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Autoinflammatory diseases

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ABSTRACT

Autoinflammatory diseases represent an expanding spectrum of genetic and non-genetic inflammatory diseases characterized by recurrent episodes of fever and systemic inflammation affecting the eyes, joints, skin, and serosal surfaces. Thus, these syndromes are recognized as disorders of innate immunity. Confirming this view, most autoinflammatory diseases are uniquely responsive to IL-1β blockade. Although many autoinflammatory diseases have a genetic cause, increasing evidence indicates that the degree of cell stress concurs to the severity of the disease phenotype. In this mini-review, I will discuss the recent advances on pathogenesis, pathophysiology and therapeutic approaches in autoinflammatory syndromes.

1. Introduction

Autoinflammatory diseases are a relatively new category of rare diseases, in which disordered inflammatory responses lead to devastating inflammatory symptoms in several tissues [1]. Although sharing some traits with autoimmune diseases, autoinflammatory diseases display unique features, including the periodicity whereas autoimmune diseases are progressive, and the lack of signs of involvement of adaptive immunity such as association with HLA aplotypes, high-titer autoantibodies or antigen-specific T cells. Furthermore, autoimmune diseases are responsive to biologic agents that targets T- and B-cell functions, including anti-TNFα, anti-IL (Interleukin) -6 receptor, anti-IL-12/IL-23 antibodies. These therapeutics however have no sustained effects in autoinflammatory diseases that, in contrast, display dramatic clinical responses to IL-1 blockers [2]. Thus, in autoinflammatory diseases, the monocyte-macrophage rather than the T-cell is the culprit and the defect in most cases is a dysregulation of IL-1β. Finally, unlike most autoimmune diseases, the majority of autoinflammatory diseases are inherited diseases, and the causative gene has been isolated.

The concept of autoinflammation was first affirmed in 1999 by McDermott and colleagues [3] who proposed TRAPS as the prototype of a family of dominantly inherited autoinflammatory syndromes sharing impaired cytokine receptor clearance as a mechanism of disease. In the following years, several studies concurred to demonstrate that not only receptor but also cytokine malfunctioning may cause the autoinflammatory phenotype of many different genetic syndromes. The cytokine implicated in the majority of autoinflammatory syndromes turned out to be IL-1β [2]. IL-1β is a powerful proinflammatory cytokine that induces systemic symptoms such as fever, anorexia, and elevated levels of serum markers of inflammation. When IL-1β activity is too high, tissue damage such as joint destruction occurs.

IL-1β induces several other proinflammatory genes, but cytokine-mediated inflammation also triggers the expression of genes encoding anti-inflammatory proteins that suppress inflammation. Among these, particularly important is IL-1receptor antagonist (IL-1Ra) that specifically inhibits IL-1 activity [4]. The IL-1Ra is structurally similar to IL-1β but devoid of biologic activity; it binds tightly to the IL-1 receptor thus blocking access of IL-1. Both IL-1 and the IL-1Ra are produced in patients with infections, trauma, or other inflammatory conditions, and compete for occupancy of the IL-1 receptor [2]. Hence, the outcome of an inflammatory process is likely to be affected by the relative amounts of IL-1β and IL-1Ra. The balance between IL-1β and IL-1Ra is indeed altered in autoinflammatory diseases, with predominance of IL-1 activity over the IL-1 inhibition, thus explaining the effective response of IL-1-blocking therapy in many of these disorders [5].

However, while in some diseases the link between gene mutation and IL-1β-mediated inflammatory phenotype is obvious, in others it is not. We have ordered the autoinflammatory syndromes in three groups, namely autoinflammatory syndromes linked to genes clearly involved in regulation of IL-1 activity; autoinflammatory syndromes linked to genes related to the innate immunity, but whose connection to IL-1β production is unclear; and finally autoinflammatory syndromes due to genes

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Table 1
Monogenic autoinflammatory diseases.

