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Invited Review

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Pathogenesis of familial periodic fever syndromes or hereditary autoinflammatory syndromes

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Simon, Anna, and Jos W. M. van der Meer. Pathogenesis of familial periodic fever syndromes or hereditary autoinflammatory syndromes. *Am J Physiol Regul Integr Comp Physiol* 292: R86–R98, 2007. First published August 24, 2006; doi:10.1152/ajpregu.00504.2006.—Familial periodic fever syndromes, otherwise known as hereditary autoinflammatory syndromes, are inherited disorders characterized by recurrent episodes of fever and inflammation. The general hypothesis is that the innate immune response in these patients is wrongly tuned, being either too sensitive to very minor stimuli or turned off too late. The genetic background of the major familial periodic fever syndromes has been unraveled, and through research into the pathophysiology, a clearer picture of the innate immune system is emerging. After an introduction on fever, interleukin-1β and inflammasomes, which are involved in the majority of these diseases, this manuscript offers a detailed review of the pathophysiology of the cryopyrin-associated periodic syndromes, familial Mediterranean fever, the syndrome of pyogenic arthritis, pyoderma gangrenosum and acne, Blau syndrome, TNF-receptor-associated periodic syndrome and hyper-IgD and periodic fever syndrome. Despite recent major advances, there are still many questions to be answered regarding the pathogenesis of these disorders.

inflammasome; interleukin-1β; nucleotide-binding oligomerization domain-leucine rich repeat proteins; tumor necrosis factor receptor; isoprenoid pathway

THE FIRST MENTION OF PERIODIC disease in medical literature probably goes back two centuries, to 1802, when Heberden (67) described a disorder characterized by periodic pain in the abdomen and sometimes the chest and extremities. Medical knowledge of and research into the periodic fever syndromes have progressed over the past 200 years along a characteristic path. The first important step was a detailed clinical description and recognition of several clinical syndromes associated with periodic fever. This was followed by a brief but eventful period of genetic discoveries, when between 1997 and 2002 each of the major syndromes was linked to mutations in its own gene. We have now reached the era of unraveling the pathophysiology: how do these gene mutations result in increased inflammation and fever?

Each of the three eras described resulted in progress in knowledge and awareness, and each has yielded new therapeutic options: good clinical observation led to the discovery of colchicine in the treatment of familial Mediterranean fever

(FMF; 42, 61, 155); the link of hyper-IgD syndrome (HIDS) to a defect in the isoprenoid pathway suggested simvastatin in the treatment of its fever episodes (131), and research into pathophysiological pathways quickly suggested the very successful use of interleukin-1 blockers (19, 25, 35, 37, 55, 66, 120). The transition through these eras of research has unfortunately also led to the usual changes in names of syndromes, following specific discoveries and (personal) preferences—which can be confusing for outsiders.

At present, the unraveling of the pathophysiology of the periodic fever syndromes is yielding new insights into innate immunity and fever: the rare defects in these genetic disorders reveal the workings of the inflammatory response. In this review, we will describe the current knowledge of pathogenesis of the major hereditary periodic fever syndromes in detail. We will start with a brief overview of what periodic fever syndromes are and an introduction on the pathophysiology of fever, activation of IL-1β, and inflammasomes.

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Table 1. *Hereditary autoinflammatory syndromes in brief*

Syndrome	Abbreviation	Distinguishing Clinical Findings	Inheritance Pattern	Gene	Protein
Cryopyrin-associated periodic syndrome	CAPS		Autosomal dominant	*CIAS1*	Cryopyrin (NALP3, PYPAF1)
Familial cold autoinflammatory syndrome	FCAS	Provoked by cold exposure, brief episodes (hours)			
Muckle-Wells syndrome	MWS	Hearing loss, amyloidosis common			
Neonatal onset multisystemic inflammatory disease	NOMID/ CINCA	Almost continuous, chronic aseptic meningitis, hearing loss, arthropathy			
Familial Mediterranean fever	FMF	Episodes 1–3 days, polyserositis, amyloidosis common	Autosomal recessive	*MEFV*	Pyrin (Marenostrin)
Syndrome of pyogenic arthritis, pyoderma gangrenosum, acne	PAPA	Pyogenic arthritis, pyoderma gangrenosum	Autosomal dominant	*PSTPIP1 (CD2BP1)*	PSTPIP1 (CD2BP1)
Blau syndrome	BS	Granulomatous inflammation	Autosomal dominant	*NOD2 (CARD15)*	NOD2/CARD15
TNF receptor-associated periodic syndrome	TRAPS	Long episodes (often >1 wk), periorbital edema, migratory myalgia and rash	Autosomal dominant	*TNFRSF1A*	TNF-receptor type 1 (p55, CD120a, TNFR1)
Hyper-IgD syndrome	HIDS	Lymphadenopathy, starts in 1st year, high IgD, attack after immunization	Autosomal recessive	*Mevalonate kinase (MVK)*	Mevalonate kinase (MK)

Hereditary Periodic Fever Syndromes

There are at least eight major clinical syndromes, which fall under the denomination "hereditary periodic fever syndromes." They each have their specific characteristics and can be distinguished by the experienced clinician (Table 1) (135). They are, however, united by a central clinical phenotype of lifelong recurring episodes of fever and other symptoms of (systemic) inflammation. There is no intrinsic periodicity or biorhythm to the inflammatory episodes (142), so "recurrent" would actually be a more appropriate designation.

The fever attacks most often start during childhood, sometimes within the first few weeks of life but can make their first appearance in adolescence (as in FMF) or even late in adulthood, especially in TNF-receptor-associated periodic syndrome (TRAPS). Their duration can vary from hardly 1 day [e.g., familial cold autoinflammatory syndrome (FCAS)] to weeks (e.g., TRAPS), and they can occur as often as every few days to once or twice a year. The symptoms that accompany the fever are also caused by increased inflammation. Symptoms caused by serositis are common, especially in FMF: these can include peritonitis, pleuritis, and pericarditis. Myalgia, arthralgia, or arthritis and erythematous skin lesions are also often observed. The symptoms resolve spontaneously, and in between fever episodes, most patients feel well in most of the syndromes, except for example in chronic infantile neurological cutaneous and articular syndrome (CINCA)/neonatal onset multisystemic inflammatory disease (NOMID) (135).

