Familial autoinflammatory diseases: genetics, pathogenesis and treatment

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Purpose of review

The systemic autoinflammatory diseases are characterized by seemingly unprovoked inflammation, without major involvement of the adaptive immune system. This review focuses mainly on a subset of these illnesses, the hereditary recurrent fevers, which include familial Mediterranean fever, the tumor necrosis factor receptor-associated periodic syndrome, the hyperimmunoglobulinemia D with periodic fever syndrome, and cryopyrin-associated periodic syndromes. This review elucidates how recent advances have impacted diagnosis, pathogenesis, and treatment.

Recent findings

More than 170 mutations have been identified in the four genes underlying the six hereditary recurrent fevers. Genetic testing has broadened the clinical and geographic boundaries of these illnesses, given rise to the concept of the cryopyrin-associated periodic syndromes as a disease spectrum, and permitted diagnosis of compound heterozygotes for mutations in two different hereditary recurrent fever genes. Genetics has also advanced our understanding of amyloidosis, a complication of the hereditary recurrent fevers, and suggested a possible role for common hereditary recurrent fever variants in other inflammatory conditions. Recent advances in molecular pathophysiology include the elucidation of the N-terminal PYRIN domain in protein-protein interactions, the description of the NALP3 (cryopyrin) inflammasome as a macromolecular complex for interleukin-1β activation, and the identification of signaling defects other than defective receptor shedding in patients with tumor necrosis factor receptor-associated periodic syndrome. These molecular insights form the conceptual basis for targeted biologic therapies.

Summary

Advances in molecular genetics extend our ability to recognize and treat patients with systemic autoinflammatory diseases and inform our understanding of the regulation of innate immunity in humans.

Keywords

genetics, hereditary recurrent fevers, inflammasome, systemic autoinflammatory diseases, therapy

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Abbreviations

ASC	apoptosis-associated specklike protein with a caspase-recruitment domain
CAPS	cryopyrin-associated periodic syndromes
CARD	caspase-recruitment domain
CINCA	chronic infantile neurologic cutaneous and articular syndrome
FCAS	familial cold autoinflammatory syndrome
FMF	familial Mediterranean fever
HIDS	hyperimmunoglubulinemia D with periodic fever syndrome
HRF	hereditary recurrent fever
LRR	leucine-rich repeat
MIM	Mendelian inheritance in man
MWS	Muckle–Wells syndrome
NACHT	domain present in neuronal apoptosis inhibitory protein, CIITA, HET-E, and TP1
NALP	NACHT, leocine-rich repeat-, and PYRIN domain-containing protein
NOMID	neonatal-onset multisystem inflammatory disease
PAPA	pyogenic arthritis with pyoderma gangrenosum and acne
PSTPIP1	proline serine threonine phosphatase interacting protein 1
SAA	serum amyloid A
TNFRSF1A	p55 tumor necrosis factor receptor
TRAPS	tumor necrosis factor receptor-associated periodic syndrome

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Introduction

The concept of autoinflammatory disease was first proposed in 1999 to describe a group of inherited disorders characterized by episodes of seemingly unprovoked inflammation that, in contrast to the traditionally defined autoimmune diseases, lack high-titer autoantibodies or antigen-specific T cells [1]. Two hereditary recurrent fevers (HRFs), familial Mediterranean fever (FMF, Mendelian inheritance in man [MIM] 249100) and the then newly recognized tumor necrosis factor receptor-associated periodic syndrome (TRAPS, MIM 142680), were the prototypes for this diagnostic category. The following year, this concept was extended to subsume several mendelian disorders, including other HRFs, the familial urticarial syndromes (now included among the HRFs), complement disorders such as hereditary angioedema (MIM 106100), and granulomatous disorders such as Blau's syndrome (MIM 186580) [2]. Several illnesses with a complex mode of inheritance, such as Behçet's disease (MIM 109650) and idiopathic pulmonary fibrosis (MIM 178500), were also included among the proposed autoinflammatory diseases, and it seems reasonable to suggest that some apparently acquired disorders of inflammation, such as the syndrome of periodic fever with aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) [3], may also properly fall under this rubric.

Subsequent advances in molecular genetics have vindicated the notion of autoinflammatory disease as a unifying concept, at both the structural and functional levels [4].

Table 1. Characteristics of the hereditary recurrent fevers and the autoinflammatory PAPA syndrome

	FMF	HIDS	TRAPS	FCAS	MWS	NOMID/CINCA	PAPA
Inheritance	Recessive	Recessive	Dominant	Dominant	Dominant	Dominant/de novo	Dominant
Gene	*MEFV*	*MVK*	*TNFRSFIA*		*CIAS1/NALP3/PYPAF1*		*CD2BP1/PSTPIP1*
Chromosome	16p13	12q24	12p13		1q44		15q24
Protein	Pyrin/marenostrin	MK	TNFRSF1A		Cryopyrin		CD2BP1/PSTPIP1
Expression	Granulocytes, monocytes, synovial fibroblasts	Ubiquitous	Ubiquitous		Granulocytes, monocytes, chondrocytes		Hematopoietic tissue, lung
Proposed pathogenesis	Increased IL-1β and NF-κB activation, impaired leukocyte apoptosis	Temperature-dependent MK activity causes a deficiency in isoprenoid products, leading to increased IL-1β secretion and/or increased mevalonate may induce inflammation	Impaired ectodomain cleavage or intracellular trafficking of TNFRSF1A, defect of TNF-induced apoptosis		Increased activity of the NALP3/Crypopyrin inflammasome with subsequent IL-1β secretion and NF-κB activation		Mutations cause increased PSTPIP1 binding to pyrin, leading to increased IL-1β secretion
Classical features							
Ethnicity	Jewish, Armenian, Arab, Turkish, Italian	Dutch, French, other European	Any ethnic group	Mostly European	Northern European	Any ethnic group	Caucasian American
Duration of episodes	1–3 days	3–7 days	Often >1 week	Usually <24 hours	24–48 hours	Almost continuous, with exacerbations	Variable
Distinguishing clinical findings	Polyserositis, erysipeloid erythema, monoarthritis, splenomegaly, constipation	Cervical lymphadenopathy, headache, elevated urinary mevalonate during attacks, reduced MK activity in between attacks	Periorbital edema, migratory nature of myalgia and rash	Cold-induced urticaria-like rash	Sensorineural hearing loss	Onset of urticarial rash in infancy, chronic aseptic meningitis, sensorineural hearing loss, arthropathy	Pyogenic arthritis, pyoderma gangrenosum
Amyloidosis	Common	Very rare	~10% of cases	Uncommon	Reported in 25% of cases	Reported in a minority of patients who reach adulthood	None reported

PAPA, pyogenic arthritis with pyoderma gangrenosum and acne; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D with periodic fever syndrome; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle–Wells syndrome; NOMID/CINCA, neonatal-onset multisystem inflammatory disease/chronic infantile neurologic cutaneous and articular syndrome; ~, approximately; MK, Mevalonate kinase.

