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REVIEW ARTICLE

Clinical and biochemical landmarks in systemic autoinflammatory diseases

LUCA CANTARINI[1], DONATO RIGANTE[2], MARIA GIUSEPPINA BRIZI[1], ORSO MARIA LUCHERINI[3], GIAN DOMENICO SEBASTIANI[4], ANTONIO VITALE[1], VALENTINA GIANNERAMO[2] & MAURO GALEAZZI[1]

[1]*Interdepartmental Research Center of Systemic Autoimmune and Autoinflammatory Diseases, Unit of Rheumatology, Policlinico Le Scotte, University of Siena, Siena, Italy,* [2]*Department of Pediatric Sciences, Università Cattolica Sacro Cuore, Rome, Italy,* [3]*Department of Evolutionary Biology, University of Siena, Siena, Italy, and* [4]*UOC of Rheumatology, S. Camillo-Forlanini Hospital, Rome, Italy*

Abstract

Systemic autoinflammatory diseases are a group of inherited disorders of the innate immune system characterized by seemingly unprovoked inflammation recurring at variable intervals and involving skin, serosal membranes, joints, and gastrointestinal apparatus, with reactive amyloidosis as a possible severe long-term complication. Recent advances in genetics and molecular biology have improved our understanding of the pathogenesis of these diseases, including familial Mediterranean fever, mevalonate kinase deficiency syndrome, tumor necrosis factor receptor-associated periodic syndrome, cryopyrin-associated periodic syndromes, and hereditary pyogenic and granulomatous disorders: the vast majority of these conditions are related to the activation of the interleukin-1 pathway, which results in (or from?) a common unifying pathogenetic mechanism. Their diagnostic identification derives from the combination of clinical data, evaluation of acute phase reactants, clinical efficacy in response to specific drugs, and recognition of specific mutations in the relevant genes, although genetic tests may be unconstructive in some cases. This review will discuss clinical and laboratory clues useful for a diagnostic approach to systemic autoinflammatory diseases.

Key words: *Autoinflammatory diseases, cytokines, diagnosis, serum amyloid A (SAA)*

Introduction

Systemic autoinflammatory diseases (SAIDs) are a heterogeneous group of genetically determined illnesses that involve the innate immune system and are by definition characterized by the apparently inexplicable recurrence of acute inflammatory episodes affecting the skin, serosal membranes, joints, gastroenteric tube, central nervous system, etc. The term 'autoinflammatory' describes the spontaneous appearance of inflammation in the absence of auto-reactive T lymphocytes or specific auto-antibodies, which in point of fact play a pathogenetic role in the autoimmune diseases (1). All SAIDs are caused by lack of regulation in the production of proinflammatory cytokines, such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α, which leads to a pathological delay in inflammatory response deactivation (2). SAIDs can be categorized as hereditary monogenic disorders—the subject of this description—and multifactorial polygenic disorders such as Behçet's disease, adult Still's disease, systemic-onset juvenile idiopathic arthritis, and PFAPA (periodic fever, adenitis, pharyngitis, and aphthosis) syndrome (3).

Correspondence: Luca Cantarini, MD, PhD, Unit of Rheumatology, Policlinico Le Scotte, University of Siena, Viale Bracci 1, 53100 Siena, Italy. Fax: +39 (0) 577 40450. E-mail: cantariniluca@hotmail.com

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Key messages

- The genes associated with systemic autoinflammatory diseases (SAIDs) have been identified in recent years and, with the exception of hyper-gammaglobulinemia D syndrome, all encode for proteins involved in the inflammatory response and in the processes of cellular apoptosis.
- The activation or deregulation of cytokine production is directly implicated in the pathogenesis of SAIDs, and the central role of interleukin-1 has been confirmed in the last decade thanks to advances in techniques used to identify human disease-causing genes, innovations in genomic analysis, and progress in effective targeted biologic therapy.
- The diagnostic identification of SAIDs derives from the combination of clinical data, evaluation of acute-phase reactants, clinical efficacy in response to specific drugs, and genetic testing.

