

Rare Autoinflammatory Diseases

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ABSTRACT

Systemic autoinflammatory diseases are disorders caused by dysregulation of the innate immune system leading to systemic inflammation. Since the first gene had been identified causing Familial Mediterranean Fever, the most common hereditary systemic autoinflammatory disease, advances in genomic techniques and awareness of the diseases have led to identifying more genes causing autoinflammatory conditions affecting different parts of the innate immune system. The aim of this review is to provide an update on some recently discovered autoinflammatory conditions and raise awareness for the clinicians. We focused on the actinopathies, interferonopathies, and NF- κ B-mediated autoinflammatory diseases.

Keywords: Actinopathy, autoinflammation, interferonopathy, NF- κ B

INTRODUCTION

Systemic autoinflammatory diseases (SAIDs) are caused by defects in the innate immune system. Systemic autoinflammatory diseases can be grouped according to the pathogenesis of the disease. Among SAIDs, inflammasopathies are the most common, and they are caused by excessive and inappropriate activation of inflammasomes. Recently, the content of autoinflammation has been extended to include diseases like actinopathies, interferonopathies, and NF- κ B-mediated diseases.

Systemic autoinflammatory diseases are in the differential diagnosis of a child with the early-onset of disease who has recurrent flares or chronic inflammation with an elevation of acute-phase reactants. Clinical findings such as serositis, rash, arthritis/myalgia, and lymphadenopathy are suggestive of SAIDs. In SAIDs that are inherited autosomal recessively, the presence of consanguinity is also a suggestive factor. Early diagnosis and treatment are important to prevent complications. This review is for pediatricians to suspect and diagnose these rare autoinflammatory diseases, actinopathies, interferonopathies, and NF- κ B-related disorders.

ACTIN CYTOSKELETON AND THE PYRIN ACTIVATION

Actin is a family member of multifunctional proteins that regulate cytoskeletal homeostasis. It plays a crucial role in cellular functions such as cell motility, cell division, and structural integrity. The actin cytoskeleton is crucial for the normal immune system and neutrophil functions.¹ Pyrin inflammasome activation depends on the actin cytoskeleton and microtubular network by the interaction of pyrin with actin and the adaptor protein ASC, which enables the inflammasome assembly. Disturbances of this actin-pyrin network can cause excessive inflammation.²

An increasing number of immune system diseases have been linked to the abnormalities of actin cytoskeleton functions, and they are currently called actinopathies.³⁻⁵ Unlike actinopathies with neurological and myologic features, those patients are characterized by autoinflammatory manifestations.⁶ Some actinopathies are associated with immunodeficiencies;

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others are characterized by auto-inflammatory features. Recently described genes associated with actin pathways are *WDR1* (WD40 repeat protein 1) gene, *ARPC1B* gene, and cell division control protein (CDC) gene.³

The first condition reported as pyrin–actin interaction was pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome. It is caused by mutations in proline-serine-threonine phosphatase-interacting protein 1. This protein is involved in cytoskeletal organization, and gain-of-function (GOF) mutations cause dysregulation of cytoskeletal resulting in activation of pyrin inflammasome.⁷ Excessive activation of the pyrin inflammasome leads to increased release of interleukin (IL)-1 β , which is a critical component of the autoinflammation.² PAPA syndrome is a rare autosomal dominant disease. Patients present in the first decade of life with oligoarticular, destructive arthritis, typically involving the elbow, knee, and ankle. Severe cystic acne develops in most patients in early adolescence, while pyoderma gangrenosum and pathergy-like sterile abscesses at injection sites occur in a subset of patients.⁸

The autoinflammatory periodic fever, immunodeficiency, and thrombocytopenia syndrome is associated with loss-of-function mutation in the actin regulatory *WDR1* gene, which encodes WD-repeated protein. This protein is also known as actin interacting protein-1.⁶ Mutated forms of *WDR1* interact with cofilin to promote F-actin severing and depolymerization.^{6,9,10} Lymphocytes of those patients show adhesion and motility defects.¹¹ In mouse models, *WDR1^{d/rd}* mouse neutrophils and macrophages revealed increased levels of polymerized actin compared to wild type.⁶ Autoinflammation in this mouse model has been linked to pyrin-dependent IL-18 production independently of IL-1 β .^{2,10,11} This autosomal recessively inherited disorder is at the border between autoinflammation and immune deficiency.¹² Patients display recurrent fever episodes lasting 3–7 days, oral and perianal ulcers, and severe recurrent infections with high inflammatory markers. Almost half of the patients developed thrombocytopenia. The treatment approaches are intravenous immunoglobulins, antibiotics, and allogeneic stem cell transplantation.^{3,11}