Although some fever attacks have an obvious trigger, e.g., exposure to cold in FCAS or vaccination in HIDS, in most cases, the trigger remains elusive. The general hypothesis is that the inflammatory response in these patients is wrongly tuned, being either too sensitive to very minor stimuli or not turned off rapidly enough at the appropriate time.

The term "autoinflammatory syndrome" was coined to reflect the phenotype of seemingly unprovoked inflammation, without high-titer autoantibodies or self-reactive T-cells, which distinguish it from autoimmune diseases (108). Whereas the defect in autoimmune disorders is located in adaptive immunity, the autoinflammatory syndromes appear to be caused by a defect in innate immunity.

Recently, a growing number of disorders, including some nonhereditary ones, have been classed under this heading, varying from Crohn's disease, gout, and Schnitzler syndrome to Behçet syndrome. These disorders will not be discussed in this review. The percentage of patients that present with a clinical phenotype fitting with an autoinflammatory disorder but in which no genetic mutation can be found and no definite diagnosis can be made is still very high. In addition, even in approximately one-third of patients who receive a clinical diagnosis of FMF, no causative mutations can be detected. These observations indicate that the list of disorders in this category is likely to be incomplete at this time.

Febrile Response

Fever is an adaptive systemic response to an inflammatory stimulus. During fever, body temperature is regulated at a higher level (123). The central mechanisms of fever are largely unknown, but many appear to be dependent on PGE_2 (123). The substances that can trigger the production of PGE_2 and lead to fever, also known as "pyrogens," are divided into two groups (39). The first group consists of exogenous substances such as components of the bacterial cell wall (e.g., LPS) and other microbial products (140), which share certain molecular patterns (pathogen-associated molecular patterns or PAMPs). PAMPs are recognized by a set of receptors of the innate immune system known as Toll-like receptors (TLRs) (32, 40). There are also certain intracellular proteins able to sense pathogenic components and mount an inflammatory response; these include nucleotide-binding oligomerization domain-

leucine rich repeat (NOD-LRR) proteins, which will be discussed further on in this review.

The second group of pyrogens comprises the pyrogenic cytokines (formerly known as "endogenous pyrogens"). Cytokines are considered to be intrinsically pyrogenic when they are able to produce a rapid onset of fever within minutes (40). This is true for interleukin IL-1β, IL-1α, TNF-α, TNF-β, IL-6, and ciliary neurotrophic factor (39). These cytokines exert their action through their own specific receptors.

Fever is accompanied by a systemic reaction called the acute phase response, which is also driven by cytokines (56). Serum concentrations of special hepatic acute phase proteins such as C-reactive protein and serum amyloid A protein can be increased 100- to 1,000-fold, while the synthesis of a variety of other proteins is increased. There are also negative acute phase proteins, whose concentration decreases during the acute-phase response; these mainly include "household proteins" such as albumin (56). The exact function of most of the acute-phase proteins is still unclear, but there are numerous speculations about their role in the immune response. The fever episodes in the hereditary periodic fever syndromes are invariably accompanied by a marked acute-phase response. Even at times between the episodes, when the patient feels well, it is not uncommon to detect raised serum concentrations of acute-phase proteins. This seems to indicate that the inflammatory cascade is turned on much more often than the patient notices and does not always reach the level of fever or other symptoms.

Synthesis and Secretion of IL-1B

Although most cytokines are produced directly ready for secretion without further posttranslational modifications, there are exceptions. The most important exception, especially with regard to the hereditary periodic fever syndromes, is IL-1β. IL-1β is a key mediator of inflammation, with a wide variety of effects ranging from induction of fever and extravasation of leukocytes to enhanced expression of adhesion molecules on endothelial cells and induction of bone resorption (38).

IL-1β is initially synthesized as an inactive 31-kDa precursor (pro-IL1β), upon stimulation of TLRs with microbial products such as LPS (41). It needs to be activated to the mature 17-kDa protein by cleavage (Fig. 1). This cleavage of pro-IL1β is performed by caspase-1 (also known as interleukin-converting enzyme). Caspase-1 is itself also produced as an inactive precursor protein (pro-caspase-1), which can be activated after stimulation of certain NOD-LRR proteins and activation of an inflammasome (see next section).

IL-1β must also have a special secretory mechanism, as it lacks a specialized leader sequence common to secreted proteins and is indeed not found in classical exocytotic vesicles (51). Most of the pro-IL1β is in the cytosol, but a fraction seems to move into specialized secretory lysosomes (10). Release of IL-1β is mediated by the P2X7 receptor for extracellular ATP, which controls efflux of potassium from the cell (41, 51). The P2X7 receptor is also thought to be involved in the maturation step of pro-IL1β to IL-1β through a role in the final activation of caspase-1 (41).

NOD-LRR Prpteoms and the Inflammasome

The NOD-LRR proteins form a protein family that seems to be deeply involved in the regulation of immune responses (147). They are also known as CATERPILLER proteins [CARD (caspase-recruitment domain)-transcription enhancer, R-binding, pyrin, lots of leucine repeats], NACHT-LRR proteins (NAIP, CIITA, HET-E and TP1 domain-leucine rich repeats; NACHT is an alternative name for the NOD) or NOD-like receptors (32, 147). The NH_2-terminal part of all the proteins in this family consists of a NOD-LRR configuration. The NOD is important for protein-protein interactions; the LRR domain is hypothesized to be involved in the interaction with PAMPs, in analogy with TLRs (147). Some of the NOD-LRR proteins have been shown to be part of an intracellular pathogen-sensing system in the innate immune response. The COOH-terminal part of the NOD-LRR proteins is variable (147).