Abbreviations

BS	Blau syndrome
CAPS	cryopyrin-associated periodic syndromes
CINCAs	chronic infantile neurological cutaneous and articular syndrome
DIRA	deficiency of interleukin-1 receptor antagonist
FCAS	familial cold urticaria syndrome
FMF	familial Mediterranean fever
HIDS	hyper-gammaglobulinemia D syndrome
IL	interleukin
MK	mevalonate kinase
MKD	mevalonate kinase deficiency syndrome
MS	Majeed syndrome
MWS	Muckle–Wells syndrome
NLRP12-ad	NLRP12-associated autoinflammatory disorder
PAPAs	pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome
PFAPA	periodic fever, adenitis, pharyngitis, and aphthosis
SAA	serum amyloid-A
SAID	systemic autoinflammatory disease
TNFRSF1A	55 kDa receptor of TNF-α
TNF-α	tumor necrosis factor-α
TRAPS	tumor necrosis factor receptor-associated periodic syndrome

Classification of the systemic autoinflammatory diseases

The hereditary monogenic SAIDs, characterized by a common clinical phenotype marked by recurrent episodes of fever and varying signs of systemic inflammation, include familial Mediterranean fever (FMF), mevalonate kinase deficiency syndrome (MKD), also known as hyper-gammaglobulinemia D syndrome (HIDS), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), the family of cryopyrin-associated periodic syndromes (CAPS), which in turn include familial cold urticaria syndrome (FCAS), Muckle–Wells syndrome (MWS), and CINCA (chronic infantile neurological cutaneous and articular) syndrome (CINCAs), NLRP12-associated autoinflammatory disorder (NLRP12-ad), hereditary pyogenic disorders including PAPA (pyogenic sterile arthritis, pyoderma gangrenosum, and acne) syndrome (PAPAs), Majeed syndrome (MS), and IL-1 receptor antagonist deficiency (DIRA), and finally a granulomatous disorder with familiar presentation, called Blau syndrome (BS) (Table I). Some of these (namely FMF, HIDS, MS, and DIRA) are transmitted by autosomal recessive inheritance, while the others (TRAPS, FCAS, MWS, CINCAs, NLRP12-ad, PAPAs, and BS) are autosomal-dominant. The genes associated with these diseases have been identified in recent years and, with the exception of HIDS, all encode for proteins involved in the inflammasome, a multi-protein complex regulating the innate immunity and activating the processing and secretion of proinflammatory cytokines (4).

Prominent clinical details of the systemic autoinflammatory diseases

FMF is the most common autoinflammatory disease in the world, with a particularly high incidence throughout the Mediterranean basin, especially among Sephardic (non-Ashkenazi) Jews, Turks, Armenians, and Arabs. The gene responsible for FMF, denominated *MEFV* (from *MEditerranean FeVer*), identified in 1997 on chromosome 16, is made up of 10 exons and encodes for a 781-amino acid protein called pyrin (or 'marenostrin', from the ancient Latin name for the Mediterranean sea, *Mare nostrum*) (5,6). Pyrin (Figure 1) is believed to orchestrate IL-1β processing and release in various types of cells, including neutrophil and eosinophil granulocytes, monocytes, dendritic cells, and fibroblasts, through a down-regulation of the inflammasome function (7–9). Diagnosis of FMF is based on the use of Tel Hashomer criteria (recurrent episodes of fever associated with serositis, presence of amyloidosis, and favorable response to colchicine) (10). Although the disease typically appears in childhood, diagnosis after age 20 is not rare, even in the presence of a clinical phenotype virtually identical to that noted in childhood cases (11), i.e. brief recurrent episodes of fever, serositis manifesting with chest

Table I. Descriptive summary of the systemic autoinflammatory diseases.