Disease	Gene	Inheritance	Treatment
CAPS (FCAS, MW, CINCA)	NLRP3, member of the NOD-like receptor family; inflammasome component	Dominant	IL-1 inhibitors
DIRA	IL1RN, encoding for IL-1 receptor antagonist	Recessive	IL-1 inhibitors
FMF	MEFV, encoding for pyrin	Recessive	Colchicine, IL-1 inhibitors in refractory cases
PAPA	PSTPIP1, encoding for the adapter protein proline-serine-threonine phosphatase-interacting protein	Dominant	Steroids, IL-1 inhibitors, TNF-a inhibitors
FCAS type 2	NLRP12, member of the NLR family	Dominant	IL-1 inhibitors
Blau syndrome	NOD2/CARD15, member of the NLR family	Dominant	Steroids, immunosuppressive agents, IL-1 inhibitors
CAMPS	CARD-14, member of the NLR family, also known as CARD-containing MAGUK protein 2 (Carma 2)	Dominant	methotrexate, cyclosporine or TNF inhibitors
TRAPS	TNFRSF1A, encoding for p55 TNF receptor (TNFR1)	Dominant	IL-1 inhibitors
MKD (HIDS)	MVK, encoding for mevalonate kinase	Recessive	IL-1 inhibitors
DITRA	IL36RN, encoding for IL-36 receptor antagonist	Dominant	IL-1 inhibitors (to be confirmed)
CANDLE, JMP Nakajo-Nishimura syndrome	PSMB8, encoding for the proteasome subunit, b-type, 8	Dominant	No definitive treatment. Steroids, IL-1, TNF and IL-6R inhibitors (poor efficacy)
EO-IBD	IL10RA and/or IL10RB, encoding for IL-10 receptor,	Dominant	Hematopoietic stem cell transplantation
Majeed syndrome	LPIN2 coding for Lipin 2	Recessive	NSAIDs, corticosteroids, bisphosphonates; anti-TNF or anti-IL-1 drugs

CAPS: cryopyrin-associated periodic syndrome; FCAS: Familial Cold Autoinflammatory Syndrome; MWS Muckle-Wells; CINCA: chronic infantile neurologic, cutaneous, articular; DIRA: deficiency of the IL-1 receptor antagonist; FMF: familial Mediterranean fever; PAPA: Pyogenic arthritis, Pyoderma gangrenosum, and acne; FCAS type 2, also known as NLRP12 Associated Periodic Syndrome; CAMPS: CARD-14-mediated pustular psoriasis; TRAPS: TNF receptor-associated periodic syndrome; MKD: mevalonate kinase deficiency, also known as HIDS: Hyperimmunoglobulinemia D syndrome; DITRA: deficiency of IL-36 receptor antagonist; CANDLE: chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; JMP: joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy and Nakajo-Nishimura syndrome; EO-IBD: early onset inflammatory bowel disease.

apparently unrelated to IL-1. Remarkably, even in the last group, most syndromes are responsive to treatment with anti-IL-1 agents (Table 1).

2. Autoinflammatory diseases linked to genes involved in regulation of IL-1 activity

2.1. Cryopyrin-associated periodic syndromes (CAPS)

Dysregulation of IL-1β activity has been first demonstrated in the group of the three CAPS. These include Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), and Chronic Infantile Neurologic, Cutaneous, Articular (CINCA) syndrome, also known as Neonatal-Onset Multisystem Inflammatory Disease (NOMID). The three nosological entities represent different phenotypes, from the milder to the most severe, in the context of a clinical continuum [1]. FCAS is characterized by episodes of rash, fever, and arthralgia after exposure to cold. MWS patients display recurrent episodes of urticarial rash, fever, and abdominal pain. Sensorineural deafness and amyloidosis may represent late complications. CINCA/NOMID syndrome has a neonatal onset, with cutaneous rash, fever, arthritis, elevation of acute-phase reactants, and early involvement of the central nervous system, eyes, and bones [1].

In 2001 [6] and 2002 [7], mutations in the CIAS1/cryopyrin gene were linked to CAPS. A few years later, Agostini and colleagues showed that CIAS1 (now renamed NLRP3) is part of the intracellular multiprotein complex, the inflammasome, which mediates processing and secretion through caspase-1 activation [8]. This observation disclosed the connection between CIAS1/cryopyrin and IL-1β providing the molecular understanding of the mechanism of IL-1-mediated inflammation in CAPS. CIAS1/cryopyrin/NLRP3 mutations in CAPS are gain-of-function, as they enhance the assembly of the inflammasome. The result is the oversecretion of IL-1β responsible for the inflammatory clinical manifestations. Confirming the key role of IL-1β in CAPS, these diseases are rapidly brought under control by treatment with IL-1-blocking agents, either anakinra [9,10], a soluble IL-1 receptor (rilonacept) [11], or a monoclonal antihuman IL-1β (canakinumab) [12].

