Since 1944, as hyper-IgD associated with bouts of fever (MKD) [6]. This disorder had been clinically described as hyperimmunoglobulinemia D and Periodic Fever Syndrome (HIDS), cryopyrin-associated periodic fever syndrome (HAPS), and familial Hibernian fever. Other similar disorders include hyper-IgD, with no apparent cause, have already been recognized in the final decades of the last century.

The most well known of these disorders, the Familial Mediterranean Fever (FMF), described since antiquity, was recognized as clinical entity in 1945 [1]. Other similar disorders include hyperimmunoglobulinemia D, periodic fever syndrome (HIDS), cryopyrin-associated periodic syndrome (CAPS), and familial Hibernian fever.

A mutation of the MEFV (Mediterranean Fever) genes, located on the short arm of 16, was discovered in 1997 in the autosomal recessive disorder FMF [2]. These genes encode a protein, pyrin, found in neutrophils, granulocytes, monocytes, dendritic cells, and skin fibroblasts [3, 4]. Pyrin is a negative regulator of caspase-1, with an important role in innate immunity [5].

Additional mutations of the MKV genes, located on the chromosome 1 and encoding the enzyme mevalonate kinase (MVK) were discovered in 1999 in another disorder called hyperimmunoglobulinemia D and Periodic Fever Syndrome (HIDS), or Mevalonate Kinase Deficiency (MKD) [6]. This disorder had been clinically described since 1944, as hyper-IgD associated with bouts of fever recurring every 4–8 weeks [7].

Another disorder of this group is the autosomal dominant Cryopyrin-Associated Periodic Syndrome (CAPS). CAPS includes three subtypes: the familial cold autoinflammatory syndrome (FCAS), the Muckle–Wells Syndrome (MWS), and the neonatal onset multisystem inflammatory disease (NOMID or CYNCA syndrome). These subtypes are clinically differentiated by their severity, FCAS being the mildest form [5].

All three CAPS subtypes show mutations in the NALP3 genes (or CIAS/NLRP 3, or PYPAF), located on the chromosome 1 [8, 9]. These encode cryopyrin, a protein that, coupled with an ASC adaptor protein, is a component of inflammasomes [10].

Another disorder of this group is the familial Hibernian fever, clinically characterized by fever bouts lasting several days, skin rash, periarterial edema, and severe localized inflammation (arthritis, peritonitis, conjunctivitis). Six different mutations in the 55-kDa TNF receptor (TNF R1) were discovered in 1999 in this autosomal dominant inherited disorder. The finding of these mutations led to changing the name of these disorders to Tumor Necrosis Factor-Associated Periodic Syndrome (TRAPS) [11, 12].

Additional inherited disorders, mostly characterized by chronic inflammation and less by fever episodes, were included in this group, based on criteria centered on the alteration of the innate immunity. These include the PFAPA syndrome (periodic fever with aphthous stomatitis, pharyngitis, and adenitis), showing recurrent skin pathogeny and also due to the large extent of clinical forms resulting from the association of skin symptoms with other disorders included in this group.

**Keywords**: autoinflammatory syndrome, pathogenetic mechanism, skin disease.
Disorder, clinically characterized by granulomatous similar disorder is the Blau syndrome, a sarcoidosis-like disorder, clinically characterized by granulomatous inflammation of the skin, joints, eyes, lungs, and lymphatic ganglia, with no fever episodes [15].

Other disorders such as Behçet’s disease, Crohn’s disease, or psoriatic arthritis, with a multifactorial etiology, have been classified as autoimmune inflammatory diseases (AIDs) because they have a significant chronic inflammatory component and show several mutant genes that are also found in other autoimmune inflammatory disorders [16–18]. This group of AIDs has also included disorders vaguely resembling the classical autoimmune inflammatory phenotype, but showing an alteration of the macrophage inborn immunity, such as the macrophage activation syndrome [17, 19].

Pathogenetic mechanisms

Currently several mechanisms have been identified as playing a major role in AIDs. In an outstanding study carried out in 2009, Masters et al. have proposed six major mechanisms, acting also as disease classification criteria [17].