Disease	*Gene* (locus)	Protein	Inheritance	Essential clinical clues	Therapies
FMF	*MEFV* (16p13.3)	Pyrin	AR	Fever, serositis, arthralgias or arthritides, erysipelas-like eruption on the legs, amyloidosis in the untreated patients	Colchicine, anakinra
HIDS	*MVK* (12q24)	Mevalonate kinase	AR	Fever, polymorphous rash, arthralgias, abdominal pain, diarrhea, lymph node enlargement, splenomegaly, aphthosis	Anti-inflammatory drugs, corticosteroids, anakinra
TRAPS	*TNFRSF1A* (12p13)	Tumor necrosis factor receptor 1	AD	Fever, migrating muscle and joint involvement, conjunctivitis, periorbital edema, arthralgias or arthritides, serosal involvement, steroid responsiveness of febrile attacks, amyloidosis	Corticosteroids, etanercept, anakinra
FCAS	*NLRP3* (1q44)	Cryopyrin	AD	Fever, cold-induced urticarial rash, conjunctivitis, arthralgias	Anakinra, rilonacept, canakinumab
MWS				Fever, urticarial rash, conjunctivitis, episcleritis, arthralgias, neuro-sensorial deafness, amyloidosis	
CINCAs				Fever, urticarial rash, uveitis, papilledema, deforming arthritis involving large joints, aseptic chronic meningopathy, neuro-sensorial deafness, amyloidosis	
NLRP12-ad	*NLRP12* (19q13)	Monarch-1	AD	Fever, arthralgia, cold-induced urticarial rash	Anakinra
PAPAs	*PSTPIP1* (15q24-25)	CD2 antigen-binding protein 1	AD	Pyogenic arthritis, pyoderma gangrenosus, acne	Corticosteroids, infliximab, anakinra
MS	*LPIN2* (18p11.31)	Lipin 2	AR	Recurrent multifocal osteomyelitis, dyserythropoietic anemia, neutrophilic dermatosis	Corticosteroids
DIRA	*IL1RN* (2q14)	Interleukin-1 receptor antagonist	AR	Multifocal osteomyelitis and diffuse pustular rash with neonatal onset	Anakinra
BS	*NOD2/CARD15* (16q12.1-13)	NOD2/ CARD15	AD	Non-erosive granulomatous polyarthritis, granulomatous uveitis, granulomatous rash	Corticosteroids, infliximab

AD = autosomal-dominant; AR = autosomal recessive; BS = Blau syndrome; CINCAs = chronic infantile neurologic cutaneous articular syndrome; DIRA = interleukin-1 receptor antagonist deficiency; FCAS = familial cold autoinflammatory syndrome; FMF = familial Mediterranean fever; HIDS = hyper-gammaglobulinemia D syndrome; MS = Majeed syndrome; MWS = Muckle–Wells syndrome; NLRP12-ad = NLRP12-associated autoinflammatory disorder; PAPAs = PAPA syndrome; TRAPS = tumor necrosis factor receptor-associated periodic syndrome.

and/or abdominal pain, arthralgia and/or arthritis of the hip, knee, or ankle, and erysipelas-like erythema, frequently on the lower limbs. Fever episodes begin suddenly, last 1–4 days, tend to resolve spontaneously, and alternate with periods of perfect health. The most worrisome complication of undiagnosed/untreated FMF is AA-amyloidosis, which can involve all of the organs, but frequently impacts the kidneys, gut, spleen, and liver (12). Possible muscular involvement has also been described, ranging from minor forms of myalgia to protracted febrile myalgias, even with no increase in muscular enzymes, except in very rare cases in which such an increase reflects the depositing of amyloid fibrils in the skeletal musculature or iatrogenic damage linked to colchicine treatment (13,14). Most patients with amyloidosis and renal involvement develop a nephrotic syndrome and may face chronic renal insufficiency (15).

MKD, better known as HIDS, or 'Dutch fever' as it was first described in 1984 in the Netherlands (16), is caused by mutations in the *MVK* gene located on chromosome 12 that encodes for mevalonate kinase (MK)—the second enzyme in the metabolic pathway of cholesterol—which lead to a reduction of enzymatic activity, but not its complete abolition (17–19): this enzyme normally catalyzes the phosphorylation of mevalonic acid into 5-phosphomevalonate and supplies numerous bioactive molecules, such as sterols with isoprenilic groups (20). However, the molecular mechanism at the root