This is particularly well illustrated among the HRFs, salient genetic and clinical features of which are summarized in Table 1. FMF, the most common and probably most thoroughly studied HRF, is caused by mutations in *MEFV*, encoding the pyrin/marenostrin protein [5,6]. Mutations in the related protein cryopyrin (alternatively called NALP3 [because it belongs to a family of proteins containing a NACHT domain, leucine-rich repeat, and PYRIN domain] or PYPAF1) give rise to the so-called cryopyrin-associated periodic syndromes (CAPS): familial cold autoinflammatory syndrome (FCAS, MIM 120100), Muckle–Wells syndrome (MWS, MIM 191900), and neonatal-onset multisystem inflammatory disease (NOMID, also called chronic infantile neurologic cutaneous and articular syndrome or CINCA, MIM 607115) [7–9]. Both pyrin and cryopyrin share an N-terminal motif, the PYRIN domain, that facilitates cognate protein-protein interactions (reviewed by Kastner and Aksentijevich [10••]). The PYRIN domain is, in turn, a member of a larger family of protein motifs, the death domain-fold superfamily [11]. Another member of this superfamily, the death domain, is found at the N-terminus of the protein mutated in TRAPS, the p55 TNF receptor (TNFRSF1A) [1]. As discussed here, through their respective PYRIN and death domains, cryopyrin, pyrin, and the p55 TNF receptor play an important role in regulating cytokine secretion, nuclear factor-κB activation, and apoptosis, and thereby the innate immune system.

Although the gene mutated in the hyperimmunoglobulinemia D with periodic fever syndrome (HIDS, MIM 260920) [12,13] does not encode such a motif, recent data suggest that it may also impinge on the innate immune system through the regulation of interleukin-1β secretion. There are also structural and functional relationships between the HRF proteins and the proteins mutated in several other autoinflammatory disorders, including Blau's syndrome and the syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA, MIM 604416).

Increased awareness of the systemic autoinflammatory diseases, coupled with the widespread availability of genetic testing, has catalyzed the evolution of our concepts of diagnosis, genotype-phenotype interaction, and the broader role of the causative genes and proteins in health and disease, while concomitant advances in our understanding of pathophysiology have allowed dramatic breakthroughs in targeted biologic therapy. This review focuses on significant advances of the past year.

Clinical genetics

Although no new HRF genes have been identified over the past year, mutational studies of cohorts of affected patients have substantially advanced our understanding of the biologic role of the relevant genes and proteins. Areas of progress include refinement of the relationships between gene mutations and specific disease-associated clinical manifestations; analysis of the role of specific mutations and modifier factors in the risk of amyloidosis; and delineation of the relation between common gene variants and the broader spectrum of inflammatory disease.

Population genetics and genotype-phenotype relationships

Given the relative accessibility of DNA diagnostics and the absence of reliable biochemical markers for FMF, TRAPS, and CAPS, genetic testing has become an important adjunct in the diagnosis of the HRFs. The growing list of mutations and polymorphisms of these mendelian disorders is frequently updated in INFEVERS [14•], a mutational database accessible on the World Wide Web at http://fmf.igh.cnrs.fr/infevers. To date more than 50 disease-associated mutations are listed for FMF, more than 40 for TRAPS, more than 35 for CAPS, and more than 30 for HIDS. It is interesting to note that, among HRF-associated mutations, nearly all are missense mutations, and, with two exceptions in FMF, nearly all spare the death domain-fold motif, where present, in the respective HRF proteins.

Implementation of genetic screening has extended the diagnosis of specific HRFs to a wider range of ethnicities than originally appreciated. The recognition of FMF among Greeks, Italians, and some non-Mediterranean populations [15•] and of TRAPS in an even more global distribution [16] is already established. A recent report from Italy extends the geographic distribution of HIDS, formerly regarded as occurring primarily in individuals of northern European ancestry, to the south, with a total of 14 mutation-positive cases from Italy and Albania [17••].

Several recent reports also address specific mutations in HRF genes. A Spanish group has reported a novel H478Y *MEFV* variant associated with prolonged fevers, predominant joint involvement, colchicine resistance, and an autosomal dominant mode of inheritance in a three-generation family [18•]. This severe *MEFV* variant joins two others, ΔM694V and the M694I-E148Q complex allele, with an apparent dominant inheritance [19]. Perhaps at the opposite end of the spectrum of severity is the *MEFV* variant E148Q, which is present at sufficiently high frequency in several Middle Eastern control populations to be considered a low-penetrance variant [20] or perhaps even a benign polymorphism [21]. A recent Turkish series reported clinical features on 26 individuals homozygous for E148Q, all but four of whom were symptomatic [22•]. With the reservation that these patients did not undergo complete *MEFV* sequencing, and therefore could possibly harbor other unknown mutations, E148Q homozygotes had a distribution of symptoms similar to that of patients with other FMF-associated genotypes and a similar

responsiveness to colchicine. These data suggest that, at least under certain as-yet undefined genetic and environmental conditions, this *MEFV* variant may be associated with the FMF phenotype.