The protein encoded by actin-related protein 2/3 complex subunit 1B (*ARPC1B*) is a component of actin-related protein 2 (ARP2)–ARP3 complex, which is crucial for branching of F-actin.² In this autosomal recessive disease, patients present with platelet abnormalities, eosinophilia, and immune-mediated inflammatory disease.^{3,13–17} *ARPC1B* mutations impair platelet spreading function and immune synapse formation and reduce regulatory T cell function due to the defective actin polymerization.¹⁵ Patients with *ARPC1B* mutations present with systemic inflammation, lymphoproliferation, and immune deficiency similar to Wiscott–Aldrich syndrome (WAS).² Wiscott–Aldrich syndrome is a rare X-linked disorder characterized by microthrombocytopenia, eczema, and recurrent infections.¹⁸ Wiscott–Aldrich syndrome protein (WASP), as with *ARPC1B* protein, interacts with the ARP2–ARP3 complex and translates surface signals into actin polymerization.^{2,18} The cytoskeletal defects of megakaryocytes lead to decreased number of platelets. Wiscott–Aldrich syndrome protein deficiency promotes T-cell cytoskeletal tension decay and T-cell migration and promotes immune synapse breaking

and secondary B-cell deficiency.³ To date, only a few patients with the *ARPC1B* deficiency syndrome presenting with a wide spectrum of disease severity and complexity have been reported.^{14,15,19} Because of its recent discovery and extreme rarity, the exact mechanisms and the full spectrum of the disease remain unclear.

In 2019, a new monogenic AID characterized by excessive IL-18 secretion related to cytoskeletal abnormalities was reported in 4 patients. Those patients had neonatal onset of cytopenia with autoinflammation, rash, and hemophagocytes (NOCARH).²⁰ In the same year, another group reported their NOCARH patients.²¹ The whole-exome sequencing of these patients highlights stop-codon variations of the *CDC42* gene encoding the cell division control protein 42 (CDC42). Some patients had growth retardation and facial dysmorphisms similar to those seen in patients with cryopyrinopathies. Laboratory investigations revealed increased inflammatory markers, high serum levels of IL-18, and cytopenia. Reported patients respond well to IL-1 inhibition with complete resolution of inflammatory features.^{3,21,22}

Type-1 Interferonopathies

Type-1 interferonopathies are a group of disorders that lead to the uncontrolled secretion of interferon (IFN) α/β and auto-inflammatory features. Interferon α/β can be secreted by almost all types of cells in the human body. The activation of pattern recognition receptors that sense foreign or self-derivate nucleic acids provokes molecules like pro-inflammatory cytokines and IFNs. After secretion of IFN α and β , they act in both an autocrine and paracrine manner to engage the IFN α/β receptors. This binding activates an endonuclear Janus kinase (JAK) signal transducer and activators of the transcription (STAT) and triggers the transcription of genes called IFN-stimulated genes (ISGs) (Figure 1). Impaired regulation of this pathway leads to interferonopathies. Biomarkers commonly used for these patients are elevated type-1 IFN-related mRNAs, called IFN signature. In 2003, the ISG was described in systemic lupus erythematosus (SLE) and afterward in other autoimmune disorders like juvenile dermatomyositis, primary Sjögren disease, systemic sclerosis, and rheumatoid arthritis. However, their IFN signature is less prominent than the interferonopathy patients.^{23,24}

To date, several autoinflammatory conditions have been reported in this group, including chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), Aicardi–Goutières syndrome, STING-associated vasculopathy with onset in infancy (SAVI), proteasome-associated autoinflammatory syndromes (PRAAS), DNase II deficiency, IFN-stimulated gene 15 (ISG15) deficiency, X-linked reticulate pigmentary disorder, and ubiquitin-specific peptidase 18 (USP 18) deficiency (Pseudo-TORCH syndrome) (Table 1).²⁴

In this review, we are going to focus on 2 IFN-mediated AID: SAVI and CANDLE.

