Fevers, Genes, and Innate Immunity

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Abstract The characterization of patients with recurrent inflammatory syndromes into distinct clinical phenotypes provided early clues to the mode of inheritance of these conditions and facilitated the subsequent identification of causative gene mutations. The prototype autoinflammatory syndrome, familial Mediterranean fever, is characterized by self-limiting episodes of localized inflammation. Hallmarks of the classical autoimmune response are largely absent. The use of positional cloning techniques led to the identification of the causative gene, *MEFV*, and its product pyrin. This previously unrecognized protein plays an important role in modulating the innate immune response. Cryopyrin, the protein encoded by *CIAS1*, is mutated in a spectrum of autoinflammatory conditions, the cryopyrinopathies. In response to a wide range of potential pathogens, it forms a macromolecular complex termed the "inflammasome," resulting in caspase-1 activation and subsequent release of the active proinflammatory cytokine interleukin-1β (IL-1β). The role of an established biochemical pathway in regulating inflammation was uncovered by the discovery that the hyperimmunoglobulin D with periodic fever syndrome (HIDS) results from mutations in *MVK*, which encodes an enzyme in the isoprenoid pathway. The discovery that mutations in the gene encoding tumor necrosis factor (TNF) receptor 1

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(TNFR1) cause a proinflammatory phenotype was unanticipated, as it seemed more likely that such mutations would instead have resulted in an immunodeficiency pattern. This review describes the clinical phenotypes of autoinflammatory syndromes, the underlying gene mutations, and current concepts regarding their pathophysiology.

Introduction

The study of Mendelian recurrent inflammatory syndromes, through the identification of new proteins and the recognition of novel roles for established biochemical pathways, has led to a deeper understanding of the innate immune response. Each of these syndromes is characterized by episodic inflammation without a clear antigenic stimulus. In addition, features typical of the autoimmune diseases are notable by their absence, namely autoreactive antibodies and T cells. The term "autoinflammatory diseases" was proposed to encompass this new group of disorders (McDermott et al. 1999). These conditions result from the aberrant activation of the innate, rather than the adaptive, immune system. In the case of familial Mediterranean fever, the discovery of the causative gene resulted in the identification of a novel protein called pyrin. The discovery that hyperimmunoglobulin D with periodic syndrome resulted from a mutation in an enzyme in the isoprenoid biosynthesis pathway has suggested a novel role for this established biochemical pathway. In this chapter we will discuss the Mendelian autoinflammatory diseases, the discovery of causative genes, and current concepts regarding their pathophysiology. In addition, we will describe how knowledge of the basic science underlying these disorders has led to targeted therapies that have proven life altering for many patients with these diseases.

Familial Mediterranean Fever

Familial Mediterranean fever (FMF) [OMIM 249100 (Online Mendelian Inheritance in Man 2008)] is the prototype autoinflammatory disease. Early reports highlighted a preponderance of individuals of Mediterranean ancestry with this condition, leading to the adoption of the term FMF. It is the most common of the autoinflammatory diseases, with a modest male preponderance, and is most frequently observed in Jewish, Armenian, Arab, Turkish, and southern Italian populations (Aksentijevich et al. 1999). Carrier rates in certain high-risk populations can reach 1 in 3.

FMF is characterized by acute attacks of fever, and localized inflammation of the peritoneum, pleura, joints, or skin, sometimes in combination. Typically, episodes last 12–72 hours. Episodes may vary in nature; childhood episodes may be manifested by fever alone, while other features may develop progressively with time. Abdominal symptoms range from mild discomfort to severe pain and abdominal rigidity. The most serious complication of FMF is the development of AA amyloidosis. Prior to the advent of effective therapy for FMF, in many patients the development of amyloidosis led to chronic renal failure by age 40 (Samuels et al. 1998).

In the 1960s, segregation analysis in Israeli families manifesting typical FMF symptoms established FMF as a single-gene recessive disorder with incomplete penetrance. Attempts to identify the FMF gene by functional hypothesis-driven approaches were not productive and positional cloning was ultimately employed. Linkage studies in 1992 placed the FMF susceptibility locus on the short arm of chromosome 16, and this area of interest was narrowed by analyses of genetic recombinations in families and conserved haplotypes in populations. All genes within a refined 200-kb interval were screened for disease-associated mutations; and two independent consortia identified *MEFV* (The International FMF Consortium 1997; The French FMF Consortium 1997). An online database (Infevers 2008) has been established and provides an updated list of mutations and polymorphisms in *MEFV* and other autoinflammatory diseases. Over 50 disease-associated *MEFV* mutations have been described, with many clustered on exon 10 (Infevers 2008).

