Immunology Letters 161 (2014) 226–230

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Autoinflammatory diseases

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ARTICLE INFO

Article history:
Received 11 November 2013
Accepted 13 December 2013
Available online 19 January 2014

Keywords:
Autoinflammatory
Autoimmune
IL-1
NOD-like receptors
Stress
Biologics

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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http://dx.doi.org/10.1016/j.imlet.2013.12.013

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.