

Autoinflammatory diseases: what is behind them and what is new?

Michele Maalouly,¹ Serena Saade,² Mazen Kurban²⁻⁴

¹Department of Internal Medicine, ²Department of Dermatology, ³Department of Biochemistry and Molecular Genetics, ⁴Division of Genomics and Translational Biomedicine, American University of Beirut, Lebanon

Abstract

Autoinflammatory diseases are characterized by bouts of systemic or localized inflammation in the absence of an infection. While some autoinflammatory diseases are caused by a single gene mutation, others have been shown to be multifactorial, involving a large array of genes coupled with environmental factors. Previous studies briefly elucidated the molecular mechanisms behind the many autoinflammatory diseases, focusing on the dysregulation of interleukin (IL)-1 β or IL-18, nuclear factor- κ B activation, and Interferons secretion. In this review, we precisely highlight the autoinflammatory disease-specific signalosomes, and we aim to provide a scaffold of the link between the various affected pathways.

Correspondence: Michele Maalouly, Department of Internal Medicine, American University of Beirut, Lebanon.

Tel.: +9613003431 - Fax: +9611745320.

E-mail: mm347@aub.edu.lb

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Introduction

Both autoinflammatory and autoimmune diseases can cause repeated attacks of self-lead inflammatory immunological reactions independent of any external triggers. Notably, autoinflammatory diseases are due to hyperactivation of the innate immune system, while autoimmune diseases result from abnormalities of the adaptive immune system.¹

Inflammation is a physiological adaptive response to infection and tissue injury. Many other conditions can lead to inflammation, triggering the recruitment of leukocytes and plasma proteins to the affected tissue site. Abnormal activation of the immune system targeting self-antigens is thought to be the main culprit of autoinflammatory diseases.

In recent years, considerable progress has been made in the understanding of cellular and molecular events behind the acute inflammatory response, tissue injury, and signalosome dysregulations.²

Historical origin

Familial Mediterranean fever (FMF) was the first autoinflammatory disease to be characterized at the molecular level. In the late nineties, the second periodic fever disease emerged when the molecular basis of familial Hibernian fever was elucidated with the identification of the *TNFRSF1A* gene mutations. This disease was renamed tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS). Since then, the term autoinflammation was coined to describe new diseases involving the innate immune system. These include but are not limited to:

- i. Cleavage-resistant RIPK1-induced autoinflammatory syndrome (CRIA)
- ii. Cryopyrin-associated periodic syndromes (CAPS)
- iii. Deficiency of adenosine deaminase 2
- iv. Familial cold autoinflammatory syndromes (FCAS)
- v. Haploinsufficiency of A20
- vi. Hyper IgD syndrome (HIDS)
- vii. Muckle-Wells syndrome (MWS)
- viii. Neonatal onset multisystem inflammatory diseases (NOMID)
- ix. Otitulpenia
- x. Periodic fever, aphtous stomatitis, pharyngitis and cervical adenitis (PFAPA)
- xi. Pyogenic arthritis, pyoderma - gangrenosum and acne (PAPA)
- xii. Retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis and migraine headache (ROSAH)
- xiii. Vacuoles, E1 ligase, X-linked autoinflammatory syndrome (VEXAS)

The main culprit behind autoinflammatory diseases is a dysregulation of the pattern recognition receptors (PRR)-containing interactomes. Dysfunction of each specific interactome results in a particular disease as follows: inflammasomes cause inflammaso-

mopathies, nuclear factor (NF)- κ B-activating signalosomes cause relopathies, type I interferon-inducing signalosomes cause interferonopathies, and finally immuno-proteasomes cause proteasome-associated autoinflammatory syndromes (PRAAS)

In this review, we will explore four categories of autoinflammatory diseases: the inflammasomopathies, NF- κ B activation (relopathies), interferonopathies, and interleukin (IL)-1 receptor-related autoinflammatory diseases (Table 1).

Inflammasomopathies

Inflammasomes are a group of multiprotein signaling cascades that are known to control the inflammatory response and coordinate antimicrobial host defense mechanisms. The inflammasome is comprised of a sensor, an adaptor, and an effector all working together to establish an immune response.

Inflammasome complexes are named after their sensor.³ They are recruited by PRRs following the detection of pathogenic microorganisms and danger signals in the cytosol of host cells. This consequently leads to the activation of inflammatory caspases to produce cytokines and induce pyroptotic cell death. The clinical importance of inflammasomes reaches beyond the infectious level, as dysregulated inflammasomes are very much associated with inflammatory disorders.⁴

One of the key innate immune pathways relies on the inflammasome complexes, which consist of an array of ligand-sensing nucleotide-binding domain, leucine-rich repeat containing (NLR) proteins, the adaptor protein ASC, and caspase-1. NLR proteins patrol the content of the cytosol, when prompted by a ligand, they initiate the inflammasome cascade, pyroptotic cell death, and pro-inflammatory cytokine release.⁵

Since single-nucleotide polymorphisms were discovered in inflammasome genes, they were gradually being linked to common auto-inflammatory diseases. Examples of such associations include periodic fever syndromes. Inflammasome signaling has been further dissected at the molecular level throughout the years.⁶ Several autoinflammatory disorders such as cryopyrin-associated periodic syndromes and FMF among others have been associated with mutations of genes encoding inflammasome components.⁷

