	Affected cells	Immuno-pathogenesis	Functional defects	Associated features
FMF	MEFV	AR	PMNs, cytokine-activated MOs	Gain of pyrin function, resulting in inappropriate IL-1β release	Defects in pyrin production leads to ASC-induced IL-1 processing and inflammation following subclinical serosal injury; macrophage apoptosis decreased	Recurrent fever, serositis, and inflammation responsive to colchicine, susceptibility to vasculitis and IBD
MKD (HIDS)	MVK	AR	B cells, PBMCs	Mevalonate pathway blockage	Affecting cholesterol synthesis; IL-1β mediated inflammation	Periodic fever and leukocytosis along with high IgD serum levels
MWS	CIAS1	AD	PMNs, MOs	Activation of NLRP3 inflammasome	Defect in cryopyrin, involved in leukocyte apoptosis, NF-κβ signaling and processing of IL-1	Urticaria, amyloidosis, sensorineural hearing loss
FCAS	CIAS1, NLRP12	AD	PMNs, MOs	Activation of NLRP3 inflammasome	Defect in cryopyrin, involved in leukocyte apoptosis, NF-κβ signaling and processing of IL-1	Chills, fever, on-pruritic urticaria, arthritis, leukocytosis after cold exposure
NOMID	CIAS1	AD	PMNs, chondrocytes	Activation of NLRP3 inflammasome	Defect in cryopyrin, involved in leukocyte apoptosis, NF-κβ signaling and processing of IL-1	Neonatal onset rash, chronic meningitis, and arthropathy with fever and inflammation

FMF, familial Mediterranean fever; MKD, mevalonate kinase deficiency; HIDS, hyper IgD syndrome; MWS, Muckle-Wells syndrome; FCAS, familial cold auto-inflammatory syndrome, NOMID, neonatal onset multisystem inflammatory disease; IBD, inflammatory bowel disease; AR, autosomal recessive; AD, autosomal dominant; ASC, apoptosis-associated speck-like protein with a caspase recruitment domain; CIAS1, cold-induced auto-inflammatory syndrome 1; PMN, polymorphonuclear; MO, monocyte; PBMC, peripheral blood mononuclear cells.

Type AA amyloidosis is common in untreated patients and it presents with persistent, heavy proteinuria leading to nephrotic syndrome and progressive nephropathy leading to end-stage renal disease.[17] Data from several laboratories demonstrate that pyrin/marenostrin is intimately connected to three important cellular pathways: apoptosis, cytoskeletal signaling, and cytokine secretion. These connections occur, at least in part, through the direct interaction of the pyrin/marenostrin protein with two cytosolic protein adaptors: ASC (also called PYCARD or Tms1) and PSTPIP (also called CD2BP1).[19] Regarding that pyrin is expressed on cells of immune system, the mutation leads to functional dysregulation of these cells. It is revealed that this protein is expressed mainly in neutrophils, eosinophils and monocytes/ macrophages as well as fibroblasts of synovial fluid.[13] The normal function of pyrin is controlling inflammation by deactivating the immune response through modulating IL-1β processing, NF-κβ activation, and apoptosis process.[16,17] Therefore, defective pyrin function leads to elevated pro-inflammatory cytokines such as IL-1β, IL-8, IL-6, IL-17, IL-22 and TNF-α in affected patients.[20,21]

Simsek et al. revealed that IL-12 and IL-18 contribute to the establishment of Th1 polarization seen in FMF and play a partial role in its pathogenesis. Detection of increased levels of IL-12 and IL-18 in patients with inactive disease implies that they seem to assist Th1 activation and subclinical inflammation persisting during the attack-free period of the disease.[22] This subclinical inflammation increases the risk of developing complications such as anemia, splenomegaly, decreased bone mineral density, and heart disease in patients.[23] In the presence of subclinical inflammation, natural anticoagulant response may be

exaggerated that results in hypercoagulable state.[24] It should be noted that NLRs are crucial component of innate immunity that are included in pathogenesis of FMF with regulating NF-κβ signaling, and production of IL-1β.[25]

The evaluation of lymphocyte numbers in patient with FMF shows no changes in total count of T-cells and B-cells. However, the number of suppressive T-cells and helper cells are significantly decreased, while the number of NK cells is significantly increased.[26] Recently, it is suggested that Th17 cells are involved in the pathogenesis of FMF. Ovadia et al. revealed that Th17 population in PBMCs of healthy subjects was estimated at about 2.5% of the entire Th population while it was 4.4% in FMF patients in remission.[27]