When specific NOD-LRR proteins are triggered, a cytosolic, multiprotein complex or "activation scaffold" is formed, which has become known as an "inflammasome" (104). An inflammasome consists of a NOD-LRR protein as a sensing protein, one or more adaptor proteins, and one or more inflammatory
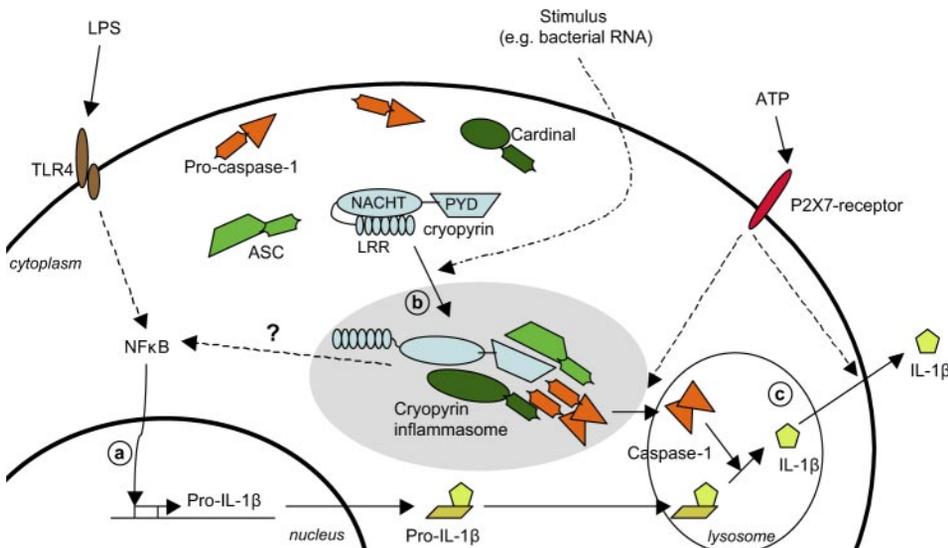

Fig. 1. Synthesis and secretion of IL-1β and formation of the cryopyrin inflammasome. *a*: Toll-like receptor (TLR)-4-stimulated NF-κB activation leads to transcription of pro-IL-1β, which then moves to the cytoplasm and to specialized lysosomes. *b*: upon activation of cryopyrin by ligands such as bacterial RNA, the NACHT-domain (the abbreviation is derived from a combination of NAIP, CIITA, HET-E, and TP1 domain) becomes exposed, and a complex of proteins called the cryopyrin inflammasome is formed. *c*: formation of the inflammasome activates pro-caspase-1 into caspase-1, which can, in its turn, activate the pro-IL-1β into IL-1β. P2X7-receptor activation, then mediates the secretion of bioactive IL-1β. There are contradictory reports on the effect of the cryopyrin inflammasome on NF-κB (see text). PYD, pyrin domain; LRR, leucine-rich repeat domain; ASC, apoptosis-associated specklike-like protein with a caspase-recruitment domain (CARD).

caspases as effector proteins (Fig. 1). One of the adaptor proteins that has been best characterized so far is ASC (apoptosis-associated specklike protein with a CARD) (106, 122, 138). ASC is built up from two domains, which are both known for their capacity to engage in homotypic domain interactions: a pyrin domain, through which it can interact with other pyrin domain-containing proteins (such as cryopyrin) and a CARD domain, important for interaction with caspases, which also contain a CARD domain.

At present, three human inflammasomes are discerned, named for the NOD-LRR protein involved: the NALP1 inflammasome, activating caspase-5 as well as caspase-1, and the NALP3 (or cryopyrin) inflammasome and Ipaf inflammasome, both activating caspase-1 (104). More variants are expected to emerge, as there is a repertoire available of at least 14 NOD-LRR proteins and 13 caspases.

Review of Pathophysiology per Syndrome

Cryopyrin: Cryopyrin-associated periodic syndrome. Cryopyrin-associated periodic syndrome (CAPS) encompasses three clinical syndromes that were originally described separately but were subsequently all linked to mutations in this one gene. Apart from a number of common symptoms such as periodic fever and inflammation, recurrent urticaria-like skin rash, and an autosomal dominant inheritance pattern, there are distinguishing features. In FCAS (OMIM 120100) symptoms can be provoked by exposure to cold. Muckle-Wells syndrome (MWS; OMIM 191900) is often associated with sensorineural hearing loss. The third syndrome, known either as NOMID or CINCA (OMIM 607115), is the most severe, with symptoms including chronic aseptic meningitis, other neurological symptoms, and peculiar joint manifestations. Overlapping forms of these clinical syndromes can be found, and families have been described with a mix of two or three of these syndromes in different family members (7, 135).

The gene involved in these syndromes was identified and characterized in 2001 by positional cloning in FCAS and MWS (69), and a year later, it was also linked to NOMID/CINCA (7, 50). It is known as *CIAS1* (for cold-induced autoinflammatory syndrome), and its 9 exons encode for a protein named cryopyrin. Cryopyrin is a member of the NOD-LRR protein family. Alternative names for cryopyrin include NALP3 [Nacht domain-, leucine-rich repeat- and pyrin domain (PYD)-containing protein] and PYPAF1 (pyrin domain-containing APAF-like protein). Cryopyrin consists of a PYD, a NOD (also known as NACHT domain) and a LRR domain (Fig. 1). All mutations are found in the NOD [for details, see the online mutation database at http://fmf.igh.cnrs.fr/infevers/ (150)].

Cryopyrin is mainly expressed in monocytes and neutrophils, but it is also expressed in human chondrocytes (50, 69, 98). It can form interactions with adaptor proteins ASC and cardinal, which results in the cryopyrin inflammasome (Fig. 1). The cryopyrin inflammasome brings two inactive pro-caspase-1 molecules together and activates it to caspase-1, which subsequently cleaves pro-IL-1β to the active IL-1β (5, 102).

There is conflicting evidence for a direct or indirect role of cryopyrin in regulation of activity of transcription factor NF-κB, from a range of studies, which are predominantly done using transfected cell lines. A number of studies seem to

indicate that cryopyrin may activate NF-κB, while others show an inhibitory effect or no effect at all (43, 44, 98, 114, 125, 139, 154). Possibly, the ultimate effect on NF-κB is determined by interaction of multiple proteins, with ASC as an important contributor. However, four recent papers by independent groups that each developed a cryopyrin-deficient mouse provide evidence that deficiency of cryopyrin has no effect on NF-κB activation in these mice, while they do confirm a clear deficiency in caspase-1 mediated IL-1β activation (91, 100, 103, 144).

The cryopyrin-deficient mice have also demonstrated that cryopyrin is indispensable for the activation of IL-1β by a number of ligands, including bacterial RNA, imidazoquinolone compounds (91), the Gram-positive bacterial toxins nigericin and maitotoxin, ATP (100, 144), and uric-acid crystals (103). Cryopyrin is not involved in caspase-1 activation by the Gram-negative *Salmonella typhimurium* (100, 144). Although one study using transfection models indicated that cryopyrin might also be a sensor for muramyl dipeptide (MDP), an active component of bacterial peptidoglycan (101), this could not be reproduced in the cryopyrin-deficient mouse model (91, 100, 144).