From a dermatological standpoint, it has been shown that ultraviolet (UV) irradiation injures the epidermis, resulting in sunburn and triggering local inflammation. UV-irradiated keratinocytes secrete IL-1 β through a caspase-1-dependent mechanism. In the search for a link between UV-irradiation and caspase-

1 activation, a prominent role for the NOD-like receptor family of innate immunity proteins was recently discovered. NLRs activate caspases through the assembly of macromolecular complexes also known as the inflammasomes. Although the mechanism by which UV-irradiation activates inflammasomes remains obscure, these recent findings shed light on the role of NLRs as intermediates between cell injury and inflammation.⁸

NLRP1-associated autoinflammation with arthritis and dyskeratosis

The *NLRP1* inflammasome was the first to be identified, it was distinguished from other inflammasome sensors by having an aminoterminal pyrin-domain (PYD) as well as a carboxyterminal caspase activation and recruitment domain (CARD). It has been established that the PYD does not act as an effector domain but is rather required for self-inhibition of *NLRP1*.⁹

Host defenses inside a cell are triggered by a signaling cascade that starts with caspase-1 and ultimately results in cytokine maturation and cell death. ASC is an adaptor protein that connects the sensor proteins with the caspase-1 to form a ternary inflammasome complex. This is achieved through PYD interactions between sensors and ASC, leading to CARD interactions between ASC and caspase-1.¹⁰

NLRP1 interacts with ASC through its PYD domain. ASC subsequently binds to pro-caspase-1 via its CARD domain, which promotes IL-1 β secretion. *NLRP1* also interacts with caspase-1 directly through its CARD domain to activate IL-1 β secretion. Several mutations in the gene coding for *NLRP1* were discovered and clinically correlated (*A54T*, *A59P*, *A66V*, *M77T*, *R726W*, *T755N*, *F787*, *R843del*, and *P1214Rn*). Patients harboring these mutations exhibit diffuse skin dyskeratosis, autoinflammation, autoimmunity, oligo/polyarthritis, recurrent fever, along with immunological dysfunction such as high translational B cell level in addition to some instances of vitamin A deficiency.¹¹ The mutations may trigger proteasome-dependent functional degradation of *NLRP1*, degraded CARD-FIIND-containing-*NLRP1* fragments act as a scaffold similar to ASC for inflammasome activation.¹²

Familial Mediterranean fever

The causative gene of FMF, *MEFV*, encodes pyrin (also named marenostrin), and it has an autosomal recessive inheritance. Mutations in pyrin are thought to result in the loss of its ability to inhibit inflammasomes which translates clinically into the phenotype of FMF. Mutations appear to result in decreased phosphorylation of pyrin and gain of function, resulting in

Table 1. Autoinflammatory disorders can be divided into four categories: inflammasomopathies, relopathies, interferonopathies and IL-1 receptor-related conditions.

Inflammasomopathy	Relopathy	Interferonopathy	IL-1 receptor-related
FMF	Blau syndrome	CANDLE syndrome	DIRA
Mevalonate kinase deficiency	A20 protein haploinsufficiency	Nakajo-Nishimura syndrome	DITRA
CAPS	-	Aicardi-Goutieres	-
TRAPS	-	Coatomer protein alpha	-
IL-1 β	-	Singleton Merten Syndrome	-
<i>NLRP1</i>	-	-	-
Pyogenic arthritis, pyoderma gangrenosum, acne syndrome	-	-	-

CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome; DIRA, deficiency of IL-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor antagonist; CAPS, cryopyrin-associated periodic syndrome; TRAPS, tumor necrosis factor receptor-associated periodic fever syndrome.

increased activation of the pyrin inflammasome and release of IL-1 β . The latest data show that pyrin assembles with ASC and procaspase-1 to form the pyrin inflammasome, as well as the *NLRP3* inflammasome. Usually, pyrin is phosphorylated by serine/threonine-protein kinases PKN1 and PKN2, and inhibited by 14-3-3 proteins. When virulence factors are expressed or secreted by bacteria and/or viruses, they inhibit RhoA GTPase, which induces activation of the pyrin inflammasome and secretion of IL-1 β . On the other hand, bacteria that resemble *Yersinia pestis* developed adaptive mechanisms to avoid and dampen the inflammatory response. They have a YopM protein that interacts with pyrin to inhibit inflammation and thus shield the pathogen from anti-bacterial response. In patients with FMF, binding to ASC is disrupted by the mutant B30.2 protein domains of pyrin, causing continuous inflammasome activation and unregulated IL-1 β secretion.

FMF is by far the most common inherited autoinflammatory disease. It occurs worldwide but is most frequent in Eastern Mediterranean populations. Typical onset is early in life, with 50% having their first attack before the age of 10, and 90% before the age of 20. Symptoms include recurring bouts of fever and extremely painful serositis lasting 12 to 72 hours. Peritonitic abdominal pains occur in 80% of attacks (40% of patients undergo exploratory laparoscopy before diagnosis), and other common symptoms include pleuritic chest pain and non-erosive arthritis. The skin manifestation is an erysipelas-like erythema, usually between the knee and the dorsum of the foot, which is more common in children and associated with the commonest and most severe mutation, M694V.