Especially in the case of TRAPS, recent publications point to a possible broadening of the clinical phenotype. The question of neurologic involvement in TRAPS has been raised in several case reports, including the description of one woman with the T50K *TNFRSF1A* mutation with abnormal findings on magnetic resonance imaging [23•], although the causal relation is not completely clear due to concomitant etanercept treatment. A second paper reported panniculitis in individuals with the T50M and R92Q mutations [24•]. A third report presented the case of an African American boy with the P46L *TNFRSF1A* variant and myocarditis and sacroiliitis, two previously unrecognized manifestations of TRAPS [25•]. Although P46L is the only *TNFRSF1A* variant that we have seen among African American TRAPS patients in our clinic, it should be noted that it is also seen in approximately 4% of African American control individuals [26], and in an even higher percentage of west African controls [27•], indicating that P46L is frequently not fully penetrant, at least for the TRAPS phenotype.

Considerable recent attention has also been focused on mutations in *CIAS1*, which can cause FCAS, MWS, and the NOMID/CINCA syndrome. According to accepted clinical definitions, FCAS is characterized by cold-induced episodes of fever and urticarial skin rash, without evidence of hearing impairment [28••]. MWS presents with febrile episodes not necessarily induced by cold, but often with sensorineural hearing loss and systemic amyloidosis [10••]. NOMID/CINCA manifests urticarial rash regardless of temperature, with central nervous system involvement (papilledema, cerebrospinal fluid pleiocytosis, or sensorineural hearing loss) and a characteristic arthropathy [29••]. Recent case reports and clinical series confirm earlier impressions of a more continuous spectrum of phenotypes [30–32], including MWS patients with features of FCAS [33•], families in which various members exhibit manifestations of FCAS, MWS, or NOMID/CINCA [34••,35•], and patients with unique variant phenotypes [36•], one of which is associated with the first mutation to be described in the cryopyrin leucine-rich repeat (LRR) domain [37•]. Moreover, several mutations have been identified in both FCAS and MWS [7,29••,38,39,40•] and in both MWS and NOMID [8,9,29••,32,38,40•,41].

Genetic screening for mutations in the HRF genes has also revealed the coexistence of mutations of two different autoinflammatory disease genes in a single subject. In one case, a 7-year-old girl was found to have the V377I mutation at the HIDS-associated mevalonate kinase (*MVK*) locus, as well as the R92Q variant at *TNFRSF1A*, and presented with mild features of HIDS but responded to steroids in a way more characteristic of TRAPS [42•]. A second patient with compound heterozygosity for V377I/S378P *MVK* was also found to have the R92Q *TNFRSF1A* variant and manifested disproportionately severe biochemical mevalonate kinase deficiency relative to her mild clinical phenotype [43•]. Another patient with V377I and G211A mutations in *MVK* and the P46L *TNFRSF1A* variant had more severe symptoms that partially responded to the TNF inhibitor etanercept [44]. Yet another patient of Chinese ancestry with prolonged episodes of fever and abdominal pain was found to have compound heterozygosity for the Y20D *TNFRSF1A* mutation and the E148Q variant of *MEFV* [45•]. Given the relatively high frequency of R92Q in the white population [26] and E148Q in the Chinese [46], it is not altogether surprising that compound heterozygosity involving these variants would be observed. Longitudinal follow-up over many years may be needed to define the phenotypic ramifications of these gene interactions.

Several important questions in the genetics of the HRFs must be resolved. Substantial numbers of patients meeting clinical criteria for FMF, HIDS, or the cryopyrinopathies, or who have clinical features resembling TRAPS, do not have demonstrable mutations at any of the known causative genes. Although noncoding mutations remain a logical possibility, it is also possible that there are additional HRF genes yet to be found. A second major area of interest is defining the factors affecting penetrance. Population-based estimates of the frequency of *MEFV* mutations among several ethnic groups [10••], of the V377I mutation in *MVK* in the Netherlands [47], and of the R92Q [26] and P46L [27•] variants of *TNFRSF1A* in whites and African Americans, respectively, all point to the likelihood of reduced penetrance of the respective mutations. Finally, for the case of the recessively inherited FMF, it remains a puzzle why as many as one third of patients with clinical disease have only one demonstrable mutation [10••]. The answer to this latter question may be tied to the resolution of the first two.

Amyloidosis in the hereditary recurrent fevers

Systemic amyloidosis is one of the most serious manifestations of the HRFs and is the result of the tissue deposition of misfolded fragments of serum amyloid A (SAA), one of the acute-phase reactants produced by the liver in response to systemic inflammation [48]. Most frequently, deposition occurs in the kidneys, gastrointestinal tract, adrenals, spleen, testes, and lung and sometimes in the liver, heart, and thyroid. In the precolchicine era, amyloidosis was a frequent cause of death in patients with FMF, particularly north African Jews, Turks, and Armenians. Amyloidosis in FMF can sometimes precede the development of febrile attacks (phenotype II), a phenomenon that

is probably due to the persistent subclinical inflammatory state seen even in the absence of symptoms in some HRF patients [16,49–52,53•,54•].

A substantial body of literature indicates an increased risk for amyloidosis among Jewish, Arab, and Armenian patients who are homozygous for the M694V mutation [55–59]. In a series of more than 1000 Turkish patients for whom mutational analysis was available [60•], however, there was no statistically significant association between this genotype and the risk of amyloidosis. Although other smaller series from Turkey have come to the same conclusion [61,62], the explanation for the difference from other populations is not clear but could involve either differences in the frequency of modifier genes or environmental effects.

One apparently important modifier factor in amyloidosis risk in FMF is the SAA1 precursor isoform, with the α/α variant conferring increased risk [63,64]. In a recent series from Turkey, seven of 23 FMF patients with this genotype had amyloidosis *vs* one of 51 patients with other SAA1 genotypes [65•]. Significant differences were also observed in a recent study of 70 Arab patients [66•]. The mechanism by which this SAA1 variant increases amyloid risk is unknown, but current speculation focuses on differences in macrophage processing or intrinsic potential for fibril formation [63].

Amyloidosis also occurs relatively frequently in patients with MWS and NOMID/CINCA, as well as TRAPS. In TRAPS, susceptibility to amyloidosis appears to be increased among patients with mutations at cysteine residues [26], although patients with noncysteine mutations, most notably T50M, have been reported [67•]. Amyloidosis is extremely rare in HIDS, with the first case having been reported only within the past year [68•]. It is not clear whether the rarity of amyloidosis in HIDS, relative to FMF, TRAPS, MWS, and NOMID/CINCA, is due to an overall lower SAA burden in HIDS, to less amyloidogenic alleles at modifier genes, or to environmental factors.