These results fit with the hypothesis that cryopyrin is an intracellular sensor of pathogens or danger signals, regulating innate immunity. It is not clear whether cryopyrin directly senses the PAMPs (e.g., through the LRR in analogy with TLRs) (147).

Monocytes from patients with mutations in the NOD of cryopyrin show increased activation of caspase-1, and subsequently increased release of IL-1β (5, 44). The key role of IL-1β in the cryopyrinopathies is confirmed by the success of treatment with IL-1 blockers (Anakinra, a synthetic analog of the IL-1 receptor antagonist) in all three clinical syndromes (20, 35, 55, 65, 66, 70, 120).

The exact effect of the cryopyrin mutations is still unclear. An attractive hypothesis involves a possible autoinhibitory loop of cryopyrin (5). When cryopyrin is not activated, the LRR domain can self-associate with the NOD of the same cryopyrin molecule and thus possibly prevent activation and interaction between adaptor protein cardinal and cryopyrin (Fig. 1). This mechanism prevents undue and excessive activation of cryopyrin and IL-1β. It is hypothesized that NOD mutations may interfere with this auto-inhibitory loop, thus resulting in increased inflammasome activation (5).

Pyrin: FMF. FMF (OMIM 249100) is the most prevalent of the hereditary autoinflammatory syndromes. It occurs mostly in people originating from the Mediterranean basin, including Armenians, Sephardic Jews, Arabs, and Turks, where rates of heterozygous carriership are very high (8, 93, 141). FMF is characterized by recurrent attacks of fever, serositis, and erythematous skin lesions; the most common symptoms are severe abdominal pain due to peritonitis, and arthritis. If left untreated, amyloidosis resulting in renal failure occurs frequently (135).

FMF is autosomal recessively inherited and caused by mutations in the *MEFV* (MEditerranean FeVer) gene, previously unknown, located on chromosome 16p (53, 86). At least 73 disease-linked mutations in the *MEFV* gene have been described so far, most of which are clustered in the 10th exon of this gene (for details, see the online mutation database at http://fmf.igh.cnrs.fr/infevers/) and are missense mutations.
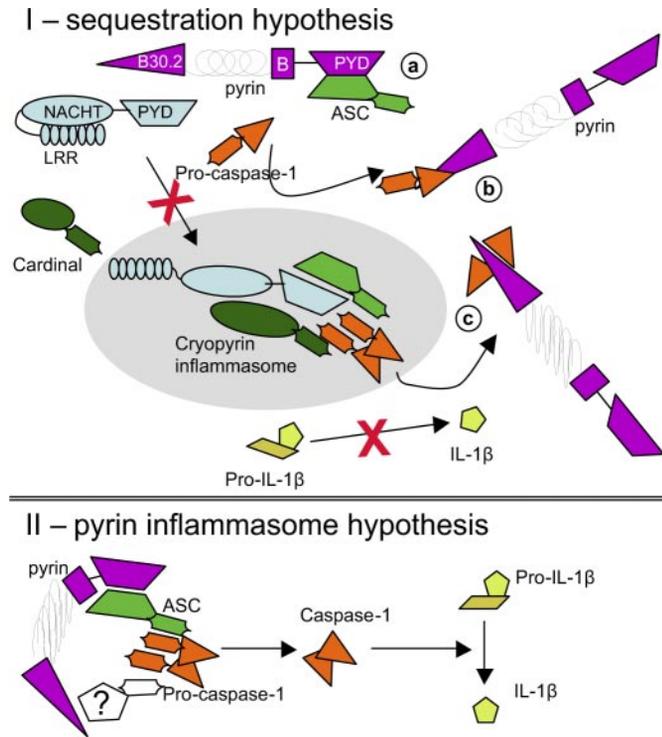
Fig. 2. Two current hypotheses on the mechanism of pyrin action. I. *Sequestration hypothesis.* Pyrin can competitively bind ASC (*a*) through its pyrin domain, and pro-caspase-1 (*b*) through its B30.2 domain and thus prevent them from being incorporated into the cryopyrin inflammasome. Pyrin can also bind cleaved caspase-1 (*c*) and prevent its action on pro-IL-1β. II. *Pyrin inflammasome hypothesis*. Pyrin forms its own inflammasome through binding ASC and another as yet unidentified adaptor protein, resulting in IL-1β activation. B, B-box domain.

The *MEFV* gene encodes for a protein of 781 amino acids known as pyrin (or marenostrin). Pyrin is primarily expressed in neutrophils, eosinophils, monocytes, dendritic cells, and fibroblasts (23, 36, 53, 86, 107). Pyrin expression is stimulated by inflammatory mediators, such as IFN-α, TNF, and IL-4. The intracellular localization of pyrin has been a puzzle from the start and is still not completely cleared up. Endogenous pyrin is cytoplasmic in monocytes, where it colocalizes with microtubules (99), but it is predominantly found in the nucleus in granulocytes, dendritic cells, and synovial fibroblasts (36). These differences in localization may be explained by the existence of different splice variants (29, 36, 116, 146). Alternatively, intracellular localization may be determined by protein interactions: Jeru et al. (88) showed that in vitro interaction of pyrin with two members of the 14.3.3 protein family stopped the transfer of pyrin to the nucleus.

Pyrin consists of four domains that can facilitate protein interactions. There is a 92-amino acid NH₂-terminal pyrin domain (PYD), member of the death domain fold superfamily (17), a B-box zinc finger, a coiled-coil region and a COOH-terminal B30.2/rfp/SPIa and ryanodine receptor (SPRY)/domain (also known as PRYSPRY domain) (22). Through its pyrin domain, pyrin can interact with ASC (122). As in the case of cryopyrin, this interaction influences activation of IL-1β but conflicting results in reports from two groups leave room for two different hypotheses for the action of pyrin (Fig. 2).