It should be noted that FMF has a relation with other inflammatory diseases.[28] Alpayci et al. demonstrated that patients with FMF have a susceptibility to develop multiple sclerosis (MS). Inflammation, disruption of blood-brain barrier (BBB), mitochondrial energy deficit, demyelination, and axonal damage, which play an important role in the pathogenesis of MS, and may occur during the course of FMF.[28] Moreover, damage can occur in myelin and mitochondria proteins due to high body temperature that arises during the FMF attacks.[29] Pyrin mutations are found about 3.5 times more in the MS patients than the healthy controls. Moreover, homozygosity for the *M694VMEFV* mutation may aggravate the phenotype of MS and predispose FMF patients to develop MS .[28] In addition; genetic researches on Behçet's disease and FMF suggest that the *MEFV* gene mutated in FMF is a probable susceptible gene for Behçet's disease. Although many observations suggest that Behçet's disease might be an auto-inflammatory disease, there is evidence implying the autoimmune pathogenesis of Behçet's disease.[30]

Mevalonate Kinase Deficiency

Mevalonate kinase deficiency (MKD)**,** also known as hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) or Dutch fever is a rare disease caused by mutations in the *MVK* gene.[31] The mutation in *MVK* gene leads to reduced mevalonate kinase activity, which results in overproduction of proinflammatory isoprenoids, reduced synthesis of cholesterol and accumulation of mevalonic acid in plasma and urine (mevalonic aciduria) that is followed by episode of fever.[32] Diagnostic hallmark of HIDS is a constitutively elevated level of serum IgD (>100 U/mL); although, few cases of HIDS with *MVK* mutations have been reported to have normal IgD levels. Therefore, an elevated serum IgD is not a specific marker for HIDS. Besides the elevated IgD levels, there are high IgA serum levels in the majority of cases. The cause of elevated IgA concentration in HIDS patients remains to be elucidated. PBMCs from MKD patients produce larger amounts of pro-inflammatory cytokines like IL-1β, IL-6, IL-18 and TNF-α.[33] It is demonstrated that elevation in circulating IL-6 is correlated with CRP and phospholipase A2 (PLA2) values during the febrile attacks. Moreover, release of IL-1β from macrophages and blood monocytes, is likely to contribute to fever attacks in MKD.[34] An enhanced activation of differentiated macrophages leading to systemic overload of inflammatory mediators characterizes the macrophage activation syndrome (MAS) which is seen in MKD.[35] Stoffels et al. proposed that increased IL-1a, IL-1b, IL-6 and TNF secretion in HIDS can be specific for toll-like receptor 2 (TLR), TLR4 and NOD2 ligation.[36] Moreover, MKD leads to formation of defective, instable mitochondria due to deficient RhoA prenylation. The improper mitochondria would normally be cleared from the cytosol by autophagia, but in MKD, clearance of the defective mitochondria is disrupted. Because of this defect, mitochondrial DNA accumulates in the cytosol and is able to bind to and activate NLRP3, and then induce IL- 1β secretion.[37]

Cryopyrin-associated Periodic Syndromes

Cryopyrin-associated periodic syndromes (CAPS) are a group of autosomal dominant auto-inflammatory diseases caused by gain-of-function mutations in the *NLRP3* gene (also called *CIAS1* or *PYPAF*) located on chromosome 1q44[38,39] while in some patients with CAPS, no detectable *NLRP3* mutations can be demonstrated.[40] CAPS presents with episodes of fever, urticarial rash and elevation of acute phase reactants. Mutations in the *NLRP3* gene lead to overproduction of cryopyrin. Cryopyrin functions as part of a NALP3 inflammasome that activates and induces IL-18 and IL-1β for inflammation.[39] Also the NALP3 inflammasome can be released from activated macrophages; it can amplify inflammation by activating IL-1β in the extracellular milieu and in neighboring phagocytes. Overproduction of IL-1 plays a major role in disease

onset and progression.[41] Investigators have reported numerous potential triggers, including microbial components, for this pathway possibly via TLRs.[42]

There are three known forms of CAPS.[38] The first one which has the least severity is familial cold auto-inflammatory syndrome (FCAS) in which exposure to cold results in a systemic inflammatory response.[39] The other form is Muckle-Wells syndrome (MWS) which has medium severity of clinical symptoms.[39] Patients have marked leukocytosis with neutrophilia and thrombocytosis, anemia, and increased acute phase reactants. The last form is chronic infantile neurological cutaneous articular (CINCA) syndrome, also known as neonatal-onset multisystem inflammatory disease (NOMID) which presents more severe clinical symptoms.[38] NOMID/CINCA is the most severe form of CAPS and characterized by continuous often low grade fever, aseptic meningitis, cutaneous rash, and arthropathy, starting in the first weeks of life.[43] If untreated, NOMID patients may develop permanent organ damage as a consequence of persistent inflammation in the affected organs.[43]