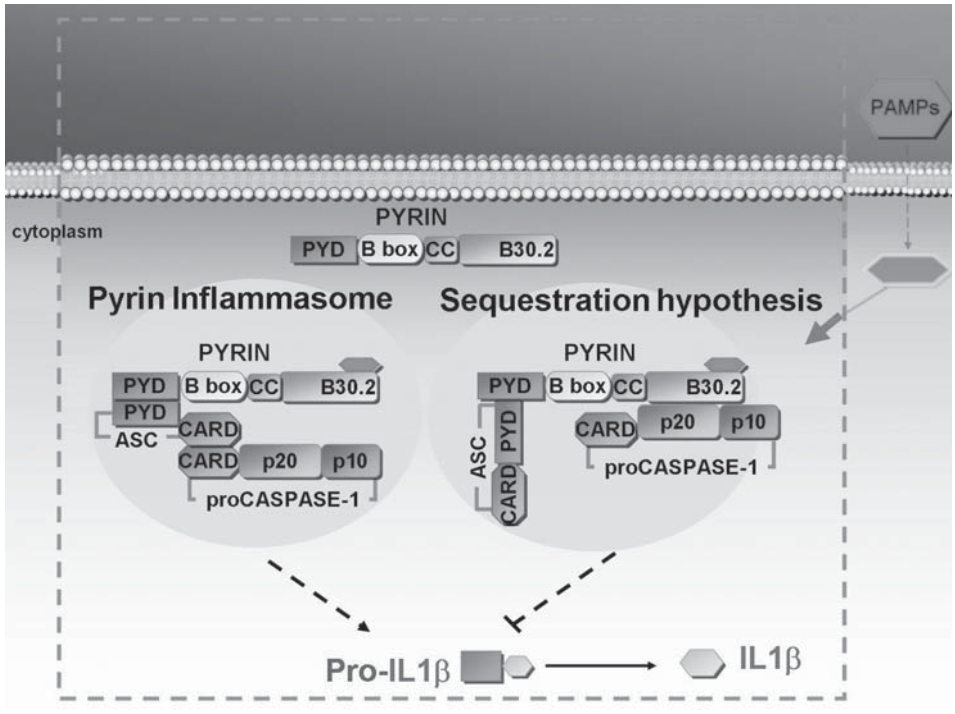

Figure 1. Proposed mechanisms of pyrin action in FMF. *Pyrin inflammasome hypothesis*: Pyrin can assemble the 'inflammasome' complex through pyrin–pyrin domain interaction with ASC, resulting in activation of caspase-1. *Sequestration hypothesis*: Pyrin has an inhibitory effect on caspase-1-mediated activation of IL-1β by competitive binding of ASC, as well as caspase-1. (PAMPs = pathogen-associated molecular patterns; PYD = pyrin domain; B-box = B-box zinc finger; CC = coiled-coiled region; ASC = apoptosis-associated speck-like protein containing a CARD; CARD = caspase recruitment domain; IL = interleukin).

of the inflammatory phenotype has not yet been identified, and the relationship between MK deficiency and inflammation remains enigmatic. In 75% of cases, the disease initially manifests itself within the first year of life and in all cases within the first 5 years; it usually persists throughout the patient's entire life, but attacks tend to diminish over time in intensity and frequency (21). From the clinical point of view, attacks start with high fever, often accompanied by chills, lasting 4–7 days and generally recurring every 3–4 weeks; these fever episodes may be preceded by headache, weakness, or irritability and are accompanied by arthralgia, lymphadenopathy, vomiting, diarrhea, abdominal pain, splenomegaly, and mouth ulcers. Cutaneous involvement is very frequent, in the form of various types of rashes, from macular and papular to urticarial and nodular (22).

TRAPS, first described in 1982 in a family of both Irish and Scottish ancestry and initially called 'Hibernian fever' in reference to the ancient Latin name for Ireland, 'Hibernia', is the most common autosomal-dominant autoinflammatory pathology (23). It is caused by mutations in the *TNFRSF1A* gene, which encodes for the 55 kDa receptor of TNF-α (TNFRSF1A or TNFR p55) (Figure 2), a member of the family of TNF receptors involved in the processes of T cell activation and B cell homeostasis (24–26). The average age at which the disease makes its appearance is around 3, but it may sometimes arise in late adolescence. Attacks last 20 days on average and recur at varying intervals, generally longer than those seen in other SAIDs (27), initiating with muscle cramps or myalgia that migrates in a centrifugal pattern, followed by fever associated with cutaneous, joint, abdominal, and ocular manifestations (28). The most common cutaneous manifestation is centrifugal migratory erythematous rash, which overlies the area affected by myalgia; this type of lesion is painful and warm to the touch. Arthralgias are common, and in rare cases arthritis may be present, mainly affecting single joints. Abdominal pain is another typical sign of TRAPS and is an indication of inflammation of the peritoneal cavity and abdominal wall muscles. Finally, eye involvement is also quite characteristic and can manifest itself in the form of conjunctivitis, periorbital edema, and uveitis (29).