The first has been called the "sequestration hypothesis" (Fig. 2, *top*) and states that pyrin has an inhibitory effect on caspase-1-mediated activation of IL-1β by competitive binding of ASC, as well as caspase-1 (24, 25). Chae et al. (24) used a mouse model with a truncated variant of pyrin, as well as transfected cell lines to demonstrate an inhibitory role for pyrin in IL-1β processing. They suggest that binding of pyrin to ASC will sequester the latter protein and prevent it from joining in the formation of the cryopyrin inflammasome (24). In a transfection model, it was shown that pyrin can directly bind pro-caspase-1, as well as caspase-1 through its B30.2/rfp/SPRY domain in an ASC-independent manner, and prevent IL-1β activation in that way (25). In concordance with these results, knockdown experiments of pyrin with small interfering RNA resulted in increased IL-1β secretion (25).

The "pyrin inflammasome hypothesis" is the second hypothesis regarding the mechanism of pyrin action (Fig. 2, bottom). Yu et al. (154) used a transfection model and showed a proinflammatory effect of pyrin on IL-1β processing. They propose that pyrin, like cryopyrin, can also assemble an inflammasome complex resulting in activation of caspase-1.

The effect on NF-κB regulation is as much unclear for pyrin as for cryopyrin, with similar conflicting results varying from activation to inhibition or no effect at all (43, 105, 139, 154). Pyrin may also either have an inhibitory (43, 105, 122) or an activating (24) effect on apoptosis. These diverse conflicting results on pyrin action may indicate that pyrin's role is strongly dependent on its context, although, of course, it may also just be a reflection of the different experimental models used.

Most mutations that cause FMF are located in the B30.2/rfp/SPRY domain (http://fmf.igh.cnrs.fr/infevers/). Exactly how these mutations lead to the proinflammatory phenotype of FMF is still unclear. Modeling of the structure of this domain has shown that the most common mutations will most probably not result in a defect of structural integrity of the protein but most likely will affect binding of this domain to other proteins (62, 63, 152). Chae et al. (25) showed that three common FMF-mutations will interfere with the inhibitory interaction between pyrin and caspase-1, and they thus offer a way in which the mutations could have an activating effect under the sequestration hypothesis.

Researchers in favor of the pyrin inflammasome hypothesis, on the other hand, have suggested that this B30.2 domain might bind to pathogens in analogy to the LRR in TLRs and in cryopyrin (154). Although there is no supporting evidence for this conjecture at present, it is an attractive idea. FMF-associated mutations would cause increased binding of pathogens and thus lead to increased inflammation. This could also offer an explanation for the high rate of carriership for FMF-associated mutations in Mediterranean populations and the evidence for positive selection for variants in this domain in primates, which points to a survival advantage. Heterozygous carriers of FMF mutations would under this hypothesis be better able to mount an immune response to certain pathogens (147). An analogy for this hypothesis can be discovered in the tripartite motif-5α protein: the B30.2 domain of this protein has been shown to block infection by certain retroviruses and to have undergone similar positive selection (22, 117, 136).

PSTPIP1: syndrome of pyogenic arthritis, pyoderma gangrenosum, and acne. The pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome (OMIM 604416) is inher-

ited in an autosomal dominant pattern, and its main characteristics have been recognized in its name. Patients suffer from deforming sterile inflammation of joints, severe cutaneous ulcers (pyoderma gangrenosum), and expansive cystic acne (151). Fever is not a prominent symptom in this disorder. Neutrophils are the inflammatory cells most implicated in PAPA syndrome.

PAPA syndrome was linked to chromosome 15q, and subsequently a candidate gene approach identified mutations in proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1), also known as CD2-binding protein 1 (94, 127, 151). PSTPIP1 is highly expressed in neutrophils (84). This 416-amino acid protein contains three known domains: an NH_2-terminal Fer-CIP4 domain, a coiled-coil domain, and an SH3 domain. Only three mutations have been described so far (see INFEVERS mutation database: http://fmf.igh.cnrs.fr/infevers/), all of them located within the coiled-coil domain. As has been described in pyrin, the coiled-coil domain is important for protein-protein interactions (84). Through this domain, PSTPIP1 binds to pyrin (the SH3 domain is also necessary for this interaction) (84) and to protein tyrosine phosphatase with a PEST (proline, glutamate, serine, threonine) domain (PTP-PEST) (137), among others.

The mutated coiled-coil domain in PAPA syndrome results in decreased binding of PSTPIP1 to PTP-PEST (11, 151), and this, in turn, leads to hyperphosphorylation of PSTPIP1 (30). Shoham and colleagues (84) showed that this hyperphosphorylation increases the strength of the interaction between PSTPIP1 and pyrin. When they cotransfected pyrin and PSTPIP1 (together with other necessary proteins for IL-1β production), they found that IL-1β production (without other stimulation) was higher when PAPA-associated PSTPIP1 mutants were included (84). This correlated with a higher IL-1β production in response to LPS stimulation of peripheral blood leukocytes from a PAPA patient ex vivo compared with a healthy control (84). It places PAPA syndrome in the same pathogenic pathway as FMF.

Dysregulation of apoptosis may also be involved. Baum et al. (15) demonstrated that PSTPIP1 can bind to the strongly proapoptotic Fas ligand through its SH3 domain and that this interaction decreases the amount of cell surface Fas ligand and promotes its inactivation by storage in intracellular granules. Binding of the combination of PSTPIP1 and PTP-PEST to Fas ligand may also influence the phosphorylation status of Fas ligand (15). It is unknown whether apoptosis in patients with PAPA syndrome is affected.

Evidence is emerging for an additional role for PSTPIP1 in the regulation of adaptive immunity. It can interact with both the CD2 receptor on T cells and with the Wiskott-Aldrich syndrome protein (WASp), and thus it links CD2-activation with WASp-induced polymerization of actin and formation of the immunologic synapse in antigen recognition (11–13, 30, 94, 153). The PAPA-associated mutations in PSTPIP1 do not affect its interaction with either CD2 or WASp (151), and up to now, no defects in adaptive immunity have been reported in PAPA syndrome patients.

NOD2: Blau syndrome/early-onset sarcoidosis. Blau syndrome (BS; OMIM 186580) is an autosomal dominant inherited disorder with clinical manifestations caused by granulomatous inflammation of joints, eyes, and skin. It is clinically indistinguishable from early-onset sarcoidosis (OMIM

609464) (16, 90). Both BS and early-onset sarcoidosis are caused by mutations in the gene that encodes for NOD2 protein, also known as CARD15 (90, 109). NOD2 is another member of the NOD-LRR family and is structurally very similar to cryopyrin. It has a NOD-LRR segment at the NH_2 terminus and 2 CARD domains at the COOH terminus (115). NOD2 is primarily expressed in myeloid cells and intestinal epithelial cells, in particular, Paneth cells, in the small intestine (2). Expression of NOD2 can be enhanced by stimulation with TNF-α and IFN-γ (64, 124). It is considered to be a cytoplasmic sensor for pathogenic components, in a complementary capacity to the TLRs. It can be activated by MDP through its LRR domain, although whether this occurs through direct binding is unclear (59, 85). Activation of NOD2 results in a wide array of downstream effects that are still not well understood. These include activation of both NF-κB and MAPK pathways, turning on an innate immune response of diverse cytokines, including IL-1β, and defensins (2).