It is demonstrated that blood monocytes from CAPS patients maintain the high levels of secreted IL-1β and IL-18 when stimulated with lipopolysaccharides (LPS). In CAPS monocytes, LPS induces the externalization of copious amounts of ATP, which appears to be the link between cell stress and increased cytokine secretion. ATP drives IL-1β, IL-18, and IL-1α release via activation of the P2X purinoceptor 7. In the later phase after LPS stimulation, CAPS monocytes tolerate oxidative stress, which impairs production of the anti-inflammatory IL-1 receptor antagonist (IL-1Ra). Remarkably, IL-1Ra secretion is fully restored by treatment with antioxidants.[44]

Non-inflammasome Related Syndromes

Although the IL-1β inflammasome represents a major conceptual advance in our knowledge about innate immunity and related auto-inflammatory diseases, it is by no means the only molecular mechanism for auto-inflammatory syndromes in inflammasome defects. Currently, several mechanisms have been suggested for non-inflammasome related auto-inflammatory syndromes. The main type of these disorders are protein-folding disorders of the innate immune system (e.g. TRAPS), NF-kβ activation disorders (e.g. Blau syndrome), complement disorders (e.g. age-related macular degeneration), cytokine signaling disorders (e.g. cherubism) and macrophage activation syndromes (e.g. familial hemophagocytic lymphohistiocytosis) (Table 2).[45]

Tumor Necrosis Factor Receptor-associated Periodic Syndrome

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is caused due to autosomal dominant mutations in TNF receptor superfamily, member 1A (*TNFRSF1A*) gene in the 12p13 region that encodes the 55-kDa TNF receptor.[43] TRAPS is characterized by prolonged episodes of fever and local inflammation and pain in the joints, abdomen, muscles, skin, and eyes and acute phase response attacks.[46] Importantly, the number of TNFRSF1A receptors on the membrane of leukocytes carrying the mutation is abnormally high. However, soluble TNFRSF1A levels are lower than 1 ng/mL in most of the patients between the attacks and remain low or increase transiently to normal values during the attacks, which is concomitant with increased levels of TNF.[47] In some patients TNFRSF1A shedding from cell membrane is a pathologic response to stimuli. The acute phase response is along with CRP elevation, high peripheral neutrophil counts, leukocytosis, thrombocytosis, and moderate complement consumption. The level of IgA and IgD may be elevated but the level of IgD remains lower than 100 IU/mL, an important difference with hyper-IgD syndrome.[48]

The pathogenesis of TRAPS also seems to be associated with a dysregulation in the secretion of IL-1 and IL-6, and also oxidative damage correlated with the mitochondrial production of free radicals.[38,43] Treatment of TRAPS with anti-IL 6 receptor monoclonal antibody, tocilizumab, aborts the acute phase attack and relieves the pain and stiffness. This case supports the notion of prominent role of IL-6 in TRAPS.[49]

Down regulation of autophagy may account for the pathogenic effects of *TNFRSF1A* mutations and enhances the inflammatory response such as in TRAPS disease.[50] Altered NF-κβ activation and excessive secretion of IL-1β have been reported in in vitro models and monocytes from TRAPS patients, which are likely due to autophagy impairment associated with *TNFRSF1A* mutations.[50] In addition, spontaneous activation of JNK, p38 MAP kinases (MAPKs), and mitochondrial ROS-mediated IL-1 pathway may be possible reasons. Moreover, it seems that in addition to