Mevalonate kinase deficiency/hyper-IgD syndrome

Mevalonate kinase deficiency (MKD), also called hyper-IgD syndrome, is a very rare autosomal recessive entity caused by a hypomorphic mutation in the mevalonate kinase gene (*MVK*). The *MVK* protein contributes to the biosynthetic pathway that produces cholesterol and nonsterol isoprenoids. Thus, *MVK* deficiency leads to a reduced synthesis of isoprenoids, which in turn reduces prenylation of RoRetGTPases, and disrupts their role in cytoskeletal regulation and vesicular trafficking. This leads to overactivation of the pyrin inflammasome and translates into increased production of IL-1 β .

Geranylgeranyl pyrophosphate is a key mediator produced by the mevalonate pathway; it serves as a substrate for geranylgeranylation. Deficiency of *MVK* leads to depletion of geranylgeranyl pyrophosphate, resulting in the inactivation of RhoA. Consequently, MKD leads to an inflammasomopathy *via* the unrestricted activation of the pyrin inflammasome.

MKD has two clinical phenotypes. Total enzyme deficiency results in the metabolic disorder mevalonic aciduria, which is lethal unless treated with early bone marrow transplantation. Currently, there are around 300 reported patients with the milder periodic fever syndrome variant, mostly from northwestern Europe, although the disease occurs worldwide. The onset of MKD characteristically occurs in the first 6 months of life with recurrent episodes of fever lasting 3 to 7 days. Typical symptoms are gastrointestinal upset and lymphadenopathy in the vast majority of patients. Other symptoms may include arthralgia, oral aphthae, maculopapular rash, headache as well as eye inflammation. Long-term complications include AA amyloidosis, severe or recurrent infections, abdominal adhesions, and joint contractures.

Treatment is difficult, but IL-1 blockade appears to be promising. In fact, it has been shown that canakinumab, an anti-IL-1 β monoclonal antibody, is an effective treatment for MKD, suggesting that IL-1 β is a common mediator of these diseases. Patients

who are resistant to this treatment may sometimes respond to IL-6 blockade.

Interleukin-1 β -mediated autoinflammatory diseases

IL-1 β is a known potent proinflammatory cytokine that can kick-start an inflammatory cascade by recruiting immune cells and inducing IL-6 production. As such, uncontrolled IL-1 β activity underlies the pathology of common inflammatory diseases.¹³

Pyroptotic cell death occurs because caspase-1 is activated by an adaptor protein. The latter interacts with NOD-like receptors harboring a pyrin domain (PYD) such as *NLRP1*, 2, 3, 6, 9, 12 and other pyrin domain-containing PRRs such as pyrin, AIM2, and IFI-16. This interaction is triggered by the recognition of damage-associated molecular patterns (DAMPs), pathogen associated molecular patterns, and other intracellular microenvironmental changes. The adaptor that mediates this interaction is the apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC) that binds via PYD, and a pro-caspase-1 that binds via a CARD domain.

NLRP3 is a prototype for a family of proteins, known as the NLR family that is intimately involved with the innate immune system. Originally called cryopyrin, *NLRP3* is a component of the inflammasome, a macromolecular complex that senses various microbial products and intracellular danger signals (DAMPs) and activates caspase-1. Activated CASP1 triggers downstream inflammatory responses by cleaving inflammatory cytokines IL-1 β and IL-18 to their active form, a key step in the innate immune response.¹⁴ It also plays a role in the inflammatory pathway leading to cell death, also referred to as pyroptosis.¹⁵

NLRP3 inflammasome is genetically associated with some autoimmune diseases such as psoriasis. Patients with psoriasis exhibited higher plasma levels of inflammasome-generated IL-1 β and IL-18 without any correlation to skin lesion severity. Increased constitutive expression of the inflammasome sensors *NLRP3*, *NLRP1*, and *AIM2* was found in peripheral blood cells of patients with psoriasis, along with some increased caspase-1 reactivity in the myeloid blood subsets.¹⁶

The inflammasome activation in times of stress such as infection is not always negative and should be looked at as a protective mechanism. However, the uncontrolled *NLRP3* activation as a response to non-infectious or non-threatening stimuli may cause unwanted reactions and diseases, among which the auto-inflammatory entities.¹⁷ Though a number of inflammasomes have been described, the *NLRP3* inflammasome is the most extensively studied, but also the most elusive. It is distinguished by the fact that it responds to numerous physically and chemically diverse stimuli.¹⁸ The *NLRP3* inflammasome may directly or indirectly interact with proteins mutated in other autoinflammatory diseases, including pyrin (in FMF) and proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) (in PAPA syndrome).

From a mechanistic perspective, the cyclic GMP-AMP (cGAMP) synthase (cGAS) is a cytosolic DNA sensor that mainly acts by activating the innate immune response. Its action is mainly mediated by the production of a second messenger cGAMP which in its turn activates the stimulator of interferon genes adaptor (STING).¹⁹ cGAS is an intracellular enzyme that binds double-stranded DNA and activates a subsequent signaling cascade that includes the STING adaptor leading to the production of inflammatory responses.²⁰