STING-Associated Vasculopathy with Onset in Infancy

This autosomal dominant or sporadic autoinflammatory disorder is caused by GOF mutations in *TMEM173*. This gene encodes “stimulator of interferon genes protein” (STING), a

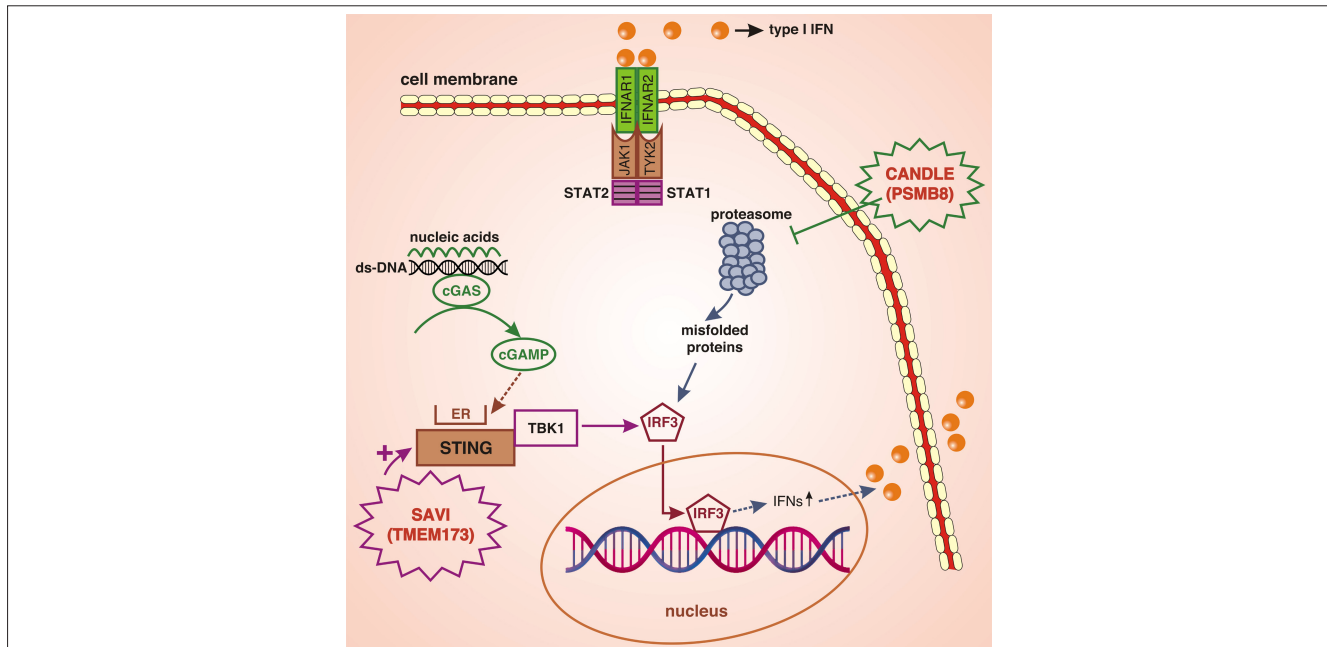


Figure 1. The interferon pathway. Gain-of-function mutations causing the constitutive activation STING drive SAVI. For CANDLE disease, after IFN activation, cells with mutated proteasome will not be able to remove waste proteins. Misfolded proteins will accumulate and this cellular stress leads to excessive type I IFNs secretion. SAVI, STING-associated vasculopathy with onset in infancy; STING, stimulator of interferon genes protein; CANDLE, chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature; IFN, interferon.

central cytosolic DNA sensor. In most cases, SAVI results from de novo variations.^{2,25,26}

SAVI is clinically characterized by systemic inflammation, cutaneous rash, interstitial lung disease, pulmonary hypertension, and growth retardation.²³ Cutaneous lesions start early in life and are usually in the cold-sensitive acral areas, including fingers, toes, ears, and nose. Skin lesions include purpuric plaques and nodules, livedo reticularis, painful ulcerative lesions evolving into eschars resulting in tissue loss or necessitating surgical amputations. Cold exposure may trigger skin flares. On the other hand, in some rare cases, cutaneous manifestations may not appear.²⁷ Raynaud phenomenon and nail fold capillary tortuosity have been reported, albeit without a clear scleroderma pattern.²⁸ Skin biopsy is consistent with diffuse capillary wall inflammation with neutrophilic infiltrates and microthrombotic changes.²³ Immune complexes (ICs) are found in destroyed vessels. Many vessels did not have IC deposition, and affected cutaneous small vessels have been surrounded by neutrophils and leukocytoclasia.²⁵