Mutations that cause BS are primarily located in the NOD domain, similar to the mutations in cryopyrin in the cryopyrin-associated syndromes. Indeed, two different BS mutations affect a codon at a homologous position in the NOD domain to the location of the cryopyrin R260W mutation (26) (see INFEVERS mutation database: http://fmf.igh.cnrs.fr/infevers/). These mutations result in MDP-independent constitutive activation of NF-κB and increased NF-κB response on MDP stimulation (26, 90). It is hypothesized that, similar to cryopyrin, the NOD and LRR domains of NOD2 self-associate when the protein is in a resting state to prevent spontaneous activation. The mutations in the NOD domain that cause Blau syndrome could interfere with this autoinhibitory loop, resulting in a mutated NOD2 protein that is overly sensitive to activation.

Mutations in the LRR segment of NOD2, the pathogen-sensing domain, are found in a certain percentage of patients with a far more common disorder: Crohn's disease, one of the major forms of inflammatory bowel disease (82, 115). Crohn's disease is characterized by recurrent granulomatous inflammatory lesions of the intestine, which can also be accompanied by inflammation of skin, joints, and eyes. This discovery seems to indicate that Crohn's disease could also be categorized as an autoinflammatory disease. Later, polymorphisms in the LRR domain of NOD2 were also associated with psoriatic arthritis (119). There is intense debate on how NOD2 variants contribute to the pathogenesis of Crohn's disease and whether they result in either gain or loss of function. For example, mice carrying the NOD2 variant showed an increased IL-1β production (96), while humans with the same variant had an impaired IL-1β production (113); this might be a species effect. For a detailed discussion of this question, we refer to a recent review by Eckmann and Karin (48).

TNF receptor type 1: TRAPS. TRAPS (OMIM 142680) is the most common of the autosomal dominant periodic fever syndromes. The long duration of the attacks in TRAPS, which is generally longer than a week, is its most distinguishing symptom. TRAPS does not have a clear direct link with NOD-LRR proteins, as found in the pathogenesis of the syndromes described above, and neither has the HIDS described in the next section.

TRAPS is caused by a mutation in the TNFRSF1A gene, which encodes for the type 1 TNF receptor (TNFR1) (108),

member of the TNFR superfamily. This receptor is the main mediator of signaling by TNF-α and is thus an important segment of the inflammatory cascade. TNF-α is a pleiotropic molecule, which can induce cytokine secretion, activation of leukocytes, fever, and cachexia (18). TNFR1 is a transmembrane receptor, with four cysteine-rich domains (CRDs) in the extracellular region and a death domain in the intracellular region. Only a small amount of TNFR1 is actually expressed at the cell surface; the remainder is stored intracellularly in the trans-Golgi network (21, 27, 52, 57, 89, 143). Upon binding of TNF-α to the extracellular region of cell-surface TNFR1, three TNFR1 molecules will form a trimer on the cell surface. The united and activated intracellular death domains will subsequently recruit a complex of several proteins resulting in activation of NF-κB. A second, more time-consuming, pathway that can be activated by TNFR1 leads to apoptosis. The NF-κB activation pathway can inhibit this second pathway in certain circumstances, and thus the final result of activation of TNFR1 can vary.

More than 40 different mutations have been described in association with TRAPS. Remarkably, all but three of these mutations occur in the first and second CRDs. No mutations have been found in the transmembrane or intracellular regions of TNFR1, and none of the mutations result in a large deletion or truncation of TNFR1 (see INFEVERS mutation database, http://fmf.igh.cnrs.fr/infevers/). The first CRD is thought to be involved in the formation of the receptor trimer (28), whereas the second CRD contains the majority of contact residues between ligand and receptor (14). Many of the mutations are missense mutations, which involve cysteine residues that are part of the intramolecular disulfide bonds that determine the three-dimensional structure of the CRD. Other mutations mostly occur at residues that are also predicted to have a profound effect upon the secondary structure of the receptor. The cysteine mutations are generally associated with a higher penetrance and more severe phenotype than the noncysteine mutations, although variability exists even within families (6).

There are two coding sequence variants in TNFR1, resulting in a R92Q or P46L amino acid change, which seem to differ from the other mutations. They have a certain prevalence in the general population [R92Q: 2% in North American and Irish populations; P46L 9% in African populations (6, 83, 121)]. It is still under debate whether they are either associated with low penetrance risk for TRAPS, leading to a milder phenotype, or represent polymorphisms associated with a number of inflammatory disorders, or both (9, 34, 118, 121, 134).