Role of hereditary recurrent fever genes in inflammation

Given the relatively high frequency of certain HRF alleles in the general population, there has been considerable speculation that some of these variants may also predispose to other inflammatory phenotypes [26]. It goes without saying that in situations such as this, in which common genetic variants of HRF genes are sought in other relatively common illnesses, controls that are appropriately matched, particularly for ethnic background, are essential. Particularly striking are the results of a study of the R92Q variant in a large European study of cardiovascular disease [69•]. Among 62 cigarette smokers with carotid plaque, 9.7% had R92Q, *vs* 2.1% of 338 smokers without plaque, for an odds ratio of 5.97 (95% confidence interval 1.64–15.63, $P = 0.0048$). Other less dramatic associations were also noted between R92Q and carotid intima-media thickness. R92Q and the E148Q *MEFV* variant have also been recently associated with increased susceptibility for reactive systemic AA amyloidosis in other chronic inflammatory disorders [70•].

Two studies have noted an increased incidence of Crohn's disease in patients or families with FMF [71,72]. Recently, another investigative group examined the frequency of *MEFV* mutations in a cohort of 209 Israeli patients with Crohn's disease [73•]. In this study, there was no increase in the frequency of specific *MEFV* mutations in cases relative to controls, although the E148Q variant was associated with perianal disease, with an odds ratio of 3.26 (95% confidence interval 1.2 – 8.8, $P = 0.02$).

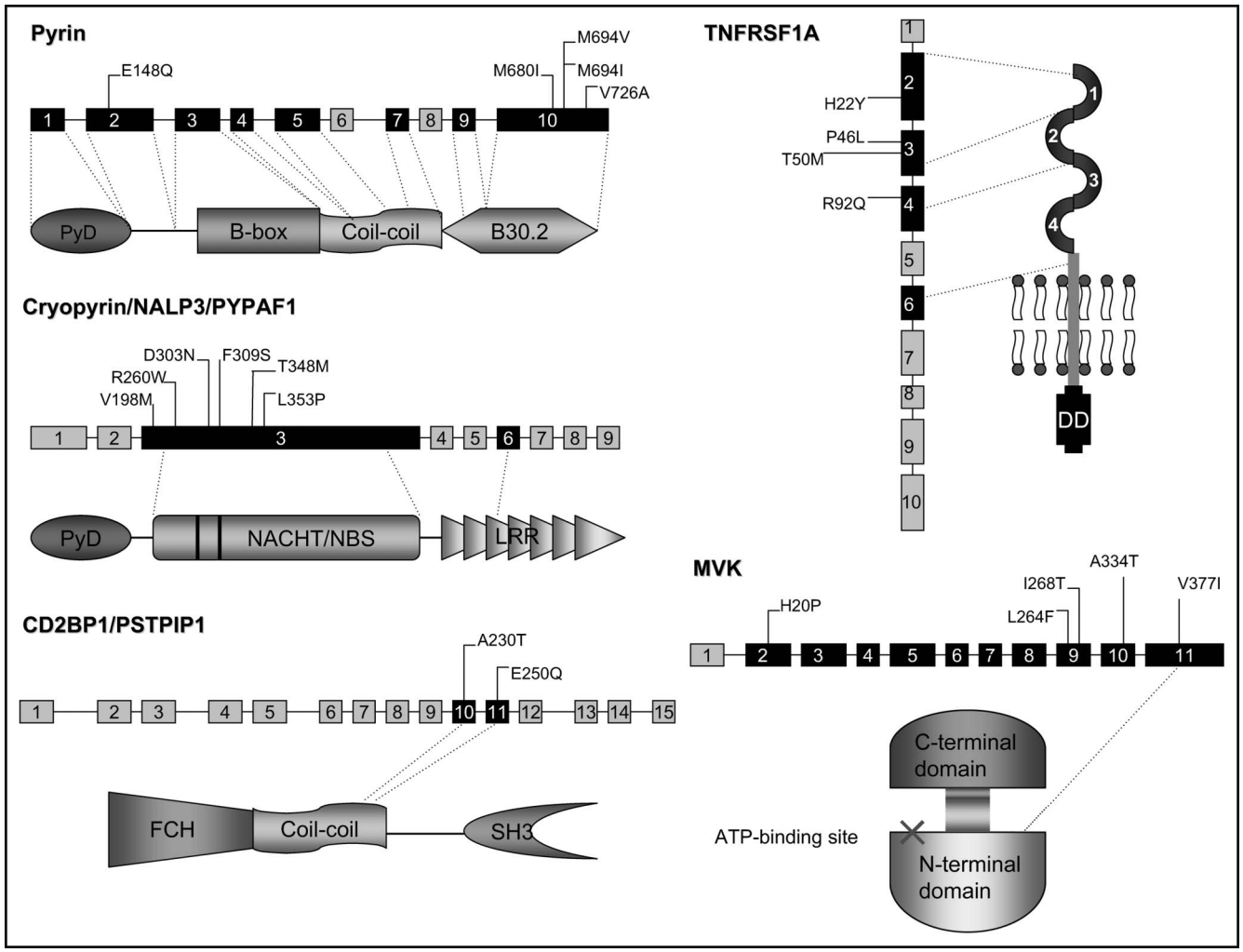
Finally, associations have been drawn between FMF and Behçet's disease. Increased frequencies of *MEFV* mutations have been reported in Behçet's patients [74], and, conversely, Behçet's disease has been reported at an increased frequency among Israeli patients with FMF [75]. A recent paper from Turkey found *MEFV* mutations in 15 of 42 Behçet's patients, but in only seven of 66 controls ($P = 0.0034$) [76•].

Although the HRF genes may, in some circumstances, conspire with other genetic and environmental factors to cause a broader spectrum of inflammatory diseases, certain disorders may actually be less common in the HRFs. Recently a group from Turkey drew attention to the complete absence of systemic lupus erythematosus among their cohort of more than 1000 FMF patients [77]. The authors speculated that high levels of C-reactive protein typically seen in FMF patients might increase clearance of apoptotic cells and autoantigens. Although this remains an intriguing hypothesis, it underscores the potentially complicated and even reciprocal interactions among autoinflammatory and autoimmune disorders, which represent respective aberrations of the innate and adaptive arms of the immune system. The suggestion of a possible positive correlation between systemic lupus erythematosus and TRAPS in the Japanese population [78] awaits confirmation.

