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Inherited autoinflammatory syndromes: An expanding new group of chronic inflammatory diseases

M. Gattorno, A. Martini

Marco Gattorno, MD; Alberto Martini, MD, Prof. and Head of Dept. of Pediatrics. Pediatria II, Istituto G. Gaslini, Dipartimento di Pediatria, Università di Genova, Genova, Italy.

Please address correspondence to: Prof. Alberto Martini, MD, Department of Pediatrics, University of Genova, Pediatria II, IRCCS G. Gaslini, Largo G. Gaslini no. 5, 16147 Genova, Italy.

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Inherited autoinflammatory syndromes (IAS) are a group of recently identified monogenic diseases characterized by recurrent episodes of systemic inflammation presenting as fever associated with a number of clinical manifestations such as rash, serositis (peritonitis, pleuritis), lymphadenopathy and arthritis. Symptoms may present with different degrees of severity and vary among different diseases as well as within the same disease. Recurrent episodes and subclinical chronic inflammation may lead to systemic reactive amyloidosis (AA) that, for some of these conditions, represents the most severe long-term complication.

The discovery of *MEFV* as the susceptibility gene for autosomal recessive familial Mediterranean fever (FMF, MIM 249100) in 1997 represented the beginning of a new era for monogenic IAS (1). FMF is characterized by fever attacks lasting 1 to 3 days accompanied by serositis (peritonitis, pleuritis), arthritis and erysipelas-like skin lesions. *MEFV* is mapped on the chromosome 16p13.3 and encodes pyrin (marenostrin). Amyloidosis is a frequent and severe complication.

TNF-receptor associated periodic syndrome (TRAPS), previously known as Hibernian fever, is an autosomal dominant disorder characterized by fever (often lasting for 3 to 4 weeks) accompanied by myalgia, arthralgia, rash and abdominal pain. The disease is due to mutations in the gene of type I TNF receptor (*TNFRSF1A*, chromosome 12p-13) (2). Reactive amyloidosis occurs in about 15-25% of patients (3, 4).

Hyper-IgD syndrome (HIDS, MIM 260920) is characterized by periodic episodes of fevers lasting 3 to 5 days, accompanied by rash, lymphoadenopathy and abdominal pain. It is caused by recessive mutations in the gene of mevalonate kinase (MVK, chromosome 12q24) causing moderate enzyme deficiency (5). The occurrence of severe infections and amyloidosis have been recently reported as possible complications (6, 7).

Muckle-Wells syndrome (MWS, MIM 191900), familial cold autoinflammatory syndrome (FCAS, MIM 120100) and chronic infantile neurological cutaneous and articular syndrome (CINCA, MIM 607115) represent a wide spectrum of autosomic dominant diseases related to different mutations in a single gene, *CIAS1* (cold-induced autoinflammatory syndrome 1, or *NALP-3*), encoding a protein called cryopyrin (8, 9, 10). FCAS is characterized by episodes of rash, fever and arthralgia after exposure to cold. MWS consists of recurrent episodes of urticarial rash, fever and abdominal pain. Sensorineural deafness and amyloidosis may present as late complications. CINCA, represents the most severe disorder and is characterized by neonatal onset urticarial-like skin lesions, persistent systemic inflammation, central nervous system involvement (chronic meningitis) and growth cartilage alterations leading to severe bone dysmorphisms (11).

Two other diseases belonging to the group of IAS are characterized by a prevalent localization of inflammation to specific organs and tissues. Blau syndrome (MIM 186580) is an autosomal dominant disorder characterized by the recurrent granulomatous inflammation of joints, skin and eyes caused by mutations in the NOD2/CARD 15 gene (12). Pyogenic sterile arthritis, pyoderma gangrenosum and acne syndrome (PAPA, MIM 604416) is a disorder caused by mutations in the CD2-binding protein 1 (CD2BP1) and is characterized by recurrent episodes of aseptic abscesses of the joints and skin due to the increased recruitment and activation of polymorphonuclear leukocytes (13).

The existence of autoinflammatory conditions caused by mutations of a single gene represents important evidence that alterations of a limited number of mechanisms involved in the regulation or activation of the inflammatory response are able to establish complex and long-lasting diseases. This issue has also relevant implications for the study of the etio-pathogenesis of multifactorial rheumatic disorders.