2.2. Deficiency of the IL-1Ra (DIRA) syndrome

As previously discussed, the successful outcome of an inflammatory response is ensured by a balance between IL-1 and IL-1RA. While in CAPS the unbalance is due to excessive IL-1β activity, in DIRA [13,14] the lack of IL-1RA caused by loss-of function-mutations of the gene causes the disequilibrium, allowing unopposed action of IL-1 with dramatic consequences. DIRA displays clinical manifestations similar to CAPS. It starts early after birth and manifests as pustular skin disease, periostitis, multifocal osteomyelitis, oral mucosal lesions and elevated acute-phase reactants. However, while in CAPS the main skin manifestation is neutrophilic urticaria, DIRA presents with a severe neutrophilic pustular skin eruption, skin pathergy, and nail dystrophy [13,14]. Since in keratinocytes IL-1RA and IL-1α are highly expressed, whereas IL-1β is not [15], these differences may be due to the loss of control of IL-1α bioactivity, rather than IL-1β, in skin from DIRA patients. Thus, while in CAPS the disease phenotype is mostly linked to hyperactivity of IL-1β, in DIRA, especially at the skin level, also IL-1α could play a relevant role.

DIRA, like CAPS, is exquisitely responsive to IL-1 blockade [13,14], confirming the key role of IL-1/IL-1Ra axis unbalance in the pathophysiology of these syndromes.

3. Autoinflammatory diseases linked to genes of the innate immunity, possibly involved in the control of IL-1β production

3.1. Familiar Mediterranean fever syndrome (FMF)

FMF, the most common autoinflammatory disease, is associated with mutations of the MEFV gene coding for the Pyrin protein [16]. The disease usually starts during childhood and is characterized by recurrent fever, limb pain, arthritis, cutaneous rash. FMF displays a general good clinical response to Colchicine. However, a variable percentage of patients are resistant or poorly compliant to the drug due to its side effects: in these patients, IL-1 blocking therapy displays high efficacy. This therapeutic result indicates that IL-1 is a main actor also in this disease, and supports the hypothesis that Pyrin is involved in IL-1β production, processing or secretion [17–22]. However, the exact role of Pyrin is still debated [17]. Pyrin has been proposed to bind pro-caspase 1 as well as its catalytic subunits [18] and other components of inflammasomes, such as NLRP3 [19], preventing caspase-1 activation and consequently inhibiting IL-1β secretion. According to these models, wild type Pyrin would exert a suppressive effect on IL-1β secretion that would be lost in the mutated protein. Pyrin mutations would then be "loss-of-function", in agreement with the autosomal recessive pattern of inheritance. In contrast, recent results obtained in a mouse model indicates that, rather, the mutant Pyrin mediates the activation of caspase-1 via ASC, independently of NLRP3, thereby supporting a "gain-of-function" effect of the MEFV mutations [20]. Interestingly, Pyrin has been also found to bind the mutant proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) [21], and the inflammasome component ASC forming a tri-molecular complex that directly recruits and activates caspase-1 and induces secretion of mature IL-1β in the absence of NLRP3. Interestingly, PSTPIP1 is the gene responsible for PAPA syndrome (see below). Studies on primary monocytes from FMF patients demonstrated enhanced IL-1β secretion, which correlates with number of high-penetrance MEFV mutations [22]. In contrast with that found in the animal model, the increased secretion of IL-1β by LPS-stimulated FMF monocytes is NLRP3-dependent, supporting the hypothesis that Pyrin plays a regulatory role, although still undefined, in NLRP3-infammasome activity.

3.2. Pyogenic sterile Arthritis, Pyoderma gangrenosum and Acne syndrome (PAPA)

As introduced above, PSTPIP1, which encodes for a cytoskeleton-associated adaptor protein, is the gene responsible for PAPA, an autoinflammatory syndrome featured by recurrent sterile, erosive arthritis in childhood [23]. By puberty, joint problems decrease and cutaneous symptoms increase with pathergy, severe cystic acne, and recurrent nonhealing sterile ulcers, often diagnosed as pyoderma gangrenosum. In spite of the evidence that PSTPIP1 may interact with Pyrin and ASC [21], its involvement in IL-1β release has not been firmly proven so far. However, although PAPA syndrome is generally responsive to glucocorticoids [21], anti-IL-1 treatment has been effective in some patients [24,25].