Pathogenesis

The elucidation of the molecular basis of the HRFs has focused attention on a group of genes encoding proteins (Fig. 1) that regulate several critical inflammatory and apoptotic pathways. Much of the past 2 to 3 years' work has concentrated on further delineating these pathways and understanding how specific disease-associated genes cause autoinflammation.

Figure 1. Genes and their encoded proteins involved in autoinflammatory syndromes



The left panel shows PYRIN domain-containing proteins (pyrin, cryopyrin) or an interacting protein (CD2BP1/PSTPIP1). The right panel depicts TNFRSF1A, the C-terminal domain of which is another member of the death domain superfamily, and MVK, the enzyme involved in the mevalonate pathway. Numbered boxes represent exons, with the black marked exons representing those for which mutations have been described. The most commonly observed mutations are indicated. Below or to the right of the genes are the encoded proteins with their functional domains. The dotted lines between the genes and the proteins indicate the domain(s) of the proteins that are encoded by the respective exon(s). The domains of the proteins on the left are represented schematically, whereas the proteins at the right side of the figure, TNFRSF1A and MVK, are drawn according to the proposed tertiary protein structure. The four numbered semi-circles to the right of the *TNFRSF1A* gene represent the four extracellular cysteine-rich domains (CRD 1-4) of the TNF receptor, followed by the transmembrane region in grey and the intracellular death domain (DD) through which signaling events such as NF-κB activation or apoptosis are initiated. The molecular structure of mevalonate kinase is defined by two domains that form a dumbbell shape, with the enzymatically active ATP-binding site located in the N-terminal domain and marked as a red cross. The single dotted line indicates the approximate location of the V377I mutation within the N-terminal domain of MVK.

Pyrin and family

Signal transduction and protein oligomerization in inflammation and apoptosis are often mediated by a group of protein-protein interaction domains, the so-called death domain-fold superfamily [11]. This family currently comprises four members, the death domain, the death effector domain, the caspase-recruitment domain (CARD), and the PYRIN domain. Each motif has an antiparallel arrangement of six α-helices that allows binding of cognate domains (death domains with death domains, etc.) through electrostatic charge interactions [11,79–81].

The pyrin protein is the prototype for the death domain-fold motif that bears its name. The recognition of the PYRIN domain, an N-terminal 92-amino-acid motif, in pyrin set the crucial cornerstone for further insights into the underlying mechanisms of the HRFs. Of the approximately 20 PYRIN domain-containing human proteins currently known [82••], pyrin and cryopyrin have been shown to harbor HRF-associated mutations. A third member of this family, apoptosis-associated specklike protein with a CARD (ASC), is a bipartite adaptor protein consisting of an N-terminal PYRIN domain, through which it can interact with pyrin [79,83–85] or cryopyrin [84,86,87], and

a C-terminal CARD, through which it can interact with several downstream molecules. Although no disease-associated ASC mutations have been identified in HRF patients to date, it is a pivotal molecule in the pathogenesis of these diseases.

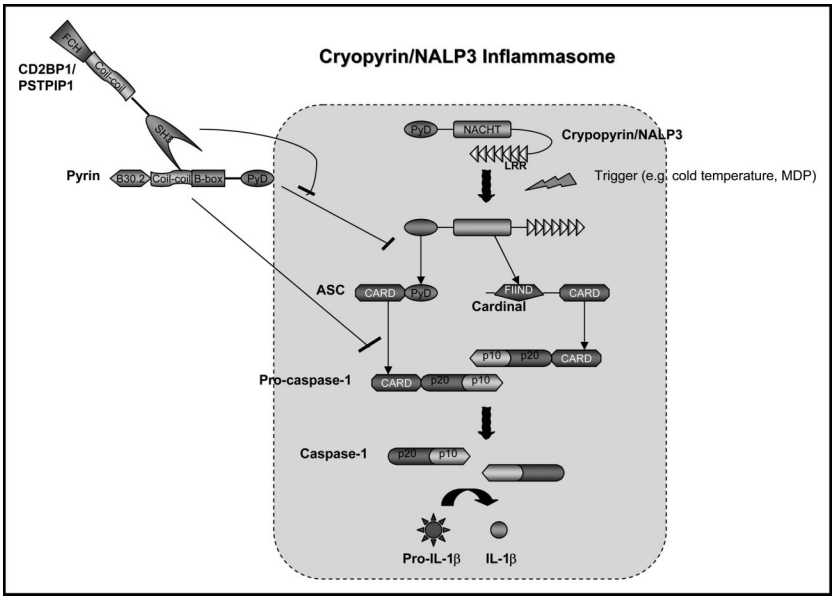
Recent biochemical evidence indicates that cryopyrin (NALP3) and ASC participate in a larger macromolecular complex termed the NALP3 inflammasome [88••,89••] that mediates the activation of interleukin-1β and interleukin-18. The NALP3 inflammasome activates interleukin-1β by bringing molecules of caspase-1 (interleukin-1β-converting enzyme) zymogen into proximity, thus allowing autocatalysis of its p20 and p10 subunits, which, when released, cleave prointerleukin-1β into its biologically active form. As depicted in Figure 2, interaction of the LRR domain of cryopyrin/NALP3 with the NACHT domain (so named because it was first observed in neuronal apoptosis inhibitor protein, CIITA, HET-E and TP1) ordinarily inhibits the interaction of cryopyrin/NALP3 with Cardinal, another protein in the complex. Stimuli that 'open' the cryopyrin/NALP3 structure permit this interaction, through which one molecule of caspase-1 is recruited to the complex. A second caspase-1 molecule is recruited through the interaction of the PYRIN domain of cryopyrin/NALP3 with ASC.