Notably, genes involved in almost the all IAS syndromes encode for proteins involved in the control of crucial mechanisms related to inflammation, such as apoptosis and activation or modulation of pro-inflammatory cytokines, such as IL-1β and TNF-α.

The TNF receptor system

The pathogenesis of TRAPS is supposed to be primarily related to a defect in the down-modulation of TNF. The binding of circulating TNF-α to membrane (TNFRs) leads to the recruitment of cytoplasmatic proteins that initiate the intracellular signalling leading to the activation of transcriptor factors, such as nuclear factor κB (NF-κB) and activation protein 1 (AP-1) which ultimately cause the production of inflammatory mediators and anti-apoptotic proteins (14). Activation of type I and type II TNFRs causes cleavage and shedding of the extra-cellular portions, which are able to bind TNF-α in the circulation and therefore act as specific inhibitors. It has been suggested that some mutations may interfere with the process of shedding, leading to lack of appropriate inhibition of circulating TNF and therefore to uncontrolled inflammation (2). However, TRAPS patients display a normal shedding of type II receptor that, in normal conditions, represent the prevalent circulating soluble TNFR and some mutations are not associated to a defect of TNFR shedding (4, 15).

Notably, in the case of TNFRI the binding to TNF-α may lead to either inflammation or apoptosis. In the latter case, different signalling proteins (TNF receptor-associated death domain, TRADD) are involved. The activation of this particular intracellular pathway leads to the activation of the caspase cascade that eventually results in cell apoptosis (14). Thus, it is possible that a lack of control of TNF-induced apoptosis could also play a role in the pathogenesis of TRAPS.

Caspase 1 and IL-1β activation

IL-1β is produced as a 33-kD inactive cytoplasmatic precursor (proIL1β) that must be cleaved to generate the biologically active 17-kD isoform by a IL-1β-converting enzyme, called Caspase 1. Factors regulating the activation of Caspase 1 have been the subject of intense investigation in recent years. Caspase 1 can be activated by an intracellular multiprotein complex called inflammasome which is structurally organized in three functional domains: i) a ligand sensing domain that is composed of multiple repeats of motifs such as the leucin-rich repeats (LRR), ii) an oligomerization domain (i.e. NACTH) essential for subsequent complex activation, iii) a recruitment domain that interacts directly with Caspase 1 through domains of the death-fold family, such as the death domain (DD), death-effector domain (DED), caspase-recruitment domain (CARD) and pyrin domain (PYD) (16). In inflammasome the above-mentioned functional domains are provided by 2 distinct proteins, the former belongs to the so called CATERPILLER family and consists in a member of the NALP subfamily (NALP1 or NALP3), the latter is a protein called ASC (apoptosis-associated speck-like protein containing a CARD) that associates with Caspase 1 through the interaction of two CARD domains (Fig. 1A) (17).

As already mentioned, different mutations in the NACTH domain of NALP3 (or CIAS-1) are responsible for the FCAS, MWS and CINCA phenotypes, which are presumably due to an alteration in the regulation of caspase 1 activation.

Recent reports have documented increased IL-1β release associated with CIAS1 mutations, (18, 19). These studies led to the therapeutic use of a recombinant IL-1 receptor antagonist (Anakinra) in patients with FCAS, MWS and CINCA, and a rapid and dramatic downregulation of the inflammatory response was seen soon after the introduction of the treatment (20-24).

Notably, FMF and PAPA syndrome also appear to primarily affect, albeit through different mechanisms, the function of caspase 1 and therefore are thought to be closely related to the ab-