CAPS include three phenotypical expressions of the same autosomal-dominant pathology: FCAS, MWS, and CINCAs, respectively, from the least to most serious. Between 1999 and 2001 these conditions were linked with mutations of the *NLRP3* gene

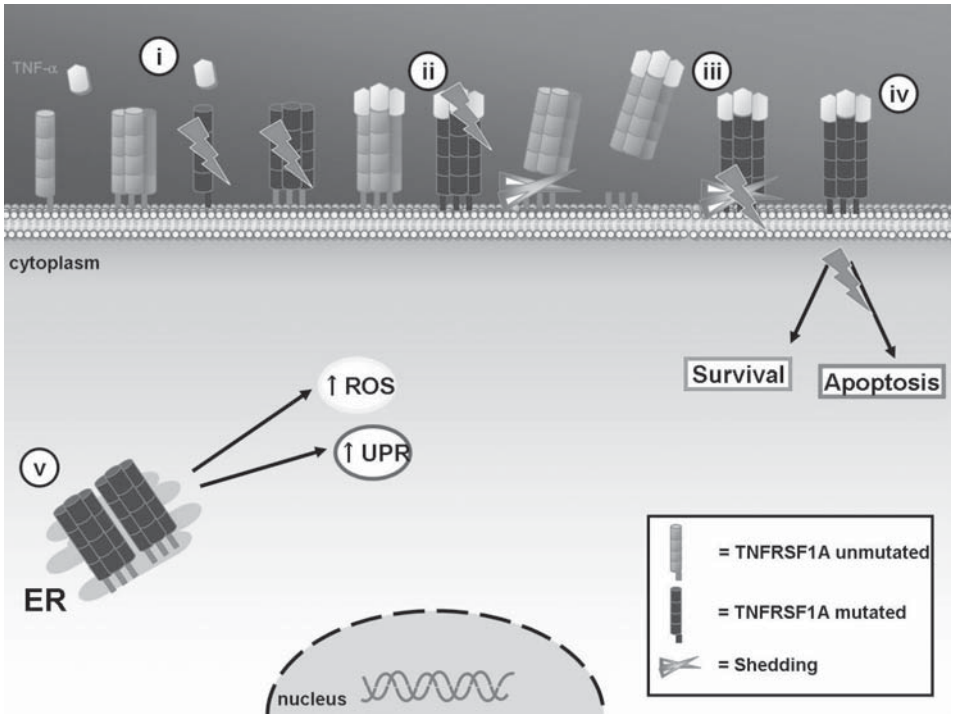

Figure 2. Mechanisms of TNFRSF1A action in the pathogenesis of TRAPS. The TNF receptor (TNFRSF1A) participates in the regulation of inflammatory responses through TNF-α binding. TRAPS-associated *TNFRSF1A* mutations may present alterations in: i) receptor trafficking to the cell surface; ii) TNF-α binding; iii) activation-induced shedding of the receptor; iv) TNF-α induced activation of transcription factors or apoptosis; and v) accumulation of aberrant receptors in the ER with increased formation of ROS and activation in UPR. (TNF = tumor necrosis factor; ER = endoplasmic reticulum; ROS = reactive oxygen species; UPR = unfolded protein response).

located on chromosome 1 (30), which encodes for a protein called 'cryopyrin', one of the intracellular sensors that participate in host defense mechanisms and induction of the inflammatory response (Figure 3) (31). In particular, FCAS is characterized by fever episodes associated with cutaneous rashes and arthralgias, most often triggered by exposure to cold (32). MWS is characterized by an analogous group of symptoms associated with migrating urticaria-like lesions, ocular abnormalities, progressive neuro-sensorial deafness, and risk of amyloidosis (33). The clinical triad of skin rash, chronic meningeal involvement, and arthropathy, usually involving the knees, distinguishes the CINCAs. A non-itching, urticaria-like rash is persistently present in 75% of cases from birth, and skin biopsy usually reveals a moderate neutrophil infiltration of derma. Central nervous system involvement manifests itself in the first years of life with seizures, ventriculomegaly, headache, and in some cases mental retardation. Eye involvement may lead to progressively worsening reduction of visual acuity and is associated with chronic anterior uveitis in half of cases (34). The major musculoskeletal deformities are caused by a premature and aberrant ossification of the knee-caps, with serious anomalies involving the epiphysis and hypertrophy of growth plates; shortening of the hands and feet and nail clubbing can often be observed as well (35). NLRP12-ad is a rare genetic disease with close similarity with FCAS, characterized by recurrent bouts of fever lasting several days, joint symptoms, and skin rash triggered by exposure to cold temperatures, requiring genetic differentiation from CAPS (36).