Rash with systemic inflammation features such as fever, elevated acute phase reactants are typically seen in the first months of life. Other manifestations include myositis, arthritis, and recurrent bacterial infections.²⁹ Most patients have recurrent low-grade fever, and all develop marked vascular inflammation resulting in tissue damage. Notably, apart from other interferonopathies, central nervous system is spared, and basal ganglia calcifications do not occur. Most of the patients develop interstitial lung disease leading to lung fibrosis.^{23,25,30} Pulmonary findings include recurrent wheezing, tachypnea, cough, pulmonary fibrosis, restrictive lung disease, multifocal lymphoid formations, and interstitial edema.²⁸ Expressing STING in alveolar macrophages, type 2 pneumocytes, and bronchial epithelium

may likely explain the pulmonary involvement of SAVI patients. Interstitial lung disease has been reported as the leading cause of death in those patients.^{23,28}

CHRONIC ATYPICAL NEUTROPHILIC DERMATITIS WITH LIPODYSTROPHY AND ELEVATED TEMPERATURE

This disorder presents in infancy and is characterized by annular erythematous skin lesions with panniculitis-induced lipodystrophy, hepatomegaly, arthralgias, recurrent fever, joint contractions with muscle atrophy, and basal ganglia calcification.³¹ CANDLE is one of the several overlapping diseases resulting from a complicated proteasome system. It results from mutations affecting *PsMB8* or related proteasome proteins, including those encoded by the proteasome subunit alpha type 3 (*PSMA3*), *PSMB4*, and *PSMB9* gene.³² Therefore, it has been proposed to use "proteasome-associated autoinflammatory syndrome" to cover them.²⁴ Most patients have homozygous or compound heterozygous deficiency of a single gene. Proteasome dysfunction results in unfolded protein response, leading to inappropriate production of type 1 and type 2 IFNs and elevated IL6 levels.³³ Immune activation exacerbates these conditions because activated immune cells exhibit accelerated protein synthesis and reactive oxygen species production, increasing the "load" of misfolded or unfolded proteins requiring proteasome-mediated disposal. These findings suggest that cellular stress responses due to proteasome dysfunction can lead to chronic type I IFN signaling.³⁴ According to this pathophysiology, CANDLE is considered to be part of the spectrum of conditions termed "protein misfolding defects."²

Patients typically present in infancy, developing recurrent skin lesions (infiltrating neutrophils and mononuclear cells),