How the mutations in TNFR1 lead to the inflammatory phenotype of TRAPS has been a puzzle from the beginning. Some of the characteristics of the mutated TNFR1 would be more likely to have an anti-inflammatory effect: there is less binding of TNF-α to the mutated receptor (58, 148), less cell-surface expression (81, 129, 148), and decreased TNF-induced NF-κB activation (128, 129). The decrease in TNF-induced apoptosis detected in neutrophils from TRAPS patients, which might result in prolonged survival of activated inflammatory cells, could have some contribution to the phenotype (34, 128). However, the fact that none of the mutations associated with TRAPS result in large deletions or truncation
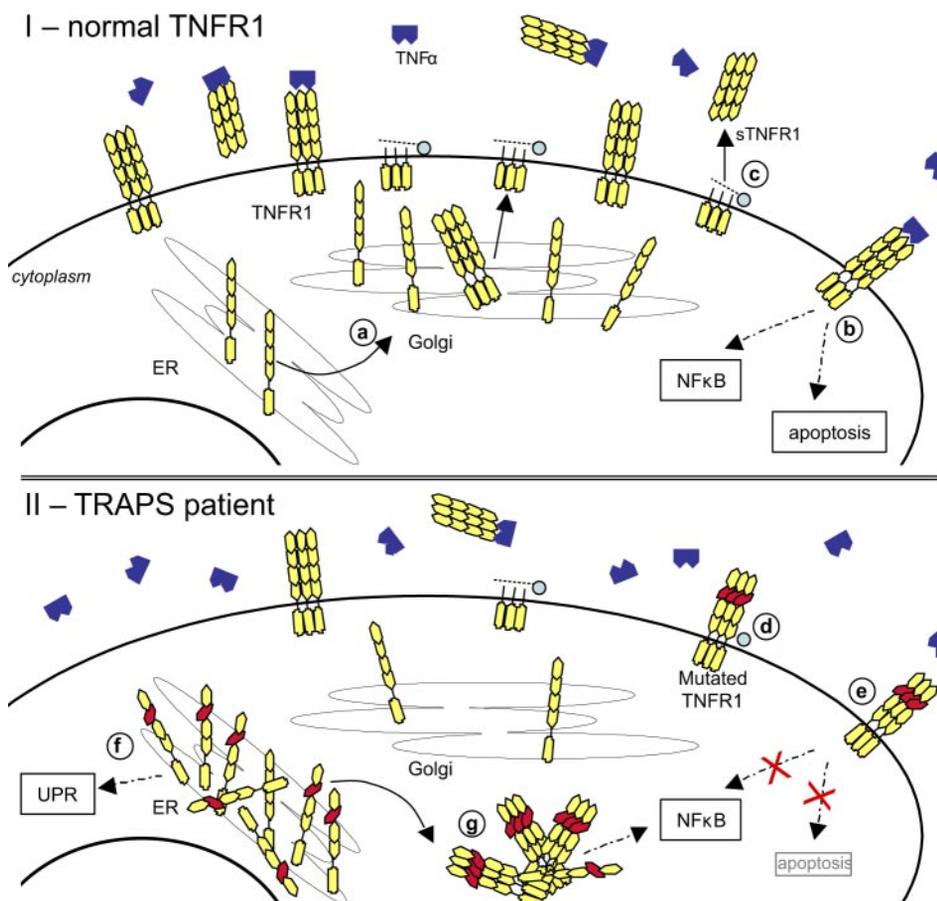

Fig. 3. Tumor necrosis factor receptor type 1 (TNFR1) and TNF receptor-associated periodic syndrome (TRAPS). I. *Normal situation.* *a*: the TNFR1 molecules are transported from endoplasmic reticulum (ER) to the Golgi, where they are pooled before going on to the cell surface. *b*: when TNF-α binds to the cell surface TNFR1 trimer, intracellular signaling results in NF-κB activation and/or apoptosis. *c*: shedding: upon activation, cell surface receptors are cleaved off by metalloproteinases. The now-soluble extracellular part of the receptor (sTNFR1) can act as a TNF antagonist. II. *Possible effects of mutated TNFR1 in TRAPS patient.* *d*: *shedding hypothesis.* Some TRAPS mutations will prevent cleavage by metalloproteinases, resulting in decreased sTNFR1. *e*: there is less cell surface expression of TNFR1, and binding of TNF-α by the mutated TNFR1 is decreased, resulting in less TNF-induced NF-κB activation and less TNF-induced apoptosis. *f*: the misfolded mutated TNFR1 remains stuck in the ER, which may cause an unfolded protein response (UPR). *g*: alternatively, the mutated TNFR1 aggregates in the cytoplasm, which may lead to ligand-independent NF-κB-activation.

of the TNFR1 indicates that mere haploinsufficiency, or decreased expression of a normal TNFR1, is not sufficient to result in the inflammatory phenotype.

Until recently, the explanation was mainly sought in the so-called "shedding hypothesis" (Fig. 3). After activation of TNFR1, the extracellular part of the receptor is shed from the cell surface by metalloprotease-mediated cleavage at a site near the transmembrane region (3). The cleaved extracellular part, now called "soluble TNFR1" (sTNFR1), is still able to bind TNF-α and can in fact act as a blocker of TNF signaling because it prevents TNF-α from binding to the intact cell-surface receptor. TRAPS patients have decreased plasma levels of sTNFR1 and leukocytes from patients with a C52F mutation in TNFR1 were shown to have decreased shedding of TNFR1 (108). The shedding hypothesis holds that decreased shedding of TNFR1 may result in increased TNF-α-signaling because the TNFR1 is retained longer at the cell surface and circulating TNF-α is not blocked sufficiently. However, subsequent studies showed conflicting results. Some of the other TNFR1 mutations also resulted in decreased shedding, but others did not or only showed reduced shedding in fibroblasts (4, 6, 81, 129), whereas conversely leukocytes from several patients without TNFR1 mutations also did show impaired shedding (4). Thus the shedding hypothesis is not tenable as the sole explanation of the pathogenesis of TRAPS.

A new hypothesis suggests that the increased inflammation of mutant TNFR1 is independent of its TNF-signaling function (Fig. 3) (95, 149). As mentioned above, mutated TNFR1 is less expressed at the cell surface (81, 129). The mutant TNFR1 that is retained intracellularly is not pooled in the Golgi but is retained in the endoplasmic reticulum (ER) (95, 148). Mutant TNFR1 cannot associate with the wild-type version but can form aggregates by self-interaction (95, 149). Either this cytoplasmic receptor aggregation results in ligand-independent signaling (149) or an accumulation of the misfolded mutant protein in the ER turns on an exaggerated unfolded protein response leading to induction of cytokines like IL-1β (95). This new hypothesis might also offer an explanation for the observation that blocking IL-1β works better in some TRAPS patients than blocking TNF (130).

Mevalonate kinase: HIDS. Major clinical characteristics of the autosomal recessive HIDS and periodic fever syndrome (OMIM 260920) that make it stand out from the other hereditary periodic fever syndromes are the prominent lymphadenopathy and enlarged spleen accompanying the fever, the fact that fever episodes can be provoked by vaccination, and a very high serum concentration of immunoglobulin D (135). Mutations for HIDS are found in the mevalonate kinase gene (45, 76), which encodes for an essential enzyme in the isoprenoid pathway, also known as the cholesterol biosynthesis pathway. Thus this autoinflammatory syndrome was unexpectedly linked to a metabolic defect.