Mitochondrial DNA (mtDNA) escaping the stressed mitochondria can mediate inflammation via the cGAS-STING pathway activation, and once oxidized, it binds cytosolic *NLRP3* and triggers inflammasome activation.²¹ However, the exact mecha-

nism by which the oxidized mitochondrial DNA exits the stressed mitochondria in non-apoptotic macrophages is still unknown. *NLRP3* inflammasome activators partly work on uniporter-mediated calcium uptake to open mitochondrial permeability transition pores (mPTP) and subsequently trigger voltage-dependent anion selective channel (VDAC) oligomerization without generating reactive oxygen species. The mPTP is an inducible channel that regulates solute exchange between the mitochondrial matrix content, and the surrounding cytoplasm, which acutely leads to loss of mitochondrial inner membrane potential, and eventually organelle swelling and rupture. Mitochondrial rupture due to prolonged mPTP engagement, which is often the result of ischemic cellular injury due to elevated intracellular Ca^{2+} levels and reactive oxygen species, leads to regulated necrotic cell death.²² Inhibition of VDAC oligomerization has been shown to decrease mtDNA release, interferon (IFN) signaling, neutrophil extracellular traps, and worsen clinical disease severity in a wide range of autoinflammatory and autoimmune diseases such as systemic lupus erythematosus (Figure 1).²³

Pharmacological inhibition of *NLRP3* activation results in adequate therapeutic effects in a wide variety of rodent models of inflammatory diseases, these effects were also replicated in models with genetic ablation of *NLRP3*. Although these findings highlight the potential of *NLRP3* as a drug target, there is not a clear and complete understanding of *NLRP3* structure and activation

mechanisms up until today, which has slowed the discovery and development of novel therapeutic agents against this molecule.²⁴

Cryopyrin-associated periodic syndrome

CAPS mainly arises following a gain-of-function mutation in the *NLRP3*.²⁵ The CAPS consists of a range of diseases that include FCAS, (formerly termed familial cold urticaria), MWS, and NOMID (also called chronic infantile neurologic cutaneous and articular syndrome). The observed pathogenesis in this spectrum of disorders is mainly a gain of function mutation in a key component of the IL-1 inflammasome.²⁶

Dysregulated production of IL-1 leads to the development of fever along with myalgia, chills, and night sweats, as well as severe fatigue, headache, ocular inflammation (resulting in red eyes), and a characteristic urticarial rash.²⁷

The described rash is distributed equally over the arms, trunk, and legs. The lesions present as erythematous macules or slightly raised papules/plaques. They are neither edematous nor annular in nature, although they may have a peripheral halo of vasoconstriction.

The lesions in question resolve within 24 hours. If CAPS remains untreated, irreversible damage may occur, which can include sensorineural hearing loss, vision loss, skeletal deformities, cognitive disability, and systemic AA amyloidosis.

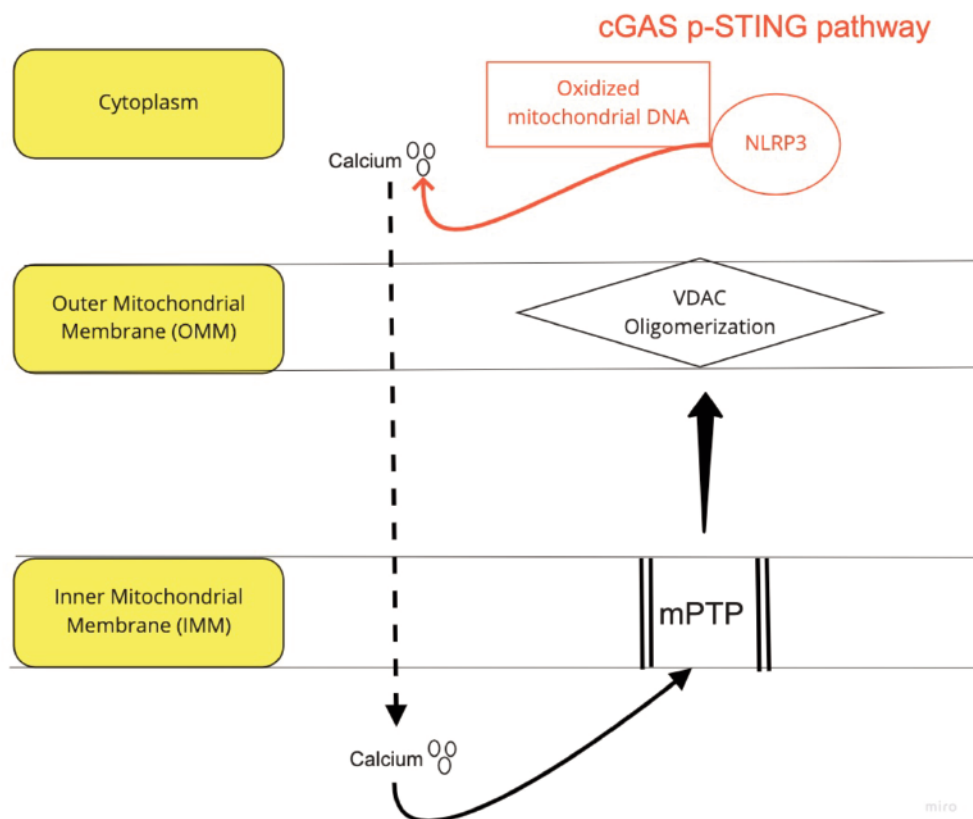


Figure 1. *NLRP3* inflammasome activators partly work on uniporter-mediated calcium uptake to open mitochondrial permeability transition pores and subsequently trigger voltage-dependent anion selective channel oligomerization without generating reactive oxygen species. Ischemic cellular injury due to elevated intracellular Ca^{2+} levels and reactive oxygen species underlies regulated necrotic cell death in interleukin-1 β -mediated autoinflammation. cGAS, cyclic GMP-AMP synthase; pSTING, stimulator of interferon genes; mPTP, mitochondrial permeability transition pores; VDAC, voltage-dependent anion selective channel.