3.3. Familial Cold Autoinflammatory Syndrome (FCAS) type 2

FCAS type 2 has clinical manifestations similar to the less severe form of CAPS, with cold-induced urticarial rash, a mild inflammatory phenotype and possible development of sensorineural hearing loss. The disease is due to mutations in the NLRP12 gene, a member of the NOD-like receptor (NLR) family [26]. NLR proteins are part of the group of pattern recognition receptors (PRR) [27] and act as intracellular sensors of pathogen products (PAMPs) or molecules released following damage associated to cell stress (DAMPs). Their activation drives inflammation. In particular, NLRP is a subfamily of NLR, characterized by the presence of a PYD (Pyrin) domain. Among NLRP members, NLRP1 and NLRP3 (the gene mutated in CAPS) take part in the assembly of inflammasomes devoted to caspase-1 activation and IL-1β secretion [28]. In contrast, the function of NLRP12 is still debated. It has been proposed that NLRP12 acts as a negative regulator of inflammation by suppressing NF-κB activation [26] but the real impact of NLRP12 mutations on the regulation of NF-κB activity in patients is unclear. Alterations in the secretion of IL-1β by monocytes from FCAS 2 patients have been reported, possibly related to a state of stress of monocytes carrying the mutated gene [29].

3.4. Blau syndrome and CARD-14-mediated pustular psoriasis (CAMPS)

Also Blau syndrome [30] and CAMPS [31] are linked to mutations in NLR genes, namely, CARD-15/NOD-2 [32] and CARD-14 [31]. Both genes code for intracellular PRR that sense PAMPs or DAMPs. Triggering these NLRs results in NF-κB activation, suggesting that gain-of-function mutations can be responsible for the inflammatory phenotypes by up-regulating NF-κB.

Blau syndromes presents with granulomatous polyarthritis, panuveitis, cranial neuropathies, and exanthema [30]. In contrast, in CAMPS the disease is characterized almost exclusively by skin involvement, with pustular psoriasis. The restriction of autoinflammatory manifestations to skin is likely due to the prevalent expression of the mutated CARD-14 in keratinocytes [32].

4. Autoinflammatory diseases linked to genes apparently unrelated to IL-1

4.1. TNF receptor-associated periodic syndrome (TRAPS)

TRAPS is characterized by recurrent episodes of long-lasting fever, abdominal and periorbital pain, myalgia, and fasciitis. As stated above, clinical manifestations of TRAPS depend on the mutations for the gene encoding p55 TNF receptor type I [3]. The genetic defect suggested that patients with TRAPS may benefit from TNF inhibition. Unexpectedly however, treatment with anti-TNF was found to induce no or modest response in TRAPS patients [33] whereas anti-IL-1 therapy displayed high efficacy and is today the treatment of choice [34,35].

4.2. Mevalonate kinase deficiency (MKD) or hyperimmunoglobulinemia D syndrome (HIDS)

This autoinflammatory disease manifests as recurrent episodes of fever associated to abdominal pain, diarrhea, vomiting, rash, and arthralgia. The disease results from mutations in *MVK* gene that encodes for mevalonate kinase [36], an enzyme involved in the cholesterol, farnesyl, and isoprenoid biosynthesis pathway. A number of observations suggest that the dysregulated isoprenoid biosynthesis leads to caspase-1 activation with increased IL1β-release [37], but the actual mechanism is still partly undefined. IL-1 blockade is the most effective therapy in patients with MKD supporting a role of IL-1 also in the pathophysiology of this disease.

4.3. Deficiency of interleukin-36 receptor antagonist (DITRA)

DITRA is a recently described autoinflammatory disease due to deficiency of IL-36R antagonist (IL-36Ra) [38]. IL-36Ra is an IL-1

family member that antagonizes the proinflammatory signals of the three IL-36 molecules (α, β, and γ) at the IL-36R, with a mechanism analogous to that used by IL-1Ra to block IL-1 [2]. The main manifestation of DITRA is generalized pustular psoriasis, in agreement with the predominant expression of IL-36R in epithelial cells in direct contact with the environment, including the skin [39]. Interestingly, efficacy of IL-1 blockers has been reported [40]. This observation, together with the similarity of the cutaneous lesions in DIRA e DITRA [39], suggests the existence of a functional loop involving IL-36 and IL-1 at the level of skin.

4.4. Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome

CANDLE is a rare autoinflammatory disease that manifests in infancy with recurrent fever, delayed physical development, purpuric skin rash, and lipodystrophy with unique facial features. Genetic studies have identified *PSMB8* gene mutations in most patients affected by CANDLE syndrome [41]. Interestingly, the same gene defect is present in two similar autoinflammatory diseases: joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy (JMP) [42] and Nakajo-Nishimura syndrome [43]. *PSMB8* gene encodes for a proteasome subunit, resulting in a defect in proteasome assembly and activity. The result is accumulation of proteins that cannot be degraded and cause cell stress thus triggering inflammatory response. However, IL-1β production and secretion are not apparently impaired, as also confirmed by the poor response to anti-IL-1 therapy.