From the foregoing analysis, it would appear that the LRR – NACHT domain interaction in cryopyrin/NALP3 is a critical control point in the activation of the inflammasome. Just as extracellular LRRs of the Toll-like receptors can interact with various pathogen-associated molecular patterns, intracellular muramyl dipeptide, a common pathogen-associated molecular pattern, can activate the NALP3/cryopyrin inflammasome [89••], presumably by binding the LRR. CAPS-associated mutations are almost exclusively in the NACHT domain, and macrophages from a patient with MWS showed increased interleukin-1β secretion in the presence of muramyl dipeptide. In some cases, CAPS-associated cryopyrin/NALP3 mutations may even permit constitutive interleukin-1β maturation [88••,90••,91•] without the requirement for exogenous muramyl dipeptide. It is also possible, although not proven, that FCAS-associated cryopyrin/NALP3 mutations destabilize the NACHT-LRR interaction in the cold, thereby permitting interleukin-1β activation.

Pyrin itself also appears to play an important role in regulating interleukin-1β activation. In-vitro data suggest that pyrin competes with both cryopyrin and caspase-1 for binding to ASC [83,84]. Mice expressing a truncated, hypomorphic pyrin variant exhibit heightened sensitivity to endotoxin challenge, with increased activation of both caspase-1 and interleukin-1β. These data suggest that one function of wild-type pyrin is the suppression of inflammasome-mediated interleukin-1β production and that FMF-associated mutations may interfere with this process (Chae *et al.*, unpublished observations). Mutations in proline serine threonine phosphatase interacting protein 1 (PSTPIP1), a protein recently shown to bind pyrin, appear to exert a dominant negative effect on this pathway [92]. Two PSTPIP1 mutations (Fig. 1) have been associated

Figure 2. Schematic of the molecular mechanisms defining the cryopyrin (NALP3) inflammasome

The grey area shows the macromolecular complex that forms the cryopyrin (NALP3) inflammasome. The main function of this complex is the proximity-induced autocatalysis of pro-caspase-1 to active caspase-1, with subsequent IL-1β activation. Pyrin is thought to have an inhibitory effect on this process, while mutations in CD2BP1/PSTPIP1 may interfere with the normal action of pyrin. Details of the interactions are discussed in the text. Arrows indicate the induced interactions between functional protein domains. The inhibitory effects of CD2BP1/PSTPIP1 and pyrin, respectively, are marked as lines with a short 'blocking' line at the end.



with increased pyrin binding, excessive interleukin-1β production, and a severe autoinflammatory disorder, the PAPA syndrome.

Both cryopyrin and pyrin also appear to regulate another process important in inflammation: apoptosis. The aforementioned pyrin-deficient mice exhibit a defect in leukocyte apoptosis through an interleukin-1β-independent, caspase-8-dependent pathway [83], suggesting a pro-apoptotic role for the wild-type protein, although in certain transfection systems it exerts an antiapoptotic effect [79,84,85]. Enforced expression of cryopyrin in HEK293T cells also induces apoptosis [84].

Depending on the cellular context, both pyrin and cryopyrin can either activate or suppress nuclear factor-κB [84,86,87,93,94], a family of transcription factors involved in the initiation and resolution of inflammation. Although the precise mechanism is still under investigation, this appears to be ASC dependent and, under some conditions, involve the inhibitor of nuclear factor-κB kinase complex [93]. Because endogenous pyrin has recently been shown to localize in the nucleus in several cell types, including synovial fibroblasts, neutrophils, and dendritic cells (but not monocytes) [95••], it is also possible that pyrin may associate with one or more components of the nuclear factor-κB complex. Moreover, in the absence of ASC, a relatively rare isoform of pyrin with an inframe deletion of exon 2 also localizes in the nucleus, regardless of FMF-associated mutations [96•].

TRAPS: the plot thickens

Stimulation through the p55 TNF receptor can lead either to nuclear factor-κB activation or apoptosis, depending on the balance of several contextual factors. Upon receptor activation through TNF, metalloprotease-induced cleavage of the extracellular TNFRSF1A domain can limit continuous signaling at the cell surface while simultaneously creating a pool of potentially antagonistic soluble receptor (Fig. 3A). Initial studies of a family with the C52F mutation indicated impaired activation-induced receptor 'shedding' [1], thereby possibly explaining the inflammatory phenotype.

Subsequent studies indicate a more complex picture, with defects in TNF receptor cleavage varying with mutation [26,97] and cell type [98••]. Moreover, in transfection experiments, certain TNFRSF1A mutants exhibit impaired intracellular trafficking and TNF binding, although their ability to signal through the death domain is unimpaired [99••]. Conceivably, the conformational changes in the p55 receptor that lead to altered intracellular trafficking could also impair metalloprotease-induced cleavage of mutant receptors that do reach the surface. Studies of dermal fibroblasts and monocytes from a patient with the newly identified C43S mutation suggest yet another possible mechanism for TRAPS: a defect in TNF-induced apoptosis, leading to an inappropriately prolonged inflammatory response [100••].

TRAPS-associated p55 mutations might also cause constitutive activation, perhaps by permitting intermolecular disulfide homodimerization and ligand-independent activation. This possibility was considered for patients with the C52F mutation in the initial description of TRAPS but appeared not to be operative [1]. Moreover, such a mechanism would appear to be inconsistent with the therapeutic effects of TNF inhibitors (*vide infra*). It may be fruitful, however, to reexamine this issue for a broader sampling of patients, given the heterogeneity of cleavage defects for different mutations, the observation of biochemical inflammation in TRAPS patients even between attacks [16], and the discovery of ligand-independent noncovalent interactions mediated by the first cysteine-rich domain of the p55 receptor [101]. Yet another conceptually attractive possibility relates to the recent finding that the predominant form of TNFRSF1A in human plasma is full length, probably the result of exosome-linked release of receptor [102•]. In light of the aforementioned defects in receptor trafficking, it is intriguing to hypothesize that TRAPS mutations might impair such a process.