Tumor necrosis factor receptor-1 associated periodic syndrome

The causative gene product of TRAPS is the tumor necrosis factor receptor superfamily member 1A (*TNFRSF1A*). So far, 180 variations of the *TNFRSF1A* gene have been reported. Disease pathogenesis is greatly mediated by the cysteine-to-cysteine disulfide bonds in the extracellular domain of *TNFRSF1A*. In TRAPS, misfolding of mutated *TNFRSF1A* leads to the accumulation of the protein in the endoplasmic reticulum (ER), which causes ER stress and increased generation of mitochondrial reactive oxygen species; this, in turn, activates inflammasomes.

TRAPS is a group of autoinflammatory diseases resulting from the biological consequences of protein misfolding in the cells of the innate immune system.²⁸

This process is mainly mediated by a missense substitution in the p55 tumor necrosis factor receptor causing the protein misfolding. This substitution subsequently leads to ligand-independent kinase activation and unregulated cytokine production.

TRAPS has an estimated prevalence of 1 per million in the UK. The median age at presentation is 7 years, with initially episodic attacks. These attacks can be discrete or become near-continuous and are often prolonged, lasting several weeks. They are accompanied by fever, abdominal pain, rash, eye manifestations, pleuritic pain, headache, and lymphadenopathy. The disease-associated rashes can be nonspecific and pleomorphic. The most commonly described skin manifestations are a swollen peri-orbital rash, and migratory erythematous plaques overlying areas of muscle pain. Less commonly, serpiginous and urticarial rashes can also occur. TRAPS are associated with an acute phase response characterized by very elevated inflammatory markers as well as leukocytosis.

Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome

The causative gene product of PAPA syndrome is proline-serine-threonine phosphatase-interacting protein 1 (*PSTPIP1*) [also called CD2-binding protein 1 (*CD2BP1*)].

In patients with PAPA syndrome, mutations in *PSTPIP1* result in hyperphosphorylation of *PSTPIP1*, which strengthens its interaction with pyrin *via* the B-box domain to activate the pyrin inflammasome. This leads to increased secretion of IL-1 β .²⁹

Nuclear factor- κ B activation syndromes (relopathies)

Dysregulations of NF- κ B signaling are closely linked to the ubiquitination system. In addition to constitutive activation of NF- κ B, loss-of-function mutations in the ubiquitin-mediated NF- κ B regulatory system cause autoinflammatory diseases.³⁰

Blau syndrome/early-onset sarcoidosis

The gene responsible for Blau syndrome (BS)/early-onset sarcoidosis is *IBDI*, and its causative gene product is *NOD2*. Usually, *NOD2* recognizes muramyl dipeptide, leading to the activation of NF- κ B. Activating mutations lead to increased production of *NOD2* resulting in more active signaling *via* the *NOD2-RIPK2*-associated activation of NF- κ B. From a clinical standpoint, BS is characterized by a triad of granulomatous uveitis, arthritis, and skin rash along with camptodactyly, a flexion contracture of the fingers.³¹

Interferonopathies

The innate immune receptors (*e.g.*, cGAS, MDA5, and RIG-I) are responsible for the first-line defense against intracellular pathogens such as viral, bacterial, or own nucleic acid. This is achieved by a signaling cascade leading up to type I interferon signaling. Interferonopathies are associated with dysfunction of these innate immune receptors, subsequent type I interferon signaling, and immunoproteasome dysfunction.³²

Proteasome-associated autoinflammatory syndromes

Nakajo–Nishimura syndrome and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE) were the first PRAAS to be described.³³ Loss-of-function mutation in immunoproteasome components such as proteasome subunit b type *PSMB8*, *PSMB4*, *PSMA3*, *PSMB9*, or proteasome maturation protein (POMP) leads to increased secretion of type I IFN by immune cells.³⁴

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome

CANDLE syndrome occurs due to an abnormal functioning of the multicatalytic system proteasome–immunoproteasome. The final result is a sustained production of type I IFN that can be very much increased by minor triggers such as cold, stress, or viral infections. In CANDLE syndrome the proteasome system dysfunction leads to an inability of the cell to get rid of its waste proteins. This situation may lead to a weak or moderate state of pro-inflammation in the absence of triggers, but under situations of stress, higher requirements of removing waste proteins cannot be met.

The first gene mutations detected in patients with CANDLE syndrome were located in the gene *PSMB8* (proteasome subunit, b-type, 8) in chromosome 6p21.32, encoding the β 5i (i=inducible) subunit of the immunoproteasome. Additionally, mutations in *PSMB8* were responsible for the development of Nakajo–Nishimura syndrome.³⁵

The CANDLE genotype kept expanding with the discovery of new mutations in genes encoding other proteasome–immunoproteasome subunits, or the regulatory protein POMP. CANDLE syndrome is a disease of proteasome–immunoproteasome dysfunction, it can be inherited in a recessive homozygous, compound heterozygous, or digenic trait, and less commonly in a dominant fashion.

