Semin Immunopathol (2015) 37:359–362
DOI 10.1007/s00281-015-0495-3

REVIEW

The autoinflammatory diseases: a fashion with blurred boundaries!

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Received: 24 March 2015 / Accepted: 5 May 2015 / Published online: 22 May 2015

Abstract Monogenic autoinflammatory diseases are defined as a group of conditions with a clinical and biological inflammatory syndrome but little or no evidence of autoimmunity. Over 17 years have passed since the discovery of the first autoinflammatory gene, MEFV, responsible for familial Mediterranean fever. Substantive progress has been made since then, highlighting the key role of the inflammasome in the maintenance of the cell homeostasis but also unravelling new pathophysiological pathways involved in these diseases. The history of autoinflammatory gene discovery demonstrates the powerfulness of next-generation sequencing approaches in linking inflammatory disorders with various overlapping phenotypes. It can be easily anticipated that new genes will be exponentially identified in the coming years. Integrating these new concepts should help to promote personalized patient care through novel therapeutic opportunities.

The autoinflammatory diseases: a fashion with blurred boundaries!

The world of autoinflammatory diseases is in perpetual motion. Its content has expanded dramatically since the discovery of the first gene (*MEFV* responsible for familial Mediterranean fever, FMF, MIM#249100) in 1997, thanks to new high-throughput sequencing approaches (Fig. 1).

A review of PubMed shows that in fact the term "autoinflammatory" appeared in 1988 [1]. The second occurrence was by McDermott in 1999 [2] when the gene responsible for TNF receptor-associated syndrome (TRAPS, MIM#142680) was discovered. He defined a new group of systemic disorders characterized by "apparently unprovoked inflammation in the lack of high-titer autoantibodies or antigen-specific T cells". At least 25 conditions have been classified in this group so far, including 5 in 2014 (Fig. 1). The corresponding mutations have been recorded in a dedicated and regularly updated online database named infevers (http://fmf.igh.cnrs.fr/ISSAID/infevers/) [3–5].

No authoritative classification has emerged in 2015, most likely because of the growing identification of phenotype overlaps and genetic heterogeneity. Originally developed to distinguish diseases of the innate immunity from those related to acquired immunity (autoimmunity), the concept of "autoinflammatory" becomes too restrictive with the emergence of syndromes with mixed autoinflammatory and autoimmune features such as autoinflammation, antibody deficiency, and immune dysregulation, PLCG2-associated (APLAID, MIM#614878) [6, 7]. McGonagle was the first to suggest an integrated classification using the autoimmune versus autoinflammatory ratio involved in each condition as a means to rank it within the continuum of immunological diseases [8]. Clinical and biological criteria are also quite vague when observing the extreme phenotypic differences between the first genetically characterized entity (FMF a hereditary recurrent fever, see S Ozen in this issue) and the latest one autoinflammation with infantile enterocolitis (AIFEC, MIM#616050). AIFEC is characterized by macrophage activation syndrome and pronounced inflammation of the gastrointestinal tract associated with mutation in the *NLRC4* (NLR

This article is a contribution to the Special Issue on The Inflammasome and Autoinflammatory Diseases - Guest Editors: Seth L. Masters, Tilmann Kallinich and Seza Ozen