Table 2. Auto-inflammatory disorders following non-inflammasome defects

Disease	Gene mutations	Inheritance	Affected cells	Immuno-pathogenesis	Functional defects	Associated features
TRAPS	TNFRSF1	AD	PMNs, MOs	Increased TNF inflammatory signaling	Mutations of TNFR leading to intracellular receptor retention or diminished soluble cytokine receptor available to bind TNF	Recurrent fever, serositis, rash, and ocular or joint inflammation
IBD	IL-10 , IL-10RA , IL-10RB	AR	MO/ MQ, activated T cells	Increased pro-inflammatory cytokines	IL-10 deficiency and mutation in IL-10 leads to increase of pro-inflammatory cytokines	Early-onset enterocolitis enteric fistulas, perianal abscesses, chronic folliculitis
PAPA syndrome	PSTPIP1	AD	Hematopoietic tissues, upregulated in activated T cells	Affects pyrin and protein tyrosine phosphatase both regulate innate and adaptive immune responses	Disordered actin reorganization leading to compromised physiologic signaling during inflammatory response	inflammatory skin rash, myositisand destructive arthritis,
Blau syndrome	NOD2	AD	MO	Various inflammatory processes	Mutations in nucleotide binding site of CARD15, possibly disrupting interactions with LPS and NF-κβ signaling	Uveitis, granulomatous synovitis, rash, camptodactyly and cranial neuropathies, some patients develop Crohn's disease
Majeed syndrome	LPIN2	AR	PMNs, Bone marrow cells	Increased expression of the pro-inflammatory genes	Mutations in the LPIN2 gene alter the structure and function of lipin-2	Chronic recurrent multifocal osteomyelitis, cutaneous inflammatory disorders and transfusion-dependent anemia,
DIRA	IL-1RN	AR	PMNs, MO	Increased IL-1β inflammatory signaling	Mutations in the IL-1 receptor antagonist allow unopposed action of Interleukin 1	Neonatal onset of sterile multifocal osteomyelitis, periostitis, pustulosis
DITRA	IL-36RN	AR	Keratinocyte, leukocytes	Increased IL-8	Mutations in IL-36RN leads to increase IL-8 production	Pustular psoriasis
H syndrome	Mutation in SLC29A3	AR	Leukocyte, bone cells	Macrophage activation	Mutations in SLC29A3 result in histiocytic and lymphocytic cells infiltration of numerous organs	Hyperpigmentation hypertrichosis, sensorineural deafness, diabetes, short stature, uveitis, and Rosai-Dorfman like histiocytosis
CAMPS	CARD14	AD	keratinocyte	IL-8 production	Mutations in CARD14 activate the NF-κβ pathway	Psoriasis
Cherubism	SH3BP2	AD	Stroma cells, bone cells	Hyperactivated MQ and increased NF-κβ	Mutations in the SH3BP2 gene lead to the production of an overly active version of this protein	Bone degeneration in jaws
CANDLE	PSMB8	AD	Keratinocyte, B cell adipose cells	Increased IL-6 production	Mutation in PSMB8 gene	Skin lesions, generalized lymphadenopathy, hepatosplenomegaly, joint contractures, hyper triglyceridemia, lipodystrophy, and autoimmune hemolytic anemia.
HOIL1 deficiency	HOIL1	AR	PMNs, fibroblast	IL-1β dysfunction	Loss-of-expression and loss-of-function mutations in *HOIL1* (*RBCK1*)	Immunodeficiency auto-inflammation amylopectinosis
PLAID	PLCG2	AD	B cells, NK, mast cells	Activation of IL-1 pathways	Mutations in the *PLCG2* gene	Cold urticarial hypogammaglobulinemia

TRAPS, TNF receptor-associated periodic syndrome; IBD, inflammatory bowel disease; PAPA, pyogenic sterile arthritis, pyodermagangrenosum, acne; DIRA, deficiency of the interleukin 1 receptor antagonist; DITRA, deficiency of IL-36 receptor antagonist; CAMPS, CARD14 mediated psoriasis; CANDLE, chronic atypical neutrophilic dermatitis with lipodystrophy; PLAID, PLCγ2-associated antibody deficiency and immune dysregulation; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; PMN, polymorphonuclear; MO, monocyte; MQ, macrophage.

mutant allele, wild-type receptor is needed to produce the clinical manifestations of TRAPS. Generally cell surface tumor necrosis factor receptor 1 (TNFR1) levels of both wild-type and mutant protein are greatly reduced.[51,52]

Assessment of neutrophil apoptosis after stimulation by TNF showed that resistance to TNF-mediated apoptosis is a pathogenic feature in TRAPS patients, who have mutations of cysteine residues or interstitial deletion.[53] How TNFR1 mutations lead to the inflammatory phenotype of TRAPS is still unclear. Shedding hypothesis express that extracellular part of TNFR was shed from the cell surface after activation. In TRAPS patients cell surface TNFR1 is increased and plasma level of soluble TNFR1 is decreased. This results in an elevated and prolonged TNF signaling and decreased blocking of circulating TNF. Other studies by Rebelo et al. revealed that the mutant TNFR1 may aggregate and be retained in the cytoplasm, resulting in defective cell surface expression and ligand-independent signaling. Also, Lobito et al. revealed that mutant TNFR1s showed reduced surface expression, which correlated with reduced apoptosis induction and NF-κβ signaling.[54]

Unlike other auto-inflammatory diseases, therapy with the anti-TNF drug, infliximab, is often ineffective in patients with TRAPS. However, corticosteroids are the most widely used treatment.[55,56]