Clinically, patients typically start manifesting signs in early infancy. They suffer from recurrent or daily fevers, characteristic skin lesions, wasting, and fat loss. The dermatologic manifestations include but are not limited to acral, and perioritic lesions. These usually appear in newborns and infants and are not regularly seen in childhood or later on. They consist of intense, red or purplish, edematous plaques mostly located on the nose, ears, fingers, or toes. Cold may be a trigger for these lesions, but there is usually no history of cold exposure in such presentations.

Annular plaques can also be seen: these lesions usually start in infancy or childhood and consist of erythematous or purpuric edematous lesions, often with an annular shape and raised borders associated with a flat, purpuric center. They may appear in crops or individually and tend to fade within days or weeks, leaving a purpuric macule behind. New, active lesions coexist with residual, purpuric macules, which give a very typical appearance to the patients. These lesions are very conspicuous during childhood, but in adult life, they may be less visible and may be absent in long-

standing disease. Perioral and periocular edema has also been observed in these patients. They usually develop a persistent erythematous to violaceous edema during infancy and childhood that mainly involves the periorbital and perioral areas. These may also be visible after puberty and in long-standing disease.³⁶

Interleukin-1 receptor-related autoinflammatory diseases

Mutations in the *IL-1RN* (interleukin-1 receptor antagonist) gene lead to an autosomal recessive autoinflammatory disease. It manifests phenotypically as a deficiency of interleukin-1 receptor antagonist (DIRA).³⁷

Deficiency of the interleukin-1 and interleukin-36 receptor antagonists

A mutated *IL1RN* gene is the main culprit in the development of DIRA. This disease is a rare autosomal recessive entity mainly caused by the absence or the dysfunction of the IL1-receptor antagonist, leading to unregulated IL-1 receptor activity. Patients with DIRA present with a neonatal-onset pustular rash, multifocal osteitis, and periarticular soft tissue swelling. It can be treated successfully with Anakinra, which mitigates the effects of this genetic deficiency. On the other hand, deficiency of the IL-36 receptor antagonist (DITRA) is an autosomal recessive disease that is mainly caused by IL-36 receptor antagonist deficiency. The onset of DITRA spans typically from childhood to the 6th decade of life and may be precipitated by stress, pregnancy, or drugs. It is characterized by a recurrent generalized sterile pustular rash accompanied by neutrophilia and fever. Several case reports have demonstrated a favorable and beneficial role for Anakinra in patients suffering from DITRA.³⁸

What is new?

Cleavage-resistant RIPK1-induced autoinflammatory syndrome

CRIA syndrome is a recently discovered entity caused by mutations within the receptor-interacting serine/threonine-protein kinase 1 (*RIPK1*) gene. Symptoms of CRIA syndrome include: episodic unexplained fevers lasting 3 to 5 days and recurring every 2 to 4 weeks, tender lymphadenopathy, headache, mouth ulcers, tonsillitis, severe gastrointestinal symptoms such as pain and diarrhea, and hepatosplenomegaly in a smaller percentage of patients.³⁹

In CRIA syndrome, mutation of *RIPK1* allows the cell to bypass normal cellular checkpoints, resulting in uncontrolled cell death and inflammation. Due to its potent influence on cell death, *RIPK1* activity is highly regulated in human cells. When *RIPK1* is divided in half, it is disarmed and thus loses its ability to induce inflammation. In CRIA, genetic mutations hinder the cleavage of the molecule in two pieces, resulting in an autoinflammatory process.⁴⁰

Vacuoles, E1 ligase, X-linked autoinflammatory syndrome

The first description of VEXAS syndrome occurred in October 2020; it was exclusively described in males, with most cases diagnosed in mid to late adult life. VEXAS syndrome is caused by an acquired somatic mutation, mosaic postzygotic in nature, involving the methionine-41 codon in *UBA1*. This gene encodes the major E1 enzyme involved in the activation of ubiquitin, a small regulatory protein that attaches to substrates destined for degradation (ubiquitylation). The p.Met 41 mutation results in decreased ubiquitylation, particularly in hematopoietic stem cells,