Hereditary pyogenic disorders pertain to the SAID group and are characterized by the recurrence of multiple inflammatory manifestations, mainly linked to the multi-site formation of a granulocytic exudate. They include PAPAs, characterized by erosive pyogenic arthritis, pyoderma gangrenosum, cutaneous abscesses, and nodule-cystic acne (37); MS, characterized by recurrent precociously arising multifocal osteomyelitis, dyserythropoietic anemia, and neutrophilic dermatosis (38); and DIRA, recently described as a neonatal autoinflammatory disorder characterized by multifocal osteomyelitis and pustular rash, caused by unopposed IL-1 activity and uncontrolled inflammatory responses involving bone and skin (39).

Among the granulomatous disorders, BS can be considered an autoinflammatory syndrome of the joints, eyes, and skin, manifesting through the association of non-erosive granulomatous polyarthritis, severe

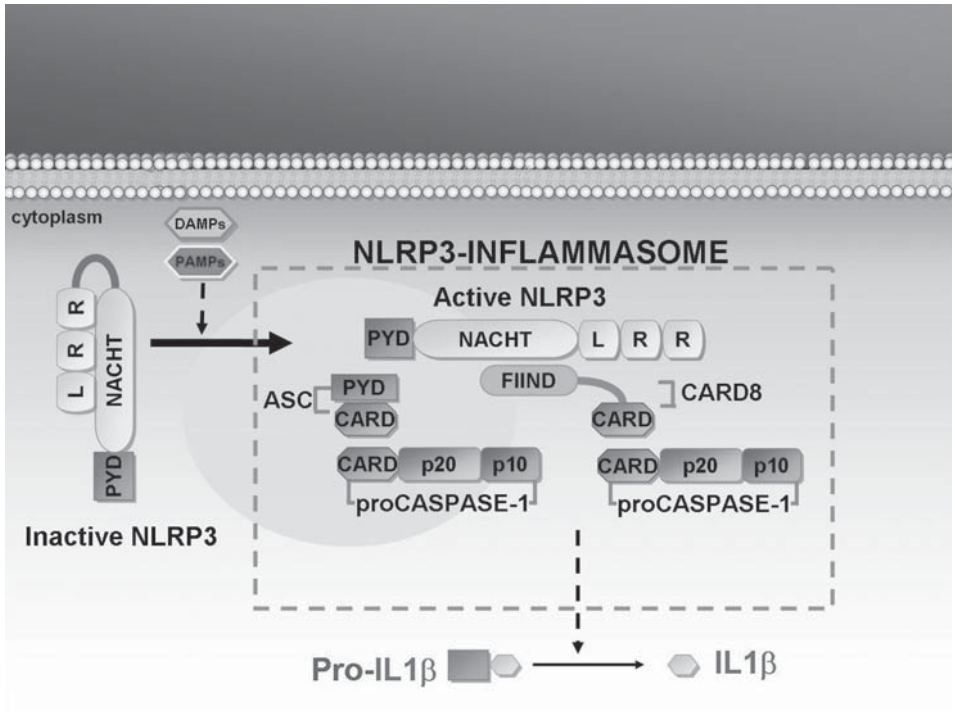

Figure 3. Mechanism of NLRP3 action in the pathogenesis of CAPS. Cryopyrin (or NLRP3) plays a key role in the inflammatory response by regulating IL-1β secretion. At rest, NLRP3 is inactive. Upon NLRP3 activation by means of agonist recognition, as with PAMPs (such as muramyl dipeptides, lipopolysaccharide, peptidoglycan, bacterial or viral RNA) and DAMPs (such as uric acid, ATP, or ultraviolet B radiations), NLRP3 interacts with several proteins (such as ASC and CARD8) to form the NLRP3–inflammasome: this multimolecular complex leads to caspase-1 activation, which in turn catalyzes the processing of IL precursor to IL-1β. (IL = interleukin; PAMPs = pathogen-associated molecular patterns; DAMPs = damage-associated molecular pattern molecules; PYD = pyrin domain; NACHT = nucleotide-binding oligomerization domain; LRR = leucine-rich repeat; ASC = apoptosis-associated speck-like protein containing a CARD; CARD = caspase recruitment domain; CARD8 = caspase recruitment domain family, member 8; FIIND = function to find domain).

granulomatous uveitis, and chronic panniculitis with juvenile onset (40).