The most important mechanism, from the viewpoint of its pathogenetic significance and presence in several AIDs, is the alteration of the regulatory processes of the transformation of the IL-1β precursors into their active forms within the inflammasomes, with excess formation of IL-1β.

Inflammasomes are intracytoplasmic protein structures found in macrophages, dendritic cells, and keratinocytes. They include receptor proteins (NLR-NOD-like receptor), adaptor proteins, and caspases. NLR, like TLR, belong to the protein recognition complex (PRR), which recognizes a complex of proteins on the surface of microorganisms, called the pathogen-associated molecular pattern (PAMP) [20].

Normally, the binding of PRRs with the PAMP found on the surface of microorganisms’ results in activation of the inflammasomes and an increase in the synthesis of IL-1β. This occurs in two phases: formation of intracellular deposits of IL-1β precursors, signaled by the PRR or TLR pathways, activation of the NF-κB and the MAPK pathways, followed by the activation of precursors into active IL-1β by caspases [20, 21].

IL-1 is a powerful pro-inflammatory agent, acting as a local mediator of inflammation when present in small amounts, and acting systematically (fever, synthesis of acute-phase proteins) when present in large amounts. IL-1β shows an IL-1R receptor with an intracytoplasmatic domain highly homologous to the cytoplasmatic domain of TLRs. There is also an IL-1Rα receptor antagonist, which binds competitively to IL-1β but does not induce a transduction signal, thus blocking the effects of IL-1β. The synthesis of IL-1β is also induced by other factors (ischemia), in the absence of microorganisms [22–24].

Mutations of pyrin (product of FMF genes) alter this protein’s interactions with the inflammasomes’ proteins, therefore the IL-1β synthesis being no longer reduced [25].

The mutant NALP3 protein found in CAPS, cryopyrin, has an increased capacity of caspase-1 activation, resulting in IL-1β formation, compared with the regular cryopyrin [22, 23].

Excess synthesis/activation of IL-1β is the final point of several mechanisms involved in AIDs. The inflammasomes may be activated by the PRR/PAMP pathway, but also by microenvironmental cellular stimuli, metabolic factors (gout, diabetes mellitus type II), cellular stress. The mutant proteins within the inflammasomes increase their activation capacity [22, 23].

Other mutant genes, such as MVK genes of HIDS or IL-1RN/IL-1RA of DIRA produce excess IL-1β through other mechanisms. DIRA (deficiency of the IL-1 receptor antagonist) shows a deficiency of this receptor, caused by mutations of the IL-1RA genes; the mutant receptor is unable to block IL-1β competitively, thus accounting for the presence of excess IL-1β [24, 26]. Mutations of the NALP1 receptor (same family as NALP3) were shown in vitiligo [27]. Unlike NALP3, the NALP1 proteins may bind directly to procaspase-1, not requiring the presence of adaptor proteins, thus increasing the synthesis of IL-1β [17].

The second mechanism involves the mutations of NOD/CARD15 proteins, resulting in an increase in the activity of the transcription factor NF-κB in the absence of bacterial component stimulation. The activation of NF-κB leads to an increase in the transcription of the genes controlling the synthesis of IL-1β [17]. The mutations of NOD genes and the activation of NF-κB represent a common pathogenetic mechanism found in Crohn’s disease, Blau syndrome, and sarcoidosis [15, 26, 28].

The third mechanism found in AIDs involves mutations in proteins composing the extracellular portion of the 55-kDa TNF receptor (TNFR1). The mutations result in misfolding of the extracellular domain of TNFR1, and consequently lack of clivation of this extracellular component, with decrease of the serum levels of soluble TNFR. Due to the excess presence of bound TNFR1 and reduced presence of antagonistic soluble TNFR1, bound TNFR1 is repeatedly stimulated, thus increasing the pro-inflammatory effect of TNFα [11, 12].

The disease prototype is TRAPS, but this mechanism is also found in ankylosing spondylitis [20].

Other mechanisms found in AIDs involve alterations of the complement system (mutations of the factor 4/CFH and the complement factor 1), mutations of the SH3BP2 genes, resulting in an increased cytokine response, particularly M-CSF and TNFa found in cherubism, and mutations of perforin-encoding genes, thus exacerbating the phagocyte function of macrophages and cytokine secretion. The disease prototype of this last mechanism is the hemophagocytic lymphohistiocytosis [29–31].