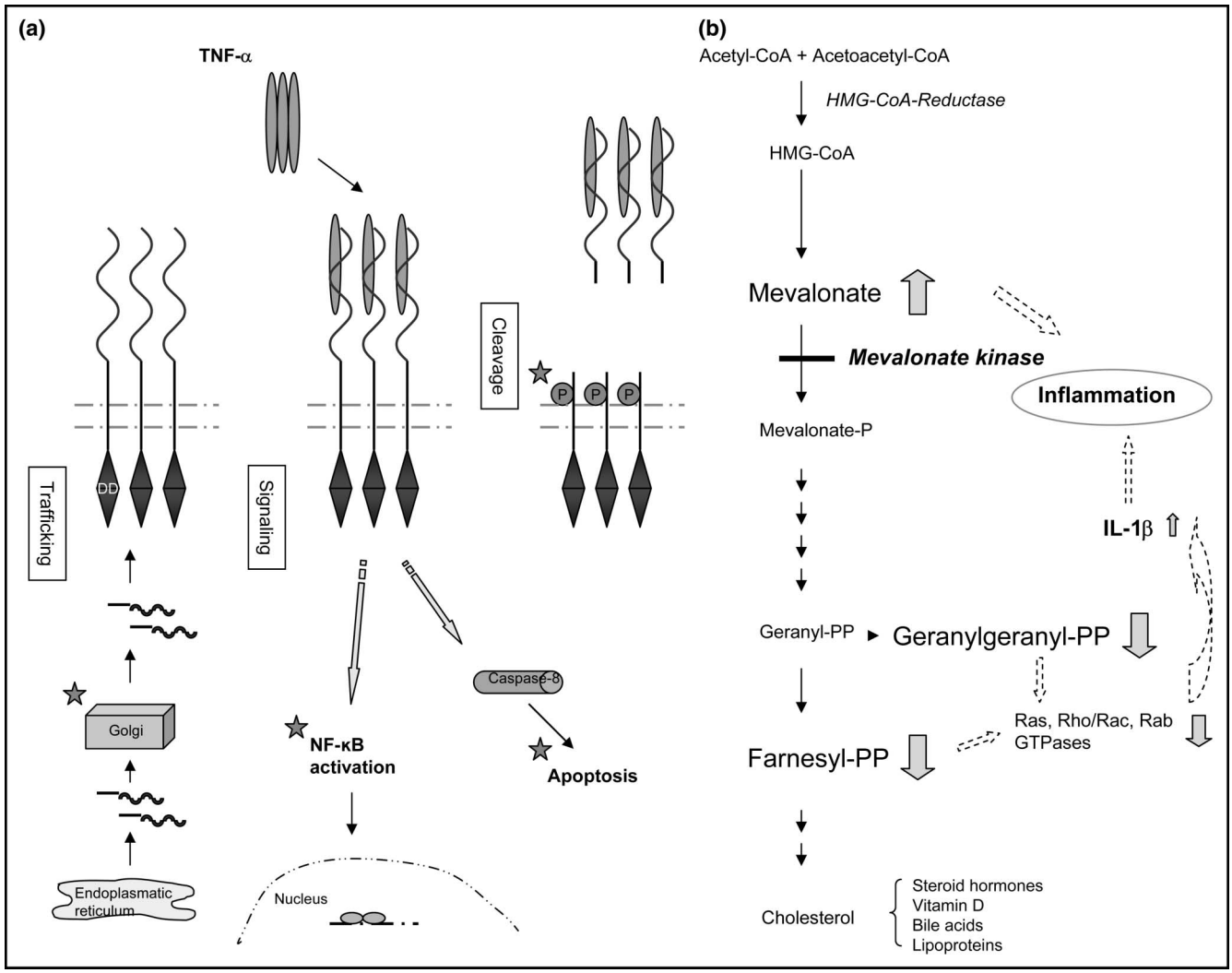
From the foregoing, it appears clear that there may be multiple mechanisms leading to the TRAPS phenotype and that the pathophysiology may be heterogeneous among patients. Clarification of these issues will undoubtedly require triangulation between studies of primary cells from patients, transfected cell lines, and knock-in animal models.

Hyperimmunoglubulinemia D with periodic fever syndrome: nature's elaborate deception?

Perhaps the most enigmatic of the HRFs is HIDS. The enzyme mutated in HIDS, called mevalonate kinase, is the only HRF protein that does not include a death domain-fold motif. Mevalonate kinase catalyzes the conversion of mevalonic acid to 5-phosphomevalonic acid in the synthesis of sterols, including cholesterol, vitamin D, bile acids, and steroid hormones (Fig. 3B). Evidence is strong that HIDS is not due to excessive IgD, because there are well-documented patients who have the HIDS phenotype and *MVK* mutations but persistently normal IgD levels [12,103–105], and, even among patients with increased serum IgD, the levels do not predictably fluctuate with attacks [106]. Moreover, the HIDS phenotype appears not to be due to a defect in cholesterol synthesis, because patients have cholesterol levels in the low-normal range, and more severe disorders of cholesterol biosynthesis do not have an autoinflammatory phenotype [107].

Currently there are two major hypotheses on the pathogenesis of HIDS: that the inflammatory attacks could result from the accumulation of mevalonic acid, the

Figure 3. Schematic of the proposed pathogenic mechanisms of TRAPS (a) and HIDS (b)



(a) The mechanisms suggested to be involved in the pathogenesis of TRAPS are shown from left to the right and include defects of TNFRSF1A intracellular trafficking with pathologic storage in the Golgi apparatus and subsequent reduced cell surface expression of TNFRSF1A, defects of the TNF-α induced signaling through TNFRSF1A with subsequent alterations of NF-κB activation and apoptosis, as well as a TNFRSF1A cleavage defect from the cell surface with subsequent reduced levels of soluble TNFRSF1A. The green circles represent the metalloproteinases that induce the receptor shedding at the cell surface. The blue curved lines represent the four extracellular domains of TNFRSF1A, followed by the transmembrane region marked as a black line and the intracellular death domain drawn as brown diamond. TNFRSF1A forms a homotrimer at the cell surface. The punctuated red lines represent the cell membrane with the area above representing the extracellular and the area below the intracellular space. The orange stars highlight the various sites for which defects in the TRAPS pathogenesis have been described so far. (b) The mevalonate pathway. Patients with HIDS show markedly reduced mevalonate kinase activity, which leads to an increase of mevalonic acid and decrease of isoprenoids. Both consequences may lead to IL-1β activation with subsequent inflammation in HIDS.

substrate for the mevalonate kinase enzyme [108•], or that the autoinflammation is caused by a shortage of isoprenoids, which are normally synthesized through the mevalonate pathway [109]. These latter compounds are involved in the post-translational prenylation (farnesylation or geranylation) of several important intracellular signaling molecules, including the Ras, Rho/Rac, and Rab families of small guanosine triphosphate-binding proteins. In an in-vitro system, accentuated interleukin-1β secretion by leukocytes from HIDS patients can be reversed by the addition of farnesol or geranyl-geraniol, lending support to the second hypothesis [109].