Genetic diagnosis of the systemic autoinflammatory diseases

The clear Mendelian inheritance of SAIDs combined with improved genetic mapping methods has allowed for the identification of the underlying genes since 1997. To date, more than 180 mutations of the *MEFV* gene have been identified, the most frequent of which affect exons 2, 3, 5, and 10; mutations described in exons 1, 7, and 9 are rarer. Although there have been reports of symptomatic heterozygous patients, genetic tests are considered positive when they reveal two mutations, one for each allele (41). Over the years, various studies have been carried out with the goal of identifying a genotype–phenotype correlation, and the results obtained indicate that the most frequent mutations in homozygous subjects, such as M694V, M680I, and M694I, are associated with a more marked clinical severity than forms linked to compound heterozygosity (42).

Most of the *MVK* gene mutations identified to date are of the missense type, and most of the patients are heterozygous for two different mutations (43): the prevalent mutation is V377I, observed in approximately 80% of patients and associated with a modest reduction in the stability and catalytic activity of the enzyme MK (44).

More than 60 mutations of the *TNFRSF1A* gene have been described, about 60% of which are associated with TRAPS, consisting mainly of point mutations that lead to the replacement of a single amino acid in the external section of the mature protein (45). For the *NLRP3* gene, approximately 100 different mutations have been described so far, nearly all present on exon 3, which encodes the NACHT domain of cryopyrin; two exceptions are mutations located on exons 4 and 5, which encode for LRR (leucine-rich repeat) domain: a common model proposes that CAPS mutations result in a gain-of-function phenotype leading to a constitutive hyperproduction of IL-1 (46). NLRP12-ad (NLRP12 stands for NACHT, LRR, and PYD domains containing protein 12, also named 'monarch-1') is related to *NLRP12* mutations, which have been

identified very recently, underlining the importance of screening for the *NLRP12* gene in patients presenting with unexplained recurrent fevers and symptoms similar to CAPS (47).

PAPAs is transmitted as an autosomal-dominant trait and is linked to the *PSTPIP1* gene located on chromosome 15; MS is linked to the *LPIN2* gene and has been described only in Jordan; and DIRA is due to mutations in the *IL1RN* gene located on chromosome 2q14, which stop the physiological secretion of the IL-1 receptor antagonist (48).

BS is linked to the *CARD15/NOD2* gene: the mutations reported involve the NACHT portion and are associated with activation of the NF-κB protein complex (49).

All information regarding mutations described in patients with SAID can be found at the web address: http://fmf.igh.cnrs.fr/infevers (50).

The biohumoral picture of the systemic autoinflammatory diseases

In SAIDs, laboratory tests commonly reveal increases in indicators of inflammation during each acute inflammatory episode; in particular, marked increases are observed for erythro-sedimentation rate and C-reactive protein, as well as fibrinogen and haptoglobin, which characteristically return to normal levels during non-acute intervals. These increases can also be associated with abnormalities in blood cell count, such as neutrophil leukocytosis, thrombocytosis, and hypo- or normochromic anemia, which is typical of chronic inflammatory diseases. Also fairly frequent are findings of polyclonal hyper-gammaglobulinemia due to stimulation of immunoglobulin synthesis by numerous proinflammatory cytokines, such as IL-6 (51).

Characteristic but not specific to MKD are reports of elevated serum IgD and IgA levels, in agreement with what has been observed in other periodic fever disorders, as well as in numerous inflammatory disorders, immunodeficiencies, lymphoproliferative diseases, and even in completely healthy subjects (52). The exact role of IgD in the pathogenesis of MKD is still unclear, but its serum level can substantiate the diagnosis: serum IgD tests carried out during phases of clinical good health with results above 100 IU/mL contribute to the diagnosis but must be repeated in at least two consecutive tests at 1-month intervals (53). More precise for diagnostic purposes is the dosage of urinary mevalonic acid during the acute inflammatory attack, although the gold standard remains the quantification of MK enzyme activity (54).

Acute-phase reactants are often elevated in patients with TRAPS even between fever attacks, although at a lower level than during attacks, but the most determinant laboratory element of the quiescent phase is the finding of low serum levels of the soluble TNF receptor (<1 ng/mL), as the illness is linked to a defective release of the receptor from cell membranes (55).