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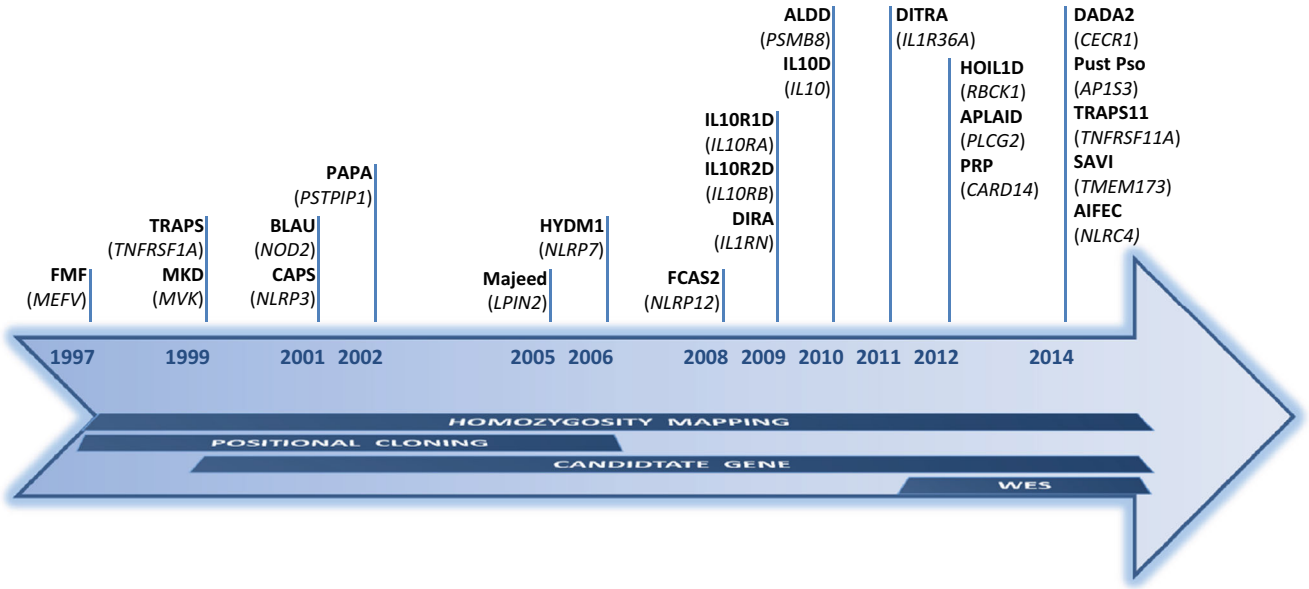

Fig. 1 Schematic representation of the autoinflammatory genes discovery over years and the related technical approaches used. Diseases names are in *bold letters*, and gene names are in *italics* and in *parentheses*. *AIFEC* autoinflammation with infantile enterocolitis, *ALDD* autoinflammation, lipodystrophy, and dermatosis syndrome, *AP1S3* adaptor-related protein complex 1, sigma-3 subunit, *APLAID* autoinflammation, antibody deficiency, and immune dysregulation, PLCG2-associated, *CAPS* cryopyrin-associated periodic syndrome, *CARD14* caspase recruitment domain-containing protein 14, CECR1 cat eye syndrome chromosome region, candidate 1, *DADA2* deficiency of adenosine deaminase 2, *DIRA* deficiency of interleukin 1 receptor antagonist, *DITRA* deficiency of interleukin 36 receptor antagonist, FCAS2 familial cold autoinflammatory syndrome 2, *FMF* familial mediterranean fever, *HOIL-1D* HOIL1 deficiency, *HYDM1* hydatidiform mole, recurrent, 1, *IL10* interleukin 10, *IL10D* interleukine 10 deficiency, *IL10R1D* interleukin 10 receptor A deficiency, *IL10R2D* interleukin 10 receptor B deficiency, *IL10RA* interleukin 10 receptor, alpha, *IL10RB* interleukin 10 receptor, beta, *IL1RN* interleukin 1 receptor antagonist, *IL36RN* interleukin 36 receptor antagonist, *LPIN2* LIPIN 2, *MEFV* Mediterranean fever, *MVK* mevalonate kinase, *MKD* mevalonate kinase deficiency, *NLRC4* NLR family, caspase recruitment domain-containing 4, *NLRP3* NLR pyrin domain-containing protein 3, *NLRP7* NLR pyrin domain-containing protein 7, *NLRP12* NLR pyrin domain-containing protein 12, *NOD2* nucleotide-binding oligomerization domain 2, *PAPA* pyogenic sterile arthritis, pyoderma gangernosum and acne, *PLCG2* phospholipase C, gamma-2, *PRP* pityriasis rubra pilaris, *PSMB8* proteasome subunit, beta-type, 8, *PSTPIP1* proline-serine-threonine phosphatase-interacting protein 1, *RBCK1* Ranbp-type and C3HC4-type inc finger-containing 1, *SAVI* sting-associated vasculopathy, infantile-onset, *TMEM173* transmembrane protein 173, *TNFRSF1A* tumour necrosis factor receptor super family 1A, *TNFRSF11A* tumour necrosis factor receptor super family, member 11A, *TRAPS* TNF receptor-associated periodic syndrome

family, caspase recruitment domain-containing 4) gene (see R Goldbach-Manski in this issue) [9, 10]. From a pathophysiological point of view, several signalling pathways have been involved, although a defect of the inflammasome regulation is thought to be the key mechanism underlying most autoinflammatory diseases (see I Aksentijevich in this issue). The inflammasome is a molecular platform triggering activation of inflammatory caspases and processing of proIL-1-beta after a proinflammatory event [11]. Intensive work performed since the discovery of the *NLRP3* (NOD-like receptor family, pyrin domain-containing protein 3) gene [12, 13] responsible for cryopyrin-associated periodic syndromes (CAPS) unravelled the pivotal role and functioning of this multimolecular complex, which became the target for the development of new dramatically effective IL-1 blocking agents [14]. To what extent the various inflammasomes dysfunction in either of the autoinflammatory disorders is being progressively elucidated.