Nowadays these pathogenetic mechanisms provide a primary explanation of the molecular pathology of the major disorders currently included in the AIDs category.

Definition

The term of “autoinflammation” was first proposed in 1999 by McDermott et al., along with the finding of mutations occurring in the extracellular domain of the
55-kDa TNF-receptor in a disorder called TRAPS, similar to FMF, HIDS, and FACS, characterized by an auto-inflammatory phenotype [11] (episodes of unexplainable recurrent fever, serosal, synovial, and cutaneous inflammation). These disorders could not be included in the category of known immunologic diseases [32].

The studies of Galon et al. (2000), and Kastner & O’Shea (2001) suggest that AIDs represent a group of rare inherited disorders where no autoantibodies or antigen-specific T-cells may be found [33, 34]. This has become part of the definition of AIDs.

McDermott & AkSENTijeVich (2002), in a consensus with other researchers, stated that there was a direct association between AIDs and the alteration of the innate immune response to microbial components [35].

Overall accepted nowadays are the Masters classification (2009) and the Galleazzi definition of AIDs, stating that AIDs are inflammatory disorders characterized by recurrent episodes of systemic inflammation in the absence of pathogens, autoantibodies or antigen-specific T-cells. These disorders are caused by a primary dysfunction of the innate immune system without evidence of adaptive immune dysregulation [36].

The particle “auto” is used in order to underline the absence of any trigger, and the exacerbations of these diseases are unpredictable [36].

As per this definition, AIDs are radically different from the autoimmune diseases. However, it is easily recognizable that IL-1β and TNFα are involved in the alterations of both inborn and adaptive immunity. Additional convergence points may exist between the two types of immunity, suggesting that alterations of both types (in various proportions) may co-exist in the same disorder.

There is currently a slight trend to classify several disorders as autoimmune, with more or less good reason. The major criteria include alterations of the innate immune mechanisms, chronic inflammation, and periodic exacerbations with no apparent cause [37].

Obviously, the finding of alterations of innate immune mechanisms in a certain disorder does not rule out the existence of other pathogenetic mechanisms that may play a major role in the onset of that disorder.

### Cutaneous alterations in autoinflammatory syndromes

In defining the autoinflammatory phenotype, McDermott et al. considered the cutaneous inflammation as one of its basic elements [11]. It is altogether apparent that most AIDs show cutaneous symptoms.

Cutaneous alterations in AIDs may take two forms.

One of these is represented by the skin lesions seen in most monogenic autoinflammatory disorders. These are non-specific cutaneous manifestations such as: erythema, rash, exanthema, urticarial plaques, generalized pustular exanthes, seen in FMF, TRAPS, HIDS, or DIRA [38].

However, these clinical signs show two particularities. One of them is the correlation with the febrile or inflammatory episode and with the onset of other symptoms (FMF, TRAPS, HIDS, and FACS). Between episodes, cutaneous symptoms are absent. TRAPS features febrile episodes lasting 1–4 weeks, abdominal pain, conjunctivitis, periocular edema, arthralgias, associated with painful erythematous lesions, erythema, urticarial non-pruriginous plaques, cellulitis on limbs. In FACS, arthralgias, conjunctivitis, headaches after general cold exposure coexist with skin manifestations including urticaria, typical exanthema with high fever and myalgias [38–40]. DIRA is characterized by skin lesions consisting in generalized pustular exanthes and bone lesions, appearing within one week after birth and persisting the entire life [41]. In the Blau syndrome, skin lesions are the first to appear, in the first three years of life, and consist in colored brownish-red papules, ichthyosiform rash, persistent small nodular exanthema with histological structure of granulomatous inflammation, weakly correlated with uvetitis and polyarthritis [39, 42]. The second particularity of these cutaneous manifestations is represented by their high prevalence in all autoinflammatory disorders.