In CAPS, and especially in CINCAs, a marked rise in the inflammatory parameters and a finding of nearly constant neutrophil leukocytosis are highly indicative (56).

The diagnostic contribution of serum amyloid-A and protein S100A12

Serum amyloid-A (SAA) is an acute-phase protein, synthesized and secreted by the liver upon stimulation by proinflammatory cytokines as IL-1, IL-6, and TNF-α (57). Its amino-terminal fragment may be deposited in various organs in the form of amyloid fibrils, leading to the development of AA-amyloidosis. The measurement of SAA is a useful diagnostic aid: elevated concentrations are associated with a risk of progressive amyloid fibril deposits in various parenchymas (58). It has been determined that a variable but considerable percentage of patients with FMF, TRAPS, and CAPS may develop renal amyloidosis: the most common clinical manifestation is peripheral edema caused by proteinuria, which may even reach the nephrotic range, the usual outcome of which is chronic renal insufficiency. In addition to the possibility of renal damage, there is also the risk of autonomous nervous system involvement—which leads to alterations in bowel habits and orthostatic hypotension—while heart involvement, with the potential development of restrictive cardiomyopathy, is rather unexpected (59). The ultimate goal of therapy in SAIDs is control of the inflammatory state, which must be accompanied by a reduction in SAA concentration to below 10 mg/L (60). In studies on the treatment of CAPS, SAA has been shown to be a useful parameter in the evaluation of clinical activity in response to therapy, as well as for response to treatment with TNF inhibitors in TRAPS (61–63).

Like that of SAA in inflammatory processes of various origins, the role of the protein S100A12 (or calgranulin C) has also been clarified (64): it is a calcium-binding protein expressed and secreted by neutrophil granulocytes which, through the NF-κB pathway, activates the inflammatory response in the endothelial cells and leukocytes of patients with CAPS. It has been demonstrated that determination of serum S100A12 levels is closely correlated not only with the disease activity, but also with the clinical efficacy of therapy, providing a reliable new marker for future utilization (65).

The cytokine pattern in the systemic autoinflammatory diseases

Cytokines are an important group of signal molecules that regulate numerous aspects of intercellular communication: cytokine signaling is fundamental for the proper functioning of the immune system, including its response to pathogens and extraneous cells, as well as self tolerance. The activation or deregulation of cytokine production is directly implicated in the pathogenesis of SAIDs, and the central role of IL-1 has been confirmed in the last decade thanks to advances in the techniques used to identify human disease-causing genes, innovations in genomic analysis, and progress in effective targeted biologic therapy. In particular, the activation of the IL-1β pathway appears to be the principal mechanism in most SAIDs (66). For example, in FMF, the mutated form of pyrin is capable of activating the caspase-1, which leads to secretion of IL-1β and triggering of the inflammatory response; there are also increases in IL-6 and IL-10 in FMF (67–69). In HIDS IL-1β, TNF-α, and IL-6 levels may all be elevated (70). A characteristic of TRAPS is increased levels of IL-6, TNF-α, IL-8, and IFN-γ (71,72), while in CAPS every clinical manifestation correlates with serum levels of IL-1β and, to a lower degree, IL-18 (73). It has been demonstrated that cultured monocytes from patients with FCAS release significant amounts of IL-1 when exposed to mild hypothermia (32°C), which in turn induces autocrine secretion of IL-6 and TNF-α (74). A similar cold-induced response has been observed in bone-marrow-derived dendritic cells isolated from mice with a common FCAS mutation (75).

Concluding remarks

The aggregate of these recent gains in knowledge have allowed physicians to establish targeted therapies with 'anti-cytokine' activity directed against those target molecules responsible for the inflammatory manifestations of SAIDs and thus to revolutionize the clinical pictures and outcomes of many patients. Although IL-1 is not the only effector cytokine driving the inflammatory process in all SAIDs, therapeutic approaches targeting the IL-1 pathway have shown dramatic responses especially in CAPS, as proven by several double-blind placebo-controlled studies, but other biologic agents have also shown mid-term clinical efficacy, as in the case of etanercept in patients with TRAPS (76,77). As new research continues to unravel the innate immune system's arsenal of sensory proteins, and the family of SAIDs expands, it is likely that the many pathways comprising IL-1 function will be explained, and new clinical uses for IL-1 inhibitors will be recognized.

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L. Cantarini and D. Rigante contributed equally to this paper.

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