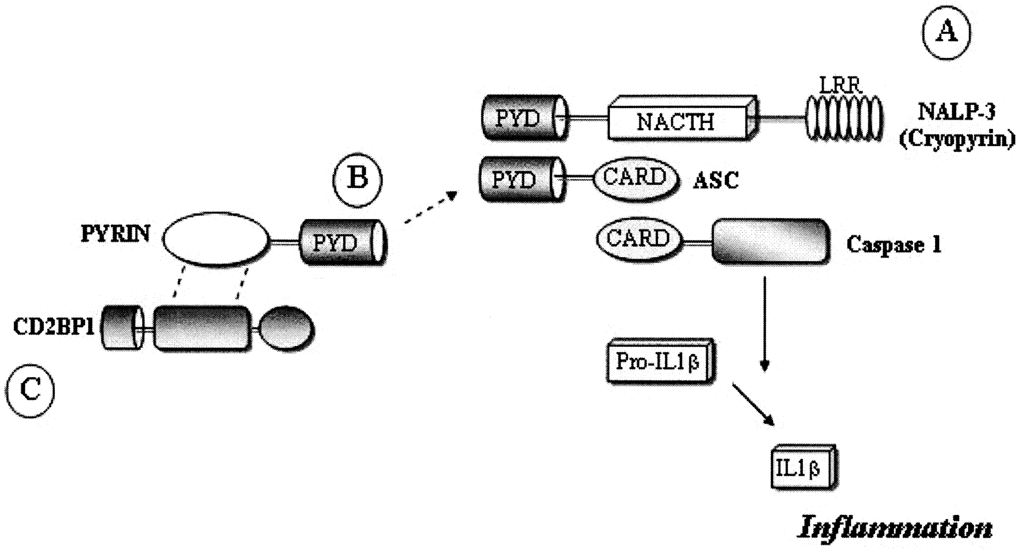

Fig. 1. Functional relationship among intracellular proteins involved in caspase 1 activation. **A**) Inflammasome is constituted by the functional interaction between NALP3 (cyropyrin) and ASC that associates and activates caspase 1. **B**) Pyrin has been proposed to associate with ASC protein and disrupt its interaction with cryopyrin. **C**) CD2BP1 protein (mutated in the PAPA syndrome) is able to interact with pyrin, blocking its anti-inflammatory regulatory function (see text for complete explanation).

normal activation and secretion of IL-1β.

Pyrin-deficient mice show increased activation of caspase-1, resulting in the enhanced processing and secretion of IL-1β. In fact, pyrin is able to interact with the inflammasome component ASC through its PYD domain, which suggests a role for pyrin in the negative regulation of the inflammatory response (Fig. 1B) (25). Moreover pyrin-deficient mice also display an impaired apoptosis of macrophages through an IL-1 independent mechanism (25).

In patients with PAPA syndrome, an increase in IL-1β secretion is also present. The CD2BP protein, which is mutated in the PAPA syndrome, has been recently found to bind to pyrin and is thought to exert a loss-of-function interaction on the IL1β regulatory activity of this latter protein (Fig. 1C) (26).

Indeed, the deregulation of the complex intracellular machinery leading to caspase 1 and IL-1β activation seems to be crucial for the development and maintenance of many autoinflammatory disorders.

The tip of an iceberg?

In various centers, including our own, involved in the genetic diagnosis of autoinflammatory syndromes, only about 20% of cases with typical clinical features submitted for genetic analysis show mutations in one of the genes thus far associated with the autoinflammatory syndromes. This strongly suggests the existence of a large number of as yet unidentified autoinflammatory disorders due to genetic alterations that remain to be discovered.

Moreover, very recently it has been shown that in systemic juvenile idiopathic arthritis (JIA) Anakinra may have a dramatic therapeutic effect, similar to that observed in patients with CIAS-1/NALP3 mutations (27, 28). Systemic JIA differs substantially from the other JIA subsets (29) and is characterized by clinical features (fever, rash, lymphadenopathy, serositis, arthritis) very similar to those observed in autoinflammatory diseases. Prominent IL-6 production has been found to characterize systemic JIA with respect to other JIA subtypes (30) and recently an anti-IL-6 receptor antibody has been shown to be a promising therapy (31, 32). However, interestingly, also familial cold autoinflammatory syndrome (FCAS), one of the *CIAS-1/NALP3*-related diseases, is characterized by elevated circulating IL-6 levels that normalize after treatment with anakinra (20).

The therapeutic effect of anankinra and the clinical similarities that exist between autoinflammatory syndromes and systemic JIA raise the possibility therefore that at least some cases of systemic JIA could be due to gene mutations leading to uncontrolled IL-1 production.

In summary, it is probable that research in the future on the intracellular pathways of IL-1β activation will shed more light on pivotal mechanisms leading to the persistence of inflammation in rheumatic conditions and will allow the identification of new disease entities.

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