4.5. Early onset inflammatory bowel disease (EO-IBD)

Recent reports on children with mutations in the receptor for IL-10 have described a very aggressive form of Crohn's disease [44]. The mutations abrogate IL-10-induced anti-inflammatory signaling and result in increased secretion of TNF-α and other proinflammatory cytokines, suggesting that IL-10-dependent "negative feedback" regulation is disrupted in patients affected by EO-IBD. These patients failed treatment with immunomodulators, corticosteroids, and anti-TNF monoclonal antibodies and required multiple bowel resections. Hematopoietic stem cell transplantation (HSCT) has been exploited as a curative treatment, with satisfactorily results [44].

4.6. Majeed syndrome

Homozygous mutations in LPIN2, the gene coding for Lipin 2, are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome) [45,46]. Although the link between Lipin 2 and the IL-1β pathway is unknown, a good response to treatment with IL-1 blocking agents was observed, suggesting that also the pathogenesis of Majeed syndrome may be IL-1 mediated.

5. Role of stress as a co-factor in the pathophysiology of autoinflammatory diseases

Although monogenic autoinflammatory diseases usually have high penetrance, it is commonly observed that individuals bearing the same disease and the same causative mutation display more or less severe clinical manifestations. This phenomenon may results from a combination of genetic, environmental, and lifestyle factors.

Increasing evidence indicates that exposure of inflammatory cells to PAMPs or DAMPs, during an infection or a sterile injury, induces stress, to which cells react with a number of stress responses, aimed at defend themselves and the organism [47]. In healthy individuals, many inflammatory responses are regulated by stress responses. In the case of IL-1β, both synthesis and processing/secretion require a redox remodeling, with production of reactive oxygen species (ROS), followed by an antioxidant response with upregulation of a number of antioxidant genes [48]. We recently showed that monocytes from CAPS patients display abnormally elevated levels of both ROS and antioxidants at the baseline, compared to monocytes from healthy donors [49]. This activated redox response causes a further raise of ROS and a faster antioxidant response after TLR triggering, which results in a fastened IL-1β secretion. However, the excessive ROS overcome the antioxidant systems that fail, resulting in oxidative stress [49]. CAPS monocytes react to stimulation-induced oxidative stress by slowing down protein synthesis, a common response of stressed cells. Consequently, production of cytokines downstream of IL-1, such as IL-1Ra and IL-6, is severely impaired [50]. The decreased IL-1Ra and IL-6 production coupled to increased IL-1β secretion contributes to the disease phenotype. Thus, the mutated NLRP3 increases inflammasome efficiency; the concomitant redox dysfunctions are responsible for the accelerated IL-1β secretion and the impaired production of downstream cytokines. In other words, the mutation and the conditions of cell stress, most likely secondary to the mutation, collude in generating a more severe disease phenotype.

A similar collusion between genetic and non-genetic factors takes place also in other autoinflammatory diseases. In NLRP12 and FMF the stress is less severe, with milder effects on cytokine production [22,29]. In TRAPS [51], retention of the mutant proteins in the endoplasmic reticulum results in increased levels of ROS with activation of intracellular inflammatory pathways, such as MAPK. Furthermore, due to overload of the mutated proteins there is an exhaustion of the autophagy system [52]. Since autophagy has been reported to limit IL-1β processing and secretion [53], insufficient autophagy may lead to oversecretion of active IL-1β (52). This mechanism would also explain the good response to IL-1 blocking therapy displayed by TRAPS patients. Along this line, mutations in PSMB-8, a subunit of the non-lysosomal degradation pathway proteasome, is responsible for CANDLE. Also in this disease the accumulation of cytoplasmic proteins, due in this case to the deficient proteasome activity, may cause stress with activation of inflammatory responses.

On these bases, it is tempting to speculate that the repertoire of stress-related genes and of factors controlling their expression in each individual patient may affect the severity of the disease phenotype. A stronger individual capacity of antioxidant gene upregulation would protect from oxidative stress. Likewise, genetic endowment of powerful degradative systems would preserve from accumulation of waste products thus raising the threshold for inflammation even in the presence of excessive metabolic activity, or of misfolded or misretained mutated proteins.

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Conflicts of interest

The author declares that she has no conflicts of interest.

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