MEFV (*ME*diterranean *FE*ver) consists of 10 exons, and covers approximately 15 kb of DNA. It encodes a 781-amino acid protein named pyrin (to denote fever) or marenostrin (from the Latin for the Mediterranean sea). Pyrin is expressed in skin, peritoneal fibroblasts (Matzner et al. 2000), synovial fibroblasts, granulocytes, dendritic cells, and monocytes (Diaz et al. 2004). Pyrin is a member of the tripartite motif (TRIM) family of proteins, and is composed of four domains. At the N-terminal end of pyrin is the pyrin domain (PYD), a 92-amino acid motif, encoded by exon 1 of *MEFV*. This domain bears structural homologies to caspase-recruitment (CARD) domains, death domains, and death effector domains, and together these four motifs constitute the death fold family (Fairbrother et al. 2001). Variants of the pyrin domain are present in approximately 20 proteins, each of which plays a role in modulating the innate immune response. The PYD of pyrin engages in homotypic interactions with an adaptor protein called ASC (apoptosis-associated speck-like protein with a CARD) influencing the activation of interleukin (IL)-1β. Deletion of the PYD of pyrin abolishes its interaction with ASC (Richards et al. 2001; Yu et al. 2006).

The C-terminal end of pyrin contains a B-box zinc-finger domain (B-box), an α-helical coiled-coil domain (CC), and a B30.2 (PRYSRPY) domain. The B-box domain is both necessary and sufficient for pyrin's interactions with proline serine threonine phosphatase interacting protein (PSTPIP1) (Shoham et al. 2003). The B-box has recently been shown to interact with the PYD and thereby to block its interaction with ASC, thus serving as an intramolecular inhibitor (Yu et al. 2007).

The CC domain of pyrin mediates the formation of a homotrimer, a process required for pyrin's recently demonstrated induction of ASC oligomerization and subsequent caspase-1 activation (Yu et al. 2007) . The CC domain is also necessary, but not by itself sufficient, for pyrin's interaction with PSTPIP1 (Shoham et al. 2003).

The B30.2 domain of pyrin is responsible for interactions with the NACHT (Koonin and Aravind 2000) domain of NALP3, a component of the inflammasome (Papin et al. 2007). The B30.2 domain interacts, albeit weakly, with pro-caspase-1, and more avidly with active cleaved caspase-1 (Chae et al. 2006; Papin et al. 2007). There is also speculation that the B30.2 domain of pyrin acts as an intracellular

pathogen-associated molecular pattern (PAMP) sensor, and that mutations in pyrin may bind PAMPs more avidly and thereby confer a heightened immune response to potential pathogens with possible survival benefit (Yepiskoposyan and Harutyunyan 2007). In support of this theory is the recognition of the role for members of the TRIM family proteins in control of retroviral infections (Yap et al. 2004). Interestingly, the amino acid changes that cause FMF are often present as wildtype in other species. For several human mutations, the mutant represents the reappearance of an ancestral amino acid state. Studies in primates suggest that these mutations are indeed counter-evolutionary changes selected to cope with a sporadically encountered pathogen (Schaner et al. 2001).

There is a general consensus that pyrin plays a role in modulating caspase-1 activity and subsequent IL-1β release; there is disagreement, however, as to its net effect on levels of IL-1β. Findings in keeping with a net negative effect include the demonstration that pyrin competitively binds with ASC, via PYD, preventing ASC binding to caspase-1 (Chae et al. 2003). Pyrin also binds caspase-1, via its B30.2 domain, thus reducing caspase-1 activation (Chae et al. 2006; Papin et al. 2007). In addition, pyrin's competitive interaction with ASC may prevent the formation of the NALP3 inflammasome. The "sequestration hypothesis" has been proposed to encompass pyrin's net negative effect on IL-1β release. Further support for an inhibitory role for wildtype pyrin comes from mouse constructs. Mice expressing truncated pyrin produce increased amounts of activated caspase-1 