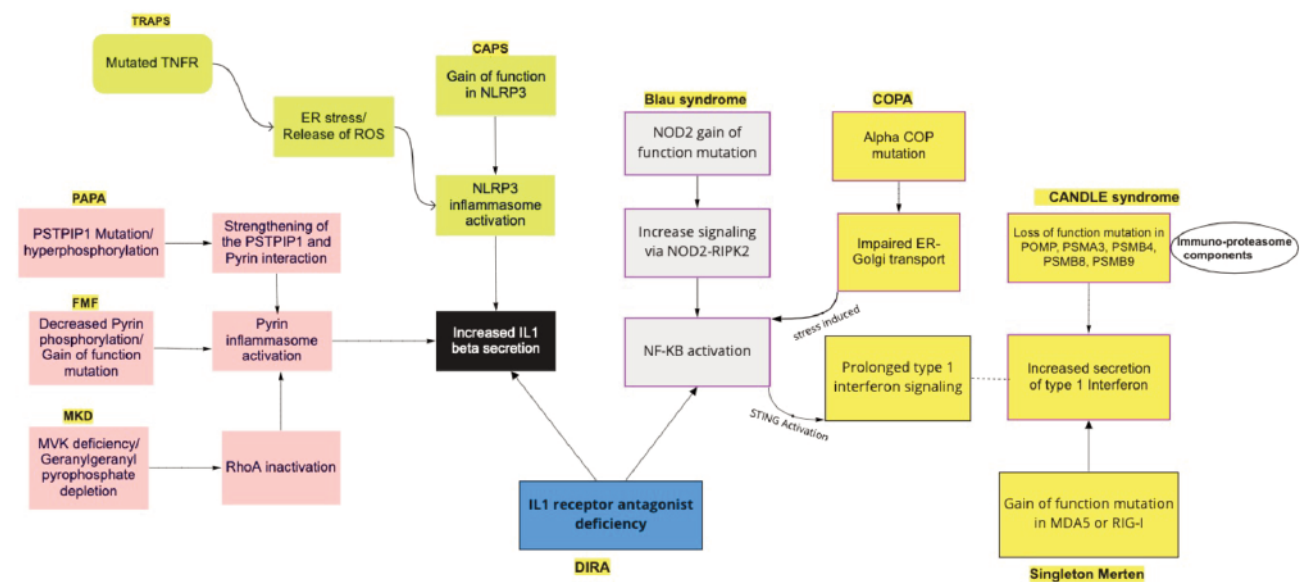


Figure 2. Pathophysiology and molecular signaling mediating autoinflammatory diseases. CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome; CAPS, cryopyrin-associated periodic syndrome; COPA, coatamer protein alpha; DIRA: deficiency of IL-1 receptor antagonist; ER, endoplasmic reticulum; FMF, familial Mediterranean fever; IL-1, interleukin-1; MKD, mevalonate kinase deficiency; MVK, mevalonate kinase gene; PAPA, pyogenic arthritis, pyoderma - gangrenosum and acne; ROS, reactive oxygen species; TNFR, tumor necrosis factor receptor; TRAPS, tumor necrosis factor receptor-associated periodic fever syndromes.

leading to undue activation of the innate immune system. Despite being clinically heterogeneous, VEXAS syndrome is characterized by treatment-resistant autoinflammatory manifestations, most commonly involving the skin and bone marrow. Hematologic features in VEXAS syndrome include macrocytic anemia, thrombocytopenia as well as myelodysplastic syndromes.⁴¹

Cutaneous manifestations include polyarthritides involving the nose and ear, vasculitis resembling polyarteritis nodosa, and neutrophilic dermatoses resembling acute febrile neutrophilic dermatosis with tender, red-violaceous, firm, and pigmented papules nodules and plaques.⁴²

Conclusions

In this review, we highlighted the pathophysiology and molecular signals mediating various autoinflammatory diseases including inflammasomopathies, NF- κ B activation (relopathies), interferonopathies, and IL-1 receptor-related autoinflammatory diseases. We also presented more recent entities mediated by *RIPK1* mutation and ubiquitin activation (Figure 2).

In conclusion, dysregulation of the disease-specific signalosome pathways greatly contributes to the pathogenesis and development of most autoinflammatory diseases. Further exploration of the molecular dysregulations behind each of these autoinflammatory diseases will facilitate the development of disease-targeting drugs. Subsequent studies should focus pathophysiology and molecular mechanisms of signalosomes which may uncover potential candidates for targeted therapy and future drug development.