Table 1. Main Features of Autoinflammatory Disorders Discussed

Actinopathies				
Name of the disease	PAPA	PFIT syndrome	ARPC1B deficiency	NOCARH
Gene (protein)	<i>PSTPIP1</i> (CD2-binding protein 1)	<i>WDR1</i> (WD repeat protein 1)	<i>ARPC1B</i> (actin-related protein 2/3 complex subunit 1B)	<i>CDC42</i> (cell division control protein 42)
Clinical manifestations	Pyoderma gangrenosum, acne, arthritis	Periodic fevers, immunodeficiency, thrombocytopenia	Platelet abnormalities, eosinophilia, and immune-mediated inflammatory disease	Neonatal-onset cytopenia with autoinflammation, rash, and hemophagocytes
Type 1 interferonopathies				
Name of the disease	SAVI	CANDLE/PRAAS	Aicardi-Goutières syndrome	DNase II deficiency
Gene (protein)	<i>TMEM173</i> (STING)	<i>PSMB3, PSMB4, PSMB8, PSMB9</i> (Proteasome)	<i>TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1</i> (Exonuclease, subunits of RNase H2 endonuclease complex, SAM domain and HD domain 1)	<i>DNASE2</i> (Deoxyribonuclease)
Clinical manifestations	Vasculopathy, skin ulcers, interstitial lung disease	Fever, systemic inflammation, panniculitis, lipodystrophy, hepatosplenomegaly, myositis	Basal ganglia calcification, acral vasculopathy/chilblain rash, CNS inflammation, with seizures, long-term cognitive defects	Neonatal pancytopenia, intermittent fevers, cholestatic hepatitis, proteinuria, and arthritis
NF-κB signal dysregulation				
Name of the disease	HA20	ORAS/Otulipenia	HOIP/HOIL-1 deficiency	Bi-allelic <i>RIPK1</i> mutation
Gene (protein)	<i>TNFAIP3</i> (A20)	<i>OTULIN</i> (Otulin)	<i>HOIP/HOIL1</i> (LUBAC components)	Bi-allelic <i>RIPK1</i> mutation
Clinical manifestations	Oral, gastrointestinal, and genital ulcers, arthralgia, ocular inflammation (Behçet disease like)	Fever, failure to thrive, diarrhea, antibody-mediated autoimmunity, lipodystrophy, neutrophilic dermatosis, panniculitis	Amylopectinosis, increased susceptibility to viral and bacterial infections, immunodeficiency	Early-onset inflammatory bowel disease, progressive polyarthritis
<p>HA20, haploinsufficiency of A20; TNF, tumor necrosis factor; ORAS, OTULIN-related autoinflammatory syndrome; PRAAS, proteasome-associated autoinflammatory syndromes; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; JAK, Janus kinase; CNS, central nervous system; IFN, interferon; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; IL-1, interleukin 1; PFIT, periodic fever, immunodeficiency, and thrombocytopenia; PSTPIP1, proline-serine-threonine phosphatase-interacting protein 1; NOCARH, neonatal onset of pancytopenia, autoinflammation, rash, and episodes of hemophagocytic lymphohistiocytosis; NF-κB, nuclear factor kappa light-chain enhancer of activated B cells.</p>				

hepatomegaly, arthralgias/arthritis, and systemic inflammation mostly accompanied by fever. The most common presenting feature is elevated temperature. Although triggers like cold exposure may activate the skin lesions, most patients do not have such a history. Basal ganglia calcification may occur. Lipodystrophy mostly starts in early childhood and is usually established before puberty. Disabling joint manifestations usually begin subsequently.³⁵

TREATMENT OF SAVI AND CANDLE

In vitro studies have shown that expression of ISGs and phosphorylation of STAT1 is decreased upon co-culture with JAK inhibitors (tofacitinib, ruxolitinib, and baricitinib).^{31,33,36} Commonly high doses of intravenous methylprednisolone, oral prednisone, and intravenous immunoglobulins are used during the flares of the disease, however, with only partial control.²³ Other options such as disease-modifying antirheumatic drugs as well as biologics (etanercept, anakinra, tocilizumab, and rituximab) have been used and resulted ineffective in most cases.^{23,25,28,30,37} Sanchez et al³⁸ reported the use of baricitinib on 18 patients severally affected with CANDLE (n = 10), SAVI (n = 4), or other presumed interferonopathies.³⁸ Clinical manifestations, inflammatory and IFN biomarkers improved in those patients. Patients with CANDLE showed more improvement compared to SAVI and other patients. They used higher doses of baricitinib to control the symptoms, and patients had infections presumably related to over-immunosuppression.³⁹

NF-κB-Mediated Autoinflammatory Diseases

The nuclear factor kappa light-chain enhancer of activated B cells (NF-κB complex) is a family of DNA transcription factors, integrating signals from multiple cell surfaces and intracellular danger sensors causing expression of proinflammatory genes. Regulation of NF-κB is tightly controlled by a set of sensor proteins, inhibitory proteins, and ubiquitin-dependent functional modifications. Defects in any of these pathways can cause enhanced activation of the NF-κB pathway.⁴⁰

Autoinflammatory diseases resulting from dysregulation in the ubiquitin pathway have expanded our view of the spectrum

of autoinflammatory diseases.⁴¹ Ubiquitination is a posttranslational protein modification and an essential mechanism for regulating many processes of cell physiology. The process of ubiquitination is dynamic and reversible. Ubiquitin is removed by deubiquitinases (DUBs).⁴²

This review will summarize the current knowledge of A20 Haploinsufficiency (HA20) and Otulipenia (Tables 1 and 2).

A20 Haploinsufficiency

A20 Haploinsufficiency (HA20) is an autoinflammatory disease presented with early-onset systemic inflammation and caused by heterozygous loss-of-function mutations in tumor necrosis factor- α -induced protein 3 gene (*TNFAIP3*).⁴³

Zhou and colleagues⁴³ had described 6 unrelated families from different ancestries who present with early-onset systemic inflammation, oral/genital ulcers, uveitis, and arthritis/arthralgia in 2016. The phenotype resembles Behçet's disease.⁴³ Since its first description, the spectrum of clinical manifestations has been expanded.