For instance, skin alterations are present in 100% of the Blau syndromes, in 80% of the TRAPS patients, approximately 60% of the HIDS patients (maculopapular or morbilliform exanthema, erythema nodosum), and 50% of the DIRA patients (aphthosis with or without genital lesions, and pustular dermatis seen in almost all cases) [38, 41]. Recurrent rash or urticarial episodes are seen in all patients with Muckle–Wells syndrome (urticaria-deafness-amyloidosis syndrome), with no correlation with cold exposure, while renal amyloidosis and neurosensory hearing loss are only seen in 25% of the cases [43]. One exception is FMF (high fever episodes lasting 1–3 days with pain), where inflammation is localized in the peritoneum, joints, pleural membranes, pericardium, and rarely in the skin. Cutaneous alterations take the form of erysipelas-like erythema (10–15 cm erythematous plaques localized on the anterior face of the legs or feet, appearing in 12–43% of the adults [44] and 25% of the children [45]. Development of renal amyloidosis is not correlated with the skin lesions in FMF [44, 45].

The second form of cutaneous alteration in autoinflammatory syndromes involves the presence herein of several well-defined clinical entities of various etiologies, evolving either individually or within other syndromes. Such entities were defined both within the category of monogenic AIDs and, particularly, within the category of polygenic AIDs. They include Henoch–Schönlein purpura, angioma, angioedema, Raynaud-like phenomena (FMF), erythema nodosum (HIDS). Cutaneous manifestations appear during the exacerbations of the autoinflammatory disorder, but are inconstant and not definitive for that disorder [38]. Other two skin disorders, pyoderma gangrenosum and pustular acne, may also be included in this form of skin alterations, as they may be encountered either isolatedly or within the autoinflammatory syndrome.

These clinical entities may be part of, and define, the autoinflammatory PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum, acne syndrome). Pyoderma gangrenosum is seen in its classic form, as torpid ulcers located on the distal limbs, but sometimes as multiple lesions scattered on the whole body. The lesions respond well to corticotherapy. Acne is nodulo-cystic, severe, persisting into adulthood, less correlated with the childhood-onset severe sterile arthritis located in knees, elbows, and ankles [38, 46].
Another category of entities classified as AIDs includes dermatological disorders (Behçet’s disease, Sweet syndrome), rheumatologic disorders (adult-onset Still’s disease), or borderline disorders (psoriatic arthritis).

Behçet’s disorder, Sweet’s syndrome, and pyoderma gangrenosum are classified in dermatology as neutrophilic dermatoses. These are a group of disorders with various clinical presentations, but histologically sharing the presence of a perivascular infiltrate and diffuse neutrophilic infiltrates in the absence of pathogens. The neutrophilic infiltrate is located both within the epidermis and dermis, but is also encountered in the eye, liver, lungs, or lymph ganglia, accounting for the common association with internal disease of these skin disorders [47].

The evolution of Behçet’s disease features recurrent episodes (oral and genital aphthous ulcers, associated with arthritis and intestinal lesions) with no apparent cause; ocular lesions and fever are rare. The histological image is of vasculitis with perivascular infiltrate with leukocytes and neutrophils, but also diffuse neutrophilic infiltrate.

The presence of the autoinflammatory phenotype in Behçet’s disease, associated with the massive neutrophilic infiltrate in the absence of microbial infection, and with the absence of ANCA, are major factors that support the classification of Behçet’s disease as an autoinflammatory syndrome [16, 47].

Adult Still’s disease is a systemic arthritis characterized by carpal ankylosis. It is part of the larger group of juvenile idiopathic arthritides that develop before the age of 16, Still’s disease being the adult form. Patients show macular exanthema in 79% of the cases, associated with sore throat in 92%, arthralgias 80%, lymphadenopathy 74%, pleuritis 33% of the cases, respectively. Fever is an important symptom, seen in 100% of the cases. It is frequently accompanied by arthralgias, myalgias, and dermography. The most common clinical picture is that of febrile arthritis. Serum leukocytosis, neutrophilia, and negative ANCA are seen, together with a histological neutrophilic or polymorphous perivascular infiltrate, without any image of vasculitis [47–49].