References

1. Arakelyan A, Nersisyan L, Poghosyan D, et al. Autoimmunity and autoinflammation: A systems view on signaling pathway dysregulation profiles. *PLoS One* 2017;12:e0187572.
2. Medzhitov R. Origin and physiological roles of inflammation. *Nature* 2008;454:428-35.
3. Christgen S, Place DE, Kanneganti T-D. Toward targeting inflammasomes: insights into their regulation and activation. *Cell Research* 2020;30:315-27.
4. Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signalling. *Nat Rev Immunol* 2016;16:407-20.
5. Zhong FL, Mamaï O, Sborgi L, et al. Germline NLRP1 mutations cause skin inflammatory and cancer susceptibility syndromes via inflammasome activation. *Cell* 2016;167:187-202.e17.
6. Lamkanfi M, Dixit VM. Inflammasomes and their roles in health and disease. *Annu Rev Cell Dev Biol* 2012;28:137-61.
7. Fenini G, Contassot E, French LE. Potential of IL-1, IL-18 and inflammasome inhibition for the treatment of inflammatory skin diseases. *Front Pharmacol* 2017;8:278.
8. Faustin B, Reed JC. Sunburned skin activates inflammasomes. *Trends Cell Biol* 2008;18:4-8.
9. Fenini G, Karakaya T, Henning P, et al. NLRP1 inflammasome activation in keratinocytes: increasing evidence of important roles in inflammatory skin diseases and immunity. *J Invest Dermatol* 2022;142:2313-22.
10. Lu A, Magupalli VG, Ruan J, et al. Unified polymerization mechanism for the assembly of ASC-dependent inflammasomes. *Cell* 2014;156:1193-206.
11. Grandemange S, Sanchez E, Louis-Plence P, et al. A new autoinflammatory and autoimmune syndrome associated with NLRP1 mutations: NAIAD (NLRP1-associated autoinflammation with arthritis and dyskeratosis). *Ann Rheum Dis* 2017;76:1191-8.
12. Masumoto J, Zhou W, Morikawa S, et al. Molecular biology of autoinflammatory diseases. *Inflamm Regen* 2021;41:33.
13. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol* 2009;27:519-50.
14. Mitchell PS, Sandstrom A, Vance RE. The NLRP1 inflammasome: new mechanistic insights and unresolved mysteries. *Curr Opin Immunol* 2019;60:37-45.
15. Gurung P, Lukens JR, Kanneganti TD. Mitochondria: diversity in the regulation of the NLRP3 inflammasome. *Trends Mol Med* 2015;21:193-201.
16. Verma D, Fekri SZ, Sigurdardottir G, et al. Enhanced inflammasome activity in patients with psoriasis promotes systemic inflammation. *J Invest Dermatol* 2021;141:586-95.e5.
17. Elliott EI, Sutterwala FS. Initiation and perpetuation of NLRP3 inflammasome activation and assembly. *Immunol Rev* 2015;265:35-52.
18. Gross O, Thomas CJ, Guarda G, Tschopp J. The inflammasome: an integrated view. *Immunol Rev* 2011;243:136-51.
19. Chen Q, Sun L, Chen ZJ. Regulation and function of the cGAS-STING pathway of cytosolic DNA sensing. *Nat Immunol* 2016;17:1142-9.
20. Ablasser A, Chen ZJ. cGAS in action: expanding roles in immunity and inflammation. *Science* 2019;363:eaat8657.
21. Xian H, Watari K, Sanchez-Lopez E, et al. Oxidized DNA fragments exit mitochondria via mPTP- and VDAC-dependent channels to activate NLRP3 inflammasome and interferon signaling. *Immunity* 2022;55:1370-85.e8.
22. Karch J, Molkentin JD. Identifying the components of the elusive mitochondrial permeability transition pore. *Proc Natl Acad Sci U S A* 2014;111:10396-7.
23. Kim J, Gupta R, Blanco LP, et al. VDAC oligomers form mitochondrial pores to release mtDNA fragments and promote lupus-like disease. *Science* 2019;366:1531-6.
24. Mangan MSJ, Olhava EJ, Roush WR, et al. Targeting the NLRP3 inflammasome in inflammatory diseases. *Nat Rev Drug Discov* 2018;17:588-606.
25. Rowczenio DM, Trojer H, Russell T, et al. Clinical characteristics in subjects with NLRP3 V198M diagnosed at a single UK center and a review of the literature. *Arthritis Res Ther* 2013;15:R30.
26. Booshehri LM, Hoffman HM. CAPS and NLRP3. *J Clin Immunol* 2019;39:277-86.
27. Oldham J, Lachmann HJ. The systemic autoinflammatory disorders for dermatologists. Part 2: disease examples. *Clin Exp Dermatol* 2020;45:967-73.
28. Ryan JG, Aksentijevich I. Tumor necrosis factor receptor-associated periodic syndrome: toward a molecular understanding of the systemic autoinflammatory diseases. *Arthritis Rheum* 2009;60:8-11.
29. Shoham NG, Centola M, Mansfield E, et al. Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. *Proc Natl Acad Sci U S A* 2003;100:13501-6.
30. Aksentijevich I, Zhou Q. NF- κ B pathway in autoinflammatory diseases: dysregulation of protein modifications by ubiquitin defines a new category of autoinflammatory diseases. *Front Immunol* 2017;8:399.
31. Wouters CH, Maes A, Foley KP, et al. Blau Syndrome, the prototypic auto-inflammatory granulomatous disease. *Pediatric Rheumatol Online J* 2014;12:33.

32. Kato H, Oh SW, Fujita T. RIG-I-like receptors and type I interferonopathies. *J Interferon Cytokine Res* 2017;37:207-13.
33. Ohmura K. Nakajo-nishimura syndrome and related proteasome-associated autoinflammatory syndromes. *J Inflamm Res* 2019;12:259-65.
34. Brehm A, Liu Y, Sheikh A, et al. Additive loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients promote type I IFN production. *J Clin Invest* 2015;125:4196-211.
35. Liu Y, Ramot Y, Torreló A, et al. Mutations in proteasome subunit β type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. *Arthritis Rheum* 2012;64:895-907.
36. Torreló A. CANDLE Syndrome as a paradigm of proteasome-related autoinflammation. *Front Immunol* 2017;8:927.
37. Aksentijevich I, Masters SL, Ferguson PJ, et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. *N Engl J Med* 2009;360:2426-37.
38. Hospach T, Glowatzki F, Blankenburg F, et al. Scoping review of biological treatment of deficiency of interleukin-36 receptor antagonist (DITRA) in children and adolescents. *Pediatr Rheumatol Online J* 2019;17:37.
39. Shabir O. What is CRIA syndrome?; 2022. Available from: <https://www.news-medical.net/health/What-is-CRIA-syndrome.aspx>.
40. Hannik N. The genetic mutation behind a new autoinflammatory disease. Available from: <https://pursuit.unimelb.edu.au/articles/the-genetic-mutation-behind-a-new-autoinflammatory-disease>.
41. Syuen Ng WH Keefe M. Vexas syndrome; 2021. Available from: <https://dermnetnz.org/topics/vexas-syndrome>.
42. Duncan M, Basu T, Salisbury J, et al. BG06: vexas syndrome: a case series. *BJD* 2022;187:91.