The protein A20, encoded by *TNFAIP3*, is a DUB with a central role in the negative regulation of the NF-κB pathway. This leads to an activation of the NF-κB pathway, an increased expression of proinflammatory cytokines, and systemic inflammation⁴¹ (Figure 2). Recently, Rajamäki et al⁴⁴ had reported enhanced NLRP3 inflammasome activation in HA20 patients' immune cells.

It is difficult to diagnose these patients due to clinical heterogeneity and overlap with other conditions.⁴⁵

The disease was characterized by early-onset systemic inflammation and recurrent oral/genital and/or gastrointestinal ulcers.⁴⁶ A group from China has reported 61 patients with a molecular diagnosis of HA20.⁴⁵ Patients were either Caucasian or Japanese, and 62% of patients were female. The disease onset was 14 years (5 days to 29 years). Patients were initially diagnosed with Behçet's disease, juvenile idiopathic arthritis or rheumatoid arthritis, periodic fever with aphthous

Table 2. Clinical Manifestations of Otulipenia and Haploinsufficiency of A20

	Otulipenia	HA20
Onset of disease	Early onset/neonatal	Early onset
Recurrent fever	+	+
Cutaneous features	Pustular rash, folliculitis, panniculitis	Pustular rash, acneiform lesions, panniculitis, neutrophilic dermatosis
Oral-genital ulcers	-	+
Gastrointestinal involvement	Severe diarrhea, abdominal pain	Bloody diarrhea, abdominal pain
Musculoskeletal system involvement	Arthritis, arthralgia, lipodystrophy	Arthritis, arthralgia
Ocular findings	Not reported	Anterior uveitis, retinal vasculitis
Cardiac involvement	Not reported	Pericarditis, pericardial effusion
Pulmonary involvement	Not reported	Interstitial lung disease
Neurologic involvement	Not reported	CNS vasculitis
Pathergy positivity	-	+
Laboratory	Elevated acute phase reactants, leukocytosis	Elevated acute phase reactants, leukocytosis
Other	Failure to thrive and developmental delay	Autoimmune features (autoimmune thyroiditis and ANA positivity)

AR, autosomal recessive; AD, autosomal dominant; CNS, central nervous system; ANA, anti-nuclear antibody; HA20, haploinsufficiency of A20.