FMF is the prototype of the prototypic autoinflammatory group, i.e. hereditary recurrent fevers (HRFs). HRFs are characterized by acute bouts of fever, arthritis, cutaneous eruption and polyserositis, starting in infancy [15]. FMF major specific feature is its almost exclusive confinement to Mediterranean populations, as the most prevalent mutations stemmed from a founder effect. FMF is basically a recessive disease; however, literature data supporting a possible gene dose effect are accumulating [16]. Carriers for *MEFV* mutations display elevated acute protein reactants and sometimes clinical criteria of the disease, although generally less severe [17]. These observations suggest that one *MEFV* mutation may confer a heightened inflammation. Colchicine is the mainstay treatment in 95 % of the patients, and IL-1 blockades may become a good option in refractory cases [18]. In the related chapter on FMF, Pr Ozen discusses the myths surrounding FMF since the discovery of *MEFV*, and how they have evolved and found (or not) answers in the past 15 years.

The hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS) is the milder arm in the mevalonate kinase deficiency (MKD) spectrum [19]. It owes its name to increased (though not specific) serum IgD concentrations

observed in these patients prior to the discovery of the gene. Recurrent fever episodes, typically ranging from 3 to 7 days, are sometimes triggered by stress, vaccination or infections. Clinical signs that may help differentiate MKD from other HRF include early onset, diarrhoea, vomiting, lymphadenopathy and aphthous lesions. *MVK* mutations result in decreased mevalonate kinase activity in the isoprenoid pathway. Although IL-1β is considered a major cytokine in its pathogenesis, IL-1 blockade is not successful in a subset of patients. Interestingly, *MVK* mutations have recently been pinpointed as responsible for some forms of retinitis pigmentosa [20] and disseminated superficial actinic porokeratosis [21] by means of whole exome sequencing.

CAPS are also rare HRFs. They owe their name to the cryopyrin protein that is encoded by the culprit gene *NLRP3* [12, 13]. As does MKD, CAPS encompass a continuum of phenotypes including the mildest familial cold autoinflammatory syndrome (FCAS, MIM#120100), Muckle–Wells syndrome (MWS, MIM191900), and the more severe chronic infantile neurologic, cutaneous and articular (CINCA)/neonatal-onset multisystem inflammatory disease (NOMID) syndrome (MIM#607115). Specific clinical features to search for are urticarial non-pruritic rash, headache or fatigue, ocular involvement, progressive sensorineural hearing loss and central nervous system symptoms (CINCA only). More recently, de Koning et al. suggested that Schnitzler syndrome might be considered also as belonging to CAPS, since somatic mosaicism for *NLRP3* mutations was found in some of these patients [22]. After the discovery that cryopyrin was the key inflammasome component, therapeutic trials have shown that IL-1 inhibitors are now safe and effective treatments for almost all patients CAPS [14].

The recent unmasking of numerous novel autoinflammatory genes underscores the power of next-generation sequencing in deciphering the pathophysiology of the associated disorders at an unprecedented speed [23]. The initial demonstration of the role of the NLRP3 inflammasome in HRFs is being completed by outstanding demonstration of unexpected cellular and molecular mechanisms underlying autoinflammation among which, protein misfolding, endoplasmic reticulum-stress response and autophagy. Studying autoinflammatory patients has also recently revealed genetic defects resulting in chronic type I interferon (IFN) signalling (see Goldback-Mansky in this issue). For example gain-of-function mutations in the transmembrane protein 173 (*TMEM173*) gene induce constitutive stimulator of interferon genes (STING) activation leading to constitutive IFN-β transcription responsible for the sting-associated vasculopathy, infantile-onset (SAVI, MIM# 615934) syndrome [24].

In conclusion, description of new autoinflammatory phenotypes associated with genetic and experimental research fuelled our understanding of immune pathways and of mechanisms of inflammation in general over the last 17 years. These insights allowed the discovery of the inflammasomes and the subsequent opportunities for novel therapeutic developments. There is no doubt that an expanding number of new monogenic and multifactorial disorders and their underlying molecular mechanisms will be highlighted in the coming years.

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