Early-onset Inflammatory Bowel Disease

Early-onset (EO-IBD) or infantile IBD is a chronic inflammatory disorder of the gastrointestinal tract in infants. Dysfunction of the mucosal immune system plays an important role in its pathogenesis.[57] IBD may be caused by autosomal recessive mutations in IL-10R and IL-10 encoding genes (anti-inflammatory cytokines), which results in hyper-responsiveness against antigens that cause inflammation.[58] In individuals with genetic risk, abnormal interactions between the host immune system and gut flora, and dysregulation of cellular responses such as autophagy and ER stress, induce an abnormal host immune response in the gut resulting in intestinal inflammation.[59] According to a study about cytokine profile in patients, the level of IL-17α significantly increased and TGF-β significantly decreased in the blood serum of the patients, and the levels of pro-inflammatory cytokines (IL-2, IL-4, IL-6, IL-12p70, TNF-α, and IFN-γ) increased.[60] TNF-α and adhesion molecules are the key molecules in IBD pathogenesis, so molecular targeting therapies based on these molecules such as anti-TNF antibody have been developed.[57] Patients with IBD present with severe enterocolitis and bloody diarrhea, colonic abscesses, perianal fistula, and oral ulcers. Symptoms usually start before 3 months of age. Impaired weight and height development, recurrent fever, acute recurrent arthritis of large joints, and recurrent folliculitis could be seen. Hematopoietic stem cell transplantation (HSCT) has been proposed as a curative treatment for IBD.[43]

Pyogenic Arthritis, Pyodermagangrenosum, and Acne

Pyogenic arthritis, pyodermagangrenosum, and acne (PAPA) syndrome which is one of the hereditary pyogenic disorders, is an autosomal dominant disease caused by mutations in the proline serine threonine phosphatase-interacting protein 1 (*PSTPIP1)* gene encoding CD2-binding protein-1 (CD2BP1), involved in the proper assembly of the cytoskeleton, which normally inhibits pyrin-mediated inflammatory signals and the activation of caspase-1. *PSTPIP1* mutants inhibits the anti-inflammatory activity of pyrin, leading to elevated IL-1β levels.[61] These mutations produce a hyper-phosphorylated PSTPIP1 protein and alter its participation in activation of the inflammasome involved in IL-1β production. Overproduction of IL-1β and TNF-α is a clear molecular feature of PAPA syndrome.[61] It usually presents in early childhood and is characterized by joint involvement (pyogenic arthiritis) and skin involvement (pyodermagangrenosum and nodular-cystic acne). Immunosuppressant drugs like corticosteroids, anti-TNF-α, and anti-IL-1 agents are useful treatments for PAPA.[38] Also, treatment with anakinra (IL-1 receptor antagonist), and infliximab (a chimeric anti-TNFα monoclonal antibody) has been recently shown to have a beneficial effect on PAPA syndrome.[61]

BLAU Syndrome

Blau syndrome (familial juvenile systemic granulomatosis) is an autosomal dominant disease characterized by a granulomatous inflammation affecting the joints, skin and eyes. The onset of this syndrome is usually in the first years of life. It is revealed that in this syndrome the mutation of *NOD2* in NACHT domain of NLRs causes a gain of the protein's function resulting in increased NF-κβ activation and

pro-inflammatory state.[2] This mutation is responsible for excess caspase-1-dependent IL-1β in cryopyrinopathies such as Muckle-Wells syndrome. For testing the hypothesis suggesting that IL-1β may mediate the inflammation seen in Blau syndrome, Martin TM et al. observed no evidence indicative of increased IL-1β production in cells obtained from subjects with Blau syndrome compared with healthy control subjects.[62] Oral steroids and immunosuppressive drugs (methotrexate, cyclosporin), anti TNF, and anti-IL-1 are useful in treatment of these patients.[2]

Deficiency of IL-1-receptor Antagonist Syndrome

Deficiency of IL-1-receptor antagonist (DIRA) syndrome is a disease that is caused by mutations in the gene encoding the IL-1R antagonist (*IL1RN*), which is a natural antagonist of the pro-inflammatory IL-1 cytokine.[63,64] Mutations in this protein result in overactivity of pro-inflammatory cytokines, IL-1α, and IL-1β. The result of these mutations in *IL1RN* is a complete loss or dysfunction of IL-1Ra protein. Lack of this competitive antagonist leads to the unchallenged action of IL-1α and beta on the IL-1 receptors happens.[65] This situation is also awaited in the state of IL-1RA deficiency.[64]

Patients manifest severe neutrophilic pustular skin eruptions, periostitis, aseptic multifocal osteomyelitis, and high acute phase reactants[66] and also present with pustular skin rashes, skin pathergy, nail dystrophy, gastrointestinal reflux, and multifocal osteomyelitis during the neonatal period. The disease has additional manifestations like osteopenia, joint swelling, mouth ulcers, interstitial pneumonia often causing hypoxemia and dyspnea, vesicular stomatitis, ribs widening, hepatosplenomegaly, periosteal reaction, vasculopathy, cervical vertebra fusion, and thrombosis.[67] It should be noted that DIRA begins quickly after child birth and presents clinical signs similar to CAPS disease.[66]

Diagnosis is accomplished by the clinical presentation of early onset dermatitis and osteitis in the absence of fever. Also, genomic testing for mutations in the *IL1RN* gene can be performed.[67]