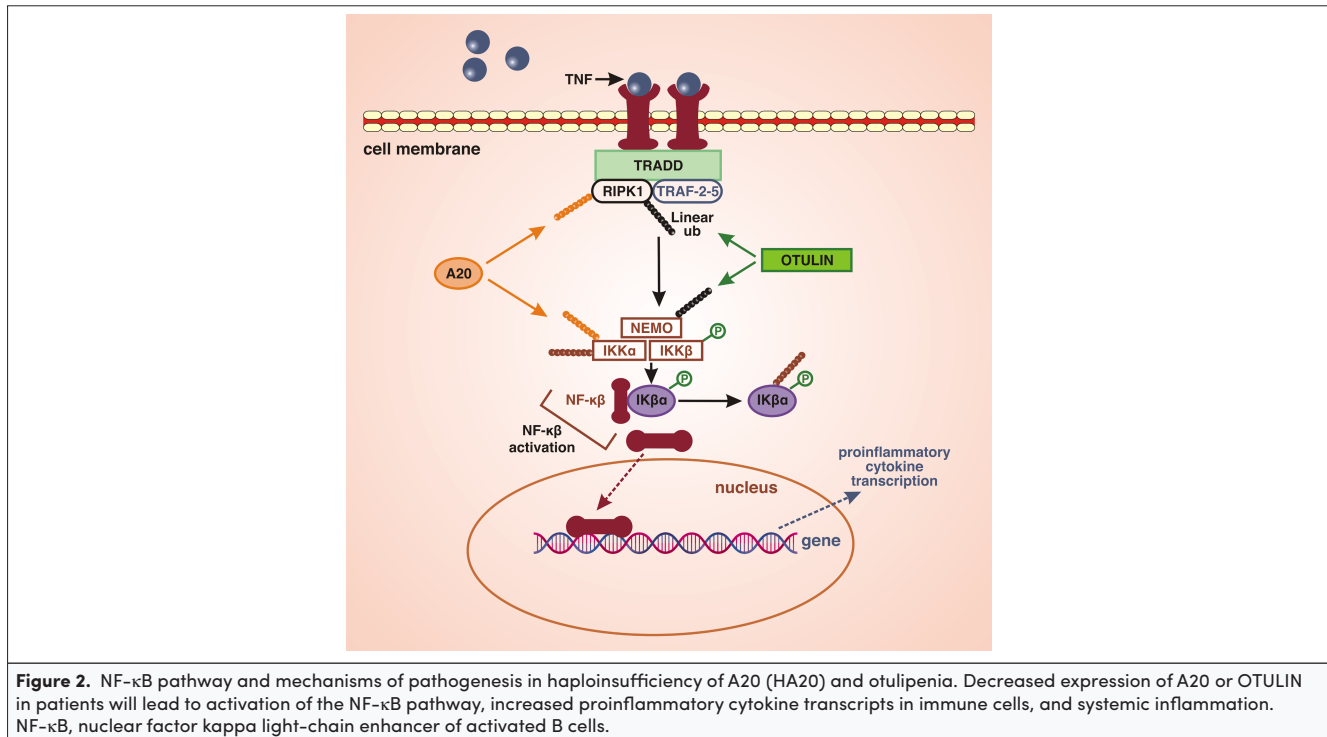


Figure 2. NF-κB pathway and mechanisms of pathogenesis in haploinsufficiency of A20 (HA20) and otulipenia. Decreased expression of A20 or OTULIN in patients will lead to activation of the NF-κB pathway, increased proinflammatory cytokine transcripts in immune cells, and systemic inflammation. NF-κB, nuclear factor kappa light-chain enhancer of activated B cells.

pharyngitis and adenitis, autoimmune thyroiditis, and others such as Crohn's disease and SLE. In total, 64% of patients had oral and/or genital ulcers, 44% had recurrent fever, 43% suffered from skin involvement, 33% had arthritis or arthralgia, and 44% had gastrointestinal symptoms.⁴⁵ Laboratory evaluations revealed increased acute phase reactants and fluctuating presence of various autoantibodies.

Treatment is controversial. Steroids are first-line drugs used to control inflammation. Colchicine had been used as varying success. Nearly half of the patients described above responded to colchicine treatment with steroid or mesalazine. Immunosuppressive agents such as cyclosporine, methotrexate, and azathioprine and biologic drugs including anakinra, rituximab, tocilizumab, and infliximab had been used in some patients.⁴⁵

A20 Haploinsufficiency disease was by unprovoked episodes of inflammatory symptoms or chronic inflammation. It should be considered in patients with early-onset inflammation, recurrent oral and genital ulcers, and fluctuating autoantibodies with a family history. It can resemble various autoinflammatory and autoimmune diseases. Treatment should be based on the severity of inflammation.

Otulipenia

Otulipenia is an autoinflammatory disease caused by loss-of-function mutations in *OTULIN* that encodes a deubiquitinase. Patients presented with neonatal-onset fever, neutrophilic dermatitis/panniculitis, and failure to thrive.⁴⁷ Otulin is a deubiquitinase that cleaves met1-linked chains and is an important gatekeeper of innate immunity like HA20.⁴⁸ Otulin deficiency leads to increased linear ubiquitination of target proteins, associated with increased NF-κB activity and NLRP3 inflammasome activity (Figure 2).

One Pakistani and 2 Turkish families with 4 affected patients presented with neonatal-onset severe inflammatory disease with prolonged fevers, joint swelling, neutrophilic dermatitis/panniculitis, diarrhea, and failure to thrive⁴⁹ (Table 2).

The steroid also compromises the mainstay of the treatment to control inflammation. Anti-IL-1 and anti-TNF agents were used for these patients with a promising result.

CONCLUSION

In conclusion, the challenge in the field of autoinflammation continues, where we need further work to understand the pathogenesis and scope of these diseases. Different abnormalities in immune pathways may cause a variety of rare autoinflammatory diseases with uniform or distinct features. Ongoing studies in autoinflammation and innate immunity will highlight a pivotal role in improving diagnostic tools and developing specific therapies.

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