The Sweet’s syndrome (acute febrile neutrophilic dermatosis) is characterized by fever, neutrophilia, and cutaneous symptoms including infiltrated papules and plaques, developing vesicles, pustules, or ulcers on their surface. Skin lesions are located on the trunk, neck, or extremities. Fever is intermittent and seen in most patients. Renal, pancreatic, meningeal, or joint lesions are variable. Histologically, a nodular, diffuse, or perivascular infiltrate is seen, but no image of vasculitis. Serum neutrophilia and increased G-CSF levels are seen during exacerbations. Supposedly, there is an increased synthesis of G-CSF, promoting the increase in number and survival of neutrophils [50, 51].

Beside the above-described disorders, there are several skin disorders with certain clinical or genetic features that bring them closer to an association with or even a classification within the group of AIDs. This is the case of psoriatic arthritis, or, more surprisingly, of contact dermatitis or vitiligo.

Psoriasis is a chronic inflammatory skin disorder, of multifactorial etiology. It is characterized by exacerbations, inflammatory changes, the positive presence of neutrophils in the infiltrate of active skin lesions, and also the presence of Munro microabscesses and involvement of cytokines such as TNFα, IL-1, IFNγ, and IL-23, which trigger the hyperproliferation and altered differentiation of epidermal keratinocytes. All these may suggest a possible classification of psoriasis in the group of autoinflammatory disorders. Currently, there is a large body of evidence showing that psoriasis is a T-helper lymphocyte mediated autoimmune disease [52]. The involvement of inborn immunity in the onset of psoriasis is possible, but may play a secondary role. It was shown that the CARD15/NOD2 single nucleotide polymorphism does not increase susceptibility to psoriasis [53].

Closer to, or even classified as, autoinflammatory disease is a certain form of psoriatic arthritis, namely the psoriatic juvenile idiopathic arthritis, where there is a proven association with a single nucleotide polymorphism across four loci of the genes NALP3, NOD2, MEFV, and PSTPIP1, which strongly supports the classification of this arthritis as an autoinflammatory disorder [54]. Adult psoriatic arthritis features several autoimmune characteristics and the involvement of T-lymphocytes [54] and the HLA system [55] in its onset, making the classification of this disorder as autoinflammatory debatable.

Vitiligo shows a decrease in the number of melanocytes, by autoimmune mechanisms. Mutations of the NALPL1 genes were shown in generalized vitiligo, associated with other autoimmune disorders (thyroiditis, rheumatoid arthritis, and diabetes mellitus). NALPL1 gene polymorphism and mutations are associated with both autoinflammatory and autoimmune diseases [27, 56, 57].

Contact dermatitis shows an activation of NALP3 inflammasomes within keratinocytes, with activation of the caspase-1 and increase in IL-1β synthesis [58]. This mechanism develops/is associated with or parallels the mechanism of delayed hypersensitivity, the major pathogenetic mechanism involved in contact dermatitis.

A new addition to the group of autoinflammatory disorders is the Nakajo–Nishimura syndrome, characterized by periodic high fever and nodular erythema-like eruption, which may progress into lipomuscular atrophy in the upper body. Missense mutations of the PSMB8 gene, encoding the β5i subunit of immunoproteasomes, were identified [59]. Proteasomes are complexes of intracellular proteases that specialize in degrading proteins that are no longer necessary. Additionally, NF-κB is activated, with an overproduction of IL-6, thus explaining the onset of the autoinflammatory phenotype.

As seen above, the cutaneous symptomatology of autoinflammatory disorders is varied but nonspecific, expressing the alteration of inborn immune mechanisms within the skin. Also, disorders like Henoch–Schönlein purpura, angioedema, pyoderma gangrenosum, or conglobate acne do not show a particular evolution in the setting of the autoinflammatory syndrome. A significant factor is the recurrence of skin symptoms and its correlation with other characteristics of the autoinflammatory phenotype.

Genes involved in the autoinflammatory syndrome

The most important genes involved in monogenic autoinflammatory disorders include the genes MEFV,
The recognition of autoinflammatory disorders introduces a new category, of inborn immune deficiencies, in the large group of general immune disorders, along with the three already known categories involving acquired immunity (acquired immune deficiencies, autoimmune diseases, and allergic diseases).

Individually, autoinflammatory disorders are well characterized clinically and genetically, but the overall definition of the autoinflammatory syndrome is much too vague, non-specific, and comprising two negations. Obviously, it is just a definition that is only useful for a certain phase in the study of these diseases.