Another surprise was that there was already a disorder connected to mutations in this gene. Mevalonic aciduria is a more classical metabolic disorder that causes mental retardation, ataxia, myopathy, failure to thrive, and often early death (71). At the same time, patients with mevalonic aciduria also display recurrent fever and inflammation, and, in fact, HIDS and mevalonic aciduria are now seen as two ends of a spectrum of disease caused by mevalonate kinase deficiency (132),

similar to the different clinical syndromes caused by cryopyrin mutations (135).

The isoprenoid pathway runs from acetyl-CoA to cholesterol and subsequent sterol compounds on the one hand, and a large and varied group of essential molecules known as isoprenoids on the other (60). Examples of isoprenoids include ubiquinone-10, heme A, dolichol, isopentenyl transfer RNAs, and isoprenylated proteins. Isoprenylation is the posttranslational modification of proteins, consisting of an addition of farnesyl or geranylgeranyl groups, which in most cases makes them membrane associated (74).

An early, rate-limiting enzymatic step in the isoprenoid pathway is undertaken by 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, which converts HMG-CoA to mevalonate. Because HMG-CoA reductase is the enzyme that is inhibited by statins, which are used by millions of patients to lower their cholesterol, it is the most extensively studied component of this pathway. Its activity is tightly controlled by numerous feedback mechanisms both at transcriptional, translational, and posttranslational level (74). Interestingly, expression of HMG-CoA reductase in Syrian hamsters can be upregulated by administration of LPS or IL-1β (49). Mevalonate kinase (MK) is the next enzyme and phosphorylates mevalonate into 5-phosphomevalonate. MK is also subject to negative feedback by sterol regulatory element binding proteins (SREBPs) at the transcriptional level (145) and through competitive inhibition at the ATP-binding site by downstream intermediates (68).

Mevalonate kinase mutations are found throughout the gene (see INFEVERS mutation database, http://fmf.igh.cnrs.fr/infevers/). The majority of them are missense mutations, and most patients have a combination of two different mutations (97). In the case of HIDS, one of the two mutations is generally one that results in a base pair change at position 377 of the protein (V377I) (33, 75). For this mutation, a founder effect could be demonstrated (133), which may explain its high prevalence in The Netherlands (79). The V377I mutation is considered to have only a relatively mild effect on mevalonate kinase activity (78). Similarly, there are a number of mutations that are most often associated with the severe phenotype of mevalonic aciduria (132).

The mutations lead to a reduction of MK enzyme activity in HIDS to about 1–10% of normal (33, 75, 76), while in mevalonic aciduria residual activity is often immeasurably low (71, 77). There is a corresponding increase of HMG-CoA reductase activity and accumulation and urinary secretion of mevalonate, the substrate for MK, which is 100 to 1,000-fold higher in mevalonic aciduria than in HIDS and which peaks during a fever episode (71, 92, 131). Intriguingly, MK enzyme activity appears to be sensitive to temperature, with lower enzyme activity measured in vitro when cells are incubated at higher temperatures (73). There is no absolute deficiency of any of the isoprenoid end-products, although in mevalonic aciduria there is a slight decrease in cholesterol, dolichol, and ubiquinone-10 (72, 74, 78, 80). The mutated MK still responds to feedback regulation by SREBPs (97, 126).

In recent years, a growing number of studies have uncovered links between the isoprenoid pathway and inflammation. These studies are mostly done by examining the effects of statins, the inhibitors of HMG-CoA reductase, on immune responses in various in vitro models and clinical studies. In most cases,

statins have anti-inflammatory effects, ranging from increased apoptosis of inflammatory cells (112) to a reduction of expression of cytokines (reviewed in Refs. 1, 87). Others report a proinflammatory effect of statins, most notably increased caspase-1 activation and IL-1β secretion by monocytes when stimulated with *Mycobacterium tuberculosis* or mitogens, through a decrease of geraniolgeraniol (31, 54, 110, 111). Similarly, there are contradictory reports on the effect of statins in patients with mevalonate kinase deficiency: two children with mevalonic aciduria developed a severe inflammatory attack after 2 wk of statin treatment (71), whereas six HIDS patients who were treated with statins for 6 mo in a double-blind, cross-over, placebo-controlled trial showed a decrease in number of days of illness (131).

A role for IL-1β in the pathogenesis of HIDS is demonstrated by the increased ex vivo production of this cytokine (46, 47, 55) and the beneficial effect of treatment with the IL-1 blocker anakinra (19). This links HIDS to the autoinflammatory disorders with a direct defect of inflammasome function. As mentioned above, patients with HIDS tend to show more lymphatic reactivity during the attacks than the other syndromes and have a high circulating concentration of IgD (and IgA). This might be explained by a defect in lymphocyte apoptosis (unpublished observation).

Whether the pathophysiological effects of mevalonate kinase deficiency are due to a transient deficiency of one or more isoprenoid end-products or toxicity of mevalonate accumulation still needs to be clarified.

To conclude, through the unraveling of the pathophysiology of these rare disorders, a clearer picture of the innate immune system and unexpected new concepts relevant for a variety of inflammatory disorders emerge. These findings open up new avenues for treatment of inflammation and for modulation of the immune response. The central hypothesis to date is that the inflammatory reaction in most of these autoinflammatory syndromes arises from undue or increased activation of pattern recognition molecules of the innate immune system. Although our knowledge of the triggers involved is still limited, it is reasonable to assume that exogenous, as well as endogenous molecules, may serve as ligands. In autoinflammatory syndromes like CAPS and FMF, defective protein components of an inflammasome (cryopyrin and pyrin, respectively) somehow give rise to an exaggerated downstream response in which caspase-1 activation is a crucial step leading to conversion of pro-IL-1β to bioactive IL-1β. Given the impressive clinical response to blocking the biological effects of IL-1β, it is now clear that IL-1β is a central mediator of symptoms and signs in many of these patients. The pathogenesis of some of the other autoinflammatory syndromes, e.g., HIDS and TRAPS, is much less clear but also seems to involve IL-1β.

Many additional questions may be asked regarding the pathogenesis of these disorders. Given the pathways they have in common, it is enigmatic how the differences in phenotype are being produced, even with different mutations in just one molecule (e.g., cryopyrin). Similarly intriguing are questions regarding differences in age of onset or duration of attacks. Especially the latter—duration of attacks—points to differences in feedback loops that regulate the inflammatory response, an area of research that has been largely neglected and should be particularly challenging to physiologists.

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