If DIRA is diagnosed at early stages, the management is the replacement of the deficient protein. The recombinant human IL-1Ra, anakinra, can make rapid and complete reduction. But if DIRA is left untreated, the disease can cause death due to multiple organs dysfunction.[65] Inhibiting IL-1 signaling with anakinra improved clinical manifestations within days, resolving osteolytic lesions, normalizing acute phase reactants and allowing appropriate growth.[64] Antibiotics and common disease-modifying antirheumatic drugs including steroids have limited benefit. However, patients with DIRA require lifelong IL-1 inhibitory therapy.[64]

CARD14-mediated Psoriasis

CARD14-mediated psoriasis (CAMPS), is a genetic defect in non-hematopoietic cells results in innate cell recruitment and tissue-specific inflammation.[68] In the familial type of psoriasis and pityriasisrubrapilaris (PRP), gain-of-function mutations in caspase recruitment domain (*CARD*) 14, potentially an upstream regulator of IkB kinase (IKK), have been identified. The lack of IKKb in the epidermis of mice and a high amount of IL-24 produced from the keratinocytes precedes the infiltration of neutrophils and lymphocytes and develop psoriasiform dermatitis. IKKb is a principal kinase at the bottleneck of the NF-kβ, IRF3, IRF7 and MAPK signaling pathways downstream of PRRs.[69]

CARD14 encodes NF-kβ activator protein and inhibits apoptosis. It is displayed by several isoforms. Wild-type *CARD14* activates NF-kβ by up-regulating transcription of this gene and psoriasis-associated missense mutations by upregulating transcription of a number of psoriasis-associated cytokines and chemokines, such as IL-8, CCL20, and IL-36G. Release a high amount of these inflammatory mediators leads to the recruitment and differentiation of inflammatory cells. The activation of keratinocytes and efficacy of IL-36G also induce the activation of the NF-kβ pathway in inflammatory cells and lead to production of cytokines and chemokines. This creates an incorrect cycle of inflammation and acanthosis that characterizes psoriasis.[70]

The pattern of *CARD14* localization differs between normal and involved lesional skin. In the normal skin it is localized in the basal layer of the skin and is away from the upper layers, including the granular layer. Whereas, in psoriatic skin, *CARD14* is away from the basal layer and is present in all suprabasal layers. This difference in expression pattern cannot be easily explained. However, it elucidates intrinsic differences between keratinocytes of healthy and psoriatic skin.[70]

CAMPS symptoms include early-onset generalized pustulosis, plaque psoriasis, pityriasis rubra pilaris,

and/or nail pitting. Recurrent fevers have been reported but may be related to infection relapse in skin lesions. CAMPS patients may respond to inhibitors of the IL-17/23 pathway, like conventional psoriasis.[68]

CANDLE Syndrome

Newly described auto-inflammatory condition is a chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. It is characterized by an onset during the first year of life, purpuric skin lesions, violaceous swollen eyelids, recurrent fevers, progressive lipodystrophy, arthralgia, delayed physical development, hypochromic and normocytic anemia, and increased levels of acute phase reactants. Hypertrichosis, acanthosis nigricans, and alopecia areata are variable clinical features. The skin biopsy results of a characteristic atypical, mixed mononuclear and neutrophilic infiltration further confirm the diagnosis.[71]

CANDLE is caused by mutations in *PSMB8* gene. *PSMB8* encodes the β5i proteasome subunit. Proteasomes are ubiquitously expressed and are involved in proteolysis and processing antigenic peptides for class I major histocompatibility complex presentation and are also preservative for cell homeostasis. It is suggested that defect of proteolysis leads to accumulation of damaged proteins, increased cellular stress and increased IFN signaling pathway. Cytokine profiling and analysis of the transcriptome was consistent with dysregulation of the IFN pathway.[72] Interestingly, CANDLE syndrome flares can be observed with infections and other stressful conditions. Some cells such as fat or muscle cells may be undergoing apoptosis due to accumulation of damaged proteins. Dysregulation of the IFN signaling pathway may play a role in the disease, which suggests that the IFN pathway may be a target for treatment in these patients. IFN-γ has an important role in the recruitment of neutrophils (through the induction of CCL3) and in the stimulation of myeloperoxidase production in monocyte/macrophages in skin. Serum level of IP10/CXCL10 is an important chemo-attractant for effector T cells. IP-10 may contribute to the pathology of CANDLE syndrome by acting as a chemo-attractant for T cells into tissues such as skin.[71]

Treatment efforts, including anti-TNF agents and tocilizumab (the IL-6R blocker Ab) were only partially effective, with normalization of the acute phase response. A more rational approach may be to use Janus kinase inhibitors to reduce IP10 production, and there is an ongoing trial for treatment of CANDLE.[72,73]