Autoinflammatory syndromes pose two dermatological challenges. The first is to identify the altered mechanisms of inborn immunity among the pathogenetic mechanisms of known dermatological diseases, and to assess the significance of these alterations in the general pathology of skin disorders. The second challenge involves the diagnosis and therapeutic intervention in both autoinflammatory disorders and known skin disorders with altered inborn immune mechanisms, with or without clinical signs suggesting an autoinflammatory phenotype.

Because of the rarity of these disorders, the dermatologist will seldom be required to recognize and classify a cutaneous symptom into one of the monogenic autoinflammatory disorders. The dermatologist will also have to recognize elements suggesting an autoinflammatory phenotype in the setting of a known disorder (purpuric syndrome, pustulosis). Factors to be considered include clinical inflammatory symptoms, a certain recurrent character of the symptoms, and increase in the serum levels of the inflammatory markers during the fever bouts, family history, and ethnicity.

Genetic investigation follows the clinical diagnosis in autoinflammatory disorders. Positive results confirm the diagnosis of the investigated disorder. If no causal mutations can be shown in the investigated disorder, Rigante & Cantarini believe that diagnosis of monogenic autoinflammatory disorders may be established without demonstrating any mutations of the target genes [62]. Inability to demonstrate causal mutations may also be due to an incomplete genetic investigation, not showing the introns or promoter regions, tests that are not carried out routinely [3]. On the other hand, Tuotou & Koné-Paut believe that, in theory, identification of a single mutation in dominantly transmitted diseases, and of a paired mutation (one inherited from each parent) in recessive disorders would suffice to confirm diagnosis [9].

Biochemical/biological tests are lacking in autoinflammatory disorders, most apparently in monogenic disorders. These are practically diagnosed on clinical and genetic bases. There are no intermediate biochemical/biological tests that could assess any alterations of the inborn immune mechanisms or the consequences thereof. For instance, serum levels of IL-1β may be determined, but their significance is low, as such levels are relatively increased in inflammations of any kind.

The DIRA syndrome offers an interesting outlook. In a recent study, Minkis et al. suggest that many cases of infantile pustulosis show IL-1 RN deficiencies, and may be classified as DIRA [75]. It is possible that many adult pustoloses, which cannot be classified into the known disease groups, could be diagnosed as DIRA, or could show acquired deficiencies of IL-1 RA, particularly if their recurrent evolution would suggest an autoinflammatory mechanism. One case of chronic cutaneous pustulosis was recently described as showing alterations of the IL-1 RN genes and of the similar adjacent IL-36 RN and 1F10 genes, with a good therapeutic response [76].

The treatment of autoinflammatory disorders is based on the general idea that these disorders are inflammations with a genetic predisposition. At the same time, the therapeutic response depends on the type of inborn immune mechanism that is altered.
Agents used in autoinflammatory disorders include general anti-inflammatory drugs (glucocorticoids) and non-steroidal anti-inflammatory drugs, and also anti-inflammatory neutrophil depressants (colchicines, daspone, and thalidomide). Immunosuppressive drugs (cyclosporine, methotrexate) are also used, particularly to minimize the risk of steroid dependence.

Biological agents aim to correct imbalances in the synthesis and regulation of pro-inflammatory cytokines [38, 77]. Recombinant IL-1\(\beta\) receptor antagonist therapy was used in DIRA (currently the only recommended therapy), CAPS, PAPA, and the Schnitzler syndrome. Symptomatology is significantly reduced, while long-term administration was shown to prevent complications (amyloidosis, macroglobulinemia) [76].

Use of this therapy is limited in FMF, HIDS, and the Blau syndrome [38, 78]. Anti-TNF receptor antagonist therapy was also used in TRAPS, but with minor results [79]. The results of biological therapy are overall difficult to interpret, due to the small number of treated cases [80].

### Conclusions

The characterization of the autoinflammatory syndrome has brought to attention several pathogenic mechanisms pertaining to the inborn immunity. Insofar these mechanisms are involved in the pathology of other general and dermatological disorders remains a matter of future investigation.

**Conflict of interests**

The authors declare that they have no conflict of interests.

### References


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