Both the isoprenoid deficiency and mevalonate accumulation hypotheses predict a worsening of symptoms with decreased mevalonate kinase enzymatic activity. In-vitro studies of cell lines harboring wild-type or HIDS-mutant *MVK* indicate that the mutant enzyme functions best at 30°C, with a diminution at 37°C and further decreases at 39°C [110]. This finding may account for the triggering

of HIDS attacks by immunizations and infections and may also account for the increased urinary mevalonate levels seen during HIDS attacks.

Treatment

Advances in our understanding of the biology of HRFs, coupled with the expanded armamentarium of new targeted therapies, have led to new approaches to the treatment of these disorders. Therapeutic goals include suppression of acute attacks, which are usually not life threatening but can be very disabling, and preventing long-term sequelae, such as amyloidosis and long-term neurologic/intellectual impairment in CAPS.

The most promising results of the past year involve the use of anakinra, a recombinant human interleukin-1β receptor antagonist, in patients with CAPS. FCAS patients who were pretreated with interleukin-1β receptor antagonist before cold challenge did not develop clinical symptoms or increase in acute-phase reactants [111••]. Serum levels of interleukin-1β and cytokine mRNA in peripheral blood mononuclear cells were normal but highly elevated in affected parts of the skin, implicating differences in the distribution of cells contributing to disease phenotype. A complete cessation of clinical symptoms and biochemical changes was also reported in MWS patients following administration of interleukin-1β receptor antagonist [112,113•]. Even children with the more severe phenotype of NOMID/CINCA responded to anakinra doses of 1–2 mg/kg per day with resolution of uveitis, rash, and fever and a significant decline in cerebrospinal fluid pressure [114•–117•]. The dramatic nature of the response of CAPS patients to interleukin-1 inhibition is, in a way, surprising, given the apparent role of cryopyrin in other inflammatory processes, such as nuclear factor-κB activation and apoptosis. Given the reduced life expectancy of NOMID/CINCA patients, who have a death rate of about 20% before the age of 20, it will be important to follow a larger series of these children on anakinra to monitor long-term outcome with regard to mental and physical development, as well as to determine whether early treatment can prevent joint deformities.

As noted in the previous section, interleukin-1β also appears to play a role in the pathogenesis of FMF, PAPA syndrome, and HIDS and may also be involved indirectly in the pathogenesis of TRAPS. Interleukin-1 inhibition could therefore represent a possible option as first-line or second-line treatment in these diseases. Anakinra has been reported effective in the treatment of one patient each with TRAPS and PAPA syndrome [118•,119•].

There is also a substantial experience with TNF inhibitors in the HRFs, most notably the use of etanercept, the p75 TNFR:Fc fusion protein, in TRAPS. The administration of 50–75 mg per week in adults, or 0.8–1.2 mg/kg/wk in children, is effective in reducing, although not usually eliminating, clinical and laboratory evidence of inflammation [4,16], thereby allowing a dose reduction in nonsteroidal anti-inflammatory drugs or glucocorticoids. In some patients, etanercept appears to prevent amyloid formation or even reduce proteinuria in patients with amyloid nephropathy [120,121•]. Unfortunately, development of amyloidosis can occur even when symptoms are controlled by etanercept [122], and it is likely that monitoring of SAA levels is necessary to titrate the optimal dosage [120,121•].

Although HIDS very rarely leads to systemic amyloidosis, and does not share the neurologic sequelae of CAPS, attacks are frequently severe enough to warrant treatment, particularly in childhood and adolescence. To date there is no accepted therapy for HIDS, other than antipyretics and palliative measures, but pilot studies have been conducted in two areas. First, a small trial has been conducted with simvastatin, an inhibitor of 3′-hydroxy-3′-methylglutaryl – coenzyme A reductase, the enzyme immediately preceding mevalonate kinase in the mevalonate pathway (Fig. 3B). It appears safe, and preliminary data suggest a possible benefit [108•]. A pilot study of etanercept showed substantial symptomatic improvement in two mutation-positive children with HIDS [105], although a third HIDS patient who did not respond to etanercept was recently reported by another group [123]. Interleukin-1 inhibition may represent yet another possible therapeutic strategy.

Daily oral colchicine therapy has been established as effective in preventing both the acute attacks of FMF and the development of amyloidosis. In the subset of patients who are poorly responsive to colchicine, lower colchicine concentrations were found in mononuclear cells [124•], suggesting that differences in responsiveness may be due to polymorphisms in transporters that control intracellular drug concentrations, such as the *MDR-1*-encoded P-glycoprotein pump. In such patients, several adjunctive approaches are under investigation, including subcutaneous interferon-α [125,126•,127•] and biologic therapies aimed at TNF [128•] or interleukin-1β. Allogeneic bone marrow transplantation has recently been proposed as a treatment for refractory FMF [129], based on the predominant expression of *MEFV* in leukocytes [5]. Although it is possible that this approach could be effective, in nearly all cases other options exist, and the risks outweigh the potential benefits [130].

Conclusion

Identification of the genes mutated in the HRFs has led to great strides in our approach to patients with these disorders. Although substantial numbers of patients with clinical recurrent fever syndromes do not have mutations in the respective genes, the availability of genetic testing as an adjunct has led to more widespread and earlier

recognition of these conditions, and recognition of important pathogenetic and therapeutic differences among patients who, 10 years ago, were largely lumped together as FMF variants. Exciting advances in molecular biology have defined new families of motifs and proteins relevant to inflammation and apoptosis, but important questions remain regarding the role of the products of the mevalonate pathway. Perhaps most notable are the great strides in therapy brought about by the happy confluence of breakthroughs in molecular pathogenesis and the new availability of targeted biologic agents. Fascinating areas for further investigation include the possible identification of additional genes that might account for patients who are currently mutation negative, the elucidation of modifier genes, the more thorough understanding of molecular pathogenesis and mechanisms of specific mutations, and a careful comparative analysis of various available treatments in multicenter trials.

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