Cherubism

Cherubism is a rare non-neoplastic disorder of bones with an estimation of only 300 cases reported in the literature.[74] The symptoms appear in early childhood with painless swelling of the jaws. Symmetrical enlargement of both jaws is a remarkably sign of typical cases.[75] The involved children have normal appearance at birth. Swellings within mandibular body or tuberosities of maxilla appear in 2 to 7 years of life. Males are affected twice more than females.[76] Enlargement of local lymph nodes often appear in early childhood.[75] Cherubism has not been considered as an inflammatory bone disorder in the past, but recent findings in mouse models raise the possibility that it is indeed an aut-oinflammatory disease. Most patients with cherubism have germ line mutations in the gene encoding SH3BP2; an adapter protein involved in adaptive and innate immune response signaling.[77] SH3BP2 is required for functional B-cell receptor (BCR) signaling. Mutation or defect of *SH3BP2* genes in mice models leads to delayed B-cell response. The ubiquitously expressed SH3BP2 protein has different functions in different immune cells. The cherubism mouse model, Sh3bp2KI/KI mice, develops inflammatory lesions independently of B- or T-cell involvement. There are at least two mechanisms that account for the cherubism-like phenotype in these mice: 1) High amount of TNFα production from macrophage (MQ) leads to inflammatory reactions; 2) Activation of hyperactive osteoclasts via activation of NFATc1 leads to bone resorption. There is preliminary evidence of elevated levels of TNF-α in a small group of cherubism patients and age-matched controls. As cherubism is expected to regress spontaneously after puberty, mild forms of cherubism without facial dysmorphology, and dental and ocular involvement may not require treatment. The management in these cases consists of longitudinal observation.[78] Annual clinical and radiographic examination with a panoramic or other appropriate imaging are suggested during the growth phase of the lesions. According to ongoing researches, abnormal inflammatory response is an important component of the pathophysiology of cherubism and reducing TNF-α level could be effective for treatment.[74] The recent work showed TNF-α

modulator treatment did not provide sufficient amelioration for patients suffering from cherubism, [79] but inhibitors of nuclear factor of activated T-cells (NFAT) activation, such as tacrolimus, may be beneficial.[80]

H Syndrome

The H syndrome is a recently described systemic manifestation of autosomal recessive genodermatosis. The term H syndrome points to the major clinical and laboratory findings including hyperpigmentation, hypertrichosis, hepatosplenomegaly, heart anomalies, hearing loss, hypogonadism, low height, and occasionally, hyperglycemia. Additional systemic features are sensorineural hearing loss, cardiac anomalies, hepatosplenomegaly, scrotal masses, endocrinopathy (short stature, gynecomastia), exophthalmos with normal thyroid function, angiopathy (varicosities, dilated lateral scleral vessels, and facial telangiectases), and camptodactyly.[81] The characteristic cutaneous hyperpigmentation with sclerodermatous thickening and hypertrichosis are the hallmark of H syndrome. These changes are the most common clinical findings, and should be considered as pathognomonic clinical signs of H syndrome. In case of uncertain diagnosis, mutation analysis will confirm the diagnosis.[82]

Laboratory evaluation showed growth-hormone deficiency and hypergonadotrophic hypogonadism accompanied by azoospermia. Histopathological examination of involved skin revealed hyperpigmentation of the basal layer with seborrheic keratosis-like acanthosis, infiltration of CD68-positive histiocytes, and a perivascular mononuclear infiltration with plasma cells and mast cells throughout the dermis and subcutaneous fat.[81]

PH-dependent equilibrates nucleoside transporter protein (hENT3) is believed to play a role in nucleotide salvage, encoded by *SLC29A3* gene. Histiocytes are main cells expressing hENT3. hENT3 is also expressed in endothelium of relatively large-sized veins, arteries, and lymphatic vessels.[83] The hENT3 protein has been recently shown to be an integral membrane protein of mitochondria, where it joins hENT1 as one of the two known nucleoside/nucleobase transporters of mitochondria. Because of hENT3's role in nucleotide salvage and its expression in mitochondria, it is not surprising that multiple tissues are involved in disorders of this protein and therefore it explains some of the observed variation in these patients. The immunological findings appear to be related to cellular proliferation and dysregulation of the immune response; however, there is no evidence to explain why some of these clinical manifestations (e.g. the sensorineural deafness and alterations in insulin signaling) is related to the loss of *SLC29A3* function. It has also been shown that mutations in the *SLC29A3* gene may induce an abnormal proliferation of histiocytes, which are key cells of immune response.[84] Increasing the permeability of blood and lymphatic vessels may also a result of the *SLC29A3* mutations. Many lymphocytic cells are supposed to be infiltrated and activated in the dermis of H syndrome patients, leading to inflammation and post-inflammatory hyperpigmentation.[83] Management of this disease is mainly supportive. In some patients, oral steroids may temporarily improve cutaneous changes, but are inappropriate for long term use due to side effects.[85]

HOIL-1 Deficiency

HOIL-1 deficiency is a new fatal inherited disorder in human. HOIL-1 is one of the three members of the linear-ubiquitin-chain-assembly complex (LUBAC), which is encoded by *RBCK1* (*HOIL1*). Mutations in *RBCK1* lead to HOIL-1 deficiency. HOIL-1 is involved in protein-protein interactions and the trafficking of proteins to specific cellular locations. It is also involved in targeting proteins for proteasomal degradation, including the targeting of NEMO. LUBAC through regulation of the canonical NF-κβ pathway is involved in the function of the innate and adaptive immune responses. The loss of HOIL-1 expression impairs LUBAC assembly, which leads to disruption in the activation of NF-κβ in fibroblasts.[86] Patients display a clinical phenotype combining an auto-inflammatory syndrome and pyogenic bacterial diseases. These patients also developed muscular amylopectinosis, consisting of intracellular glycogen inclusions, complicated by myopathy and cardiomyopathy, which have never previously been associated with any inborn error of immunity.

Probably an imbalance between cellular responses to NF-κβ-dependent pro-inflammatory stimuli, mediated by Toll/interleukin receptor domains (TIRs) and TNF receptors (TNFRs) is the reason of paradoxical association of immunodeficiency and auto-inflammation. The molecular basis of the immunodeficiency may be impaired responses to

inflammatory stimuli in fibroblasts and possibly other non-hematopoietic cell types. These patients are prone to invasive pyogenic bacterial disease, probably due to impaired NF-κβ-dependent responses to at least some key members of the TIR and TNFR families in fibroblasts and possibly other cell types.[87]

Auto-inflammation may result from enhanced responses to IL-1β in mononuclear leukocytes, particularly monocytes. These cells may be unable to normally terminate inflammation after a physiological immune response. It is also possible that deficiency in HOIL-1 impair the proteasomal degradation of one or more pro-inflammatory proteins, which may lead to the persistence of inflammatory signaling in specific cell types. However, the specific mechanism that underlies auto-inflammation in HOIL-1 deficiency is unknown.[88]

PLCG2-associated Antibody Deficiency and Immune Dysregulation

PLCG2-associated antibody deficiency and immune dysregulation (PLAID) is associated with urticaria induced by evaporative cooling or contact with cold air. Cold urticaria develops in early childhood and persists into adulthood. In this syndrome, cold temperature increases activity of PLCG2 enzyme, leading to increased mast cell degranulation.[89] The symptoms of this syndrome result from a spectrum of immune abnormalities including immunodeficiency, granulomatous rash, sinopulmonary infections, hypogammaglobulinemia and autoimmunity due to impaired B-cell receptor signaling and impaired signaling through NK cell activating receptors. After being exposed to cold temperatures all patients developed hives and 75% had antibody deficiencies. Over 50% of the patients had auto-antibodies or autoimmune disease, including elevated ANA, vitiligo, autoimmune thyroiditis, inflammatory arthritis, and connective tissue disease; and 25% had granulomatous disease presenting in early infancy.[73,90,91] Almost all patients were reported to have low serum IgM and circulating switched memory B-cells (IgM-, IgD-CD27+), while many of them, but not all, had low serum levels of IgA, and poor antibody responses to pneumococcal vaccines, as well as low or normal NK cells.[90]

PLCG2 is a member of the family of enzymes involved in transmembrane signaling, the phosphoinositide specific phospholipase C family. Stimulation by extracellular stimuli including hormones, antigens, and growth factors initiate intracellular signaling cascades through tyrosine phosphorylation and activation of phospholipase C enzyme isoforms. There are two PLCG isoenzymes: PLCG1 that is widely expressed and PLCG2 critical for signaling in B-lymphocytes, NK cells, and mast cells. PLAID-associated mutations were found in the C-terminal Src-homology domain 2 (cSH2) of PLCG2.[92] PLAID is an autosomal dominant disorder. Treatment of patients with PLAID focuses on avoidance of evaporative or systemic cooling. This includes rapidly warming after showers, toweling off sweat during and after exercise, avoiding drafts whenever possible and avoiding cold pools. Short and long-acting antihistamines can be effective as well.[92]

In conclusion, monogenic auto-inflammatory syndromes are characterized by recurrent episodes of systemic and organ-specific inflammation. Physicians need to consider auto-inflammatory diseases in children with recurrent, unexplained fevers, when infections and other common causes of inflammation have been discarded. For early detection and appropriate treatment of the auto-inflammatory conditions, identifying patients in early childhood is important. Therefore, further studies should focus on determining specific diagnostic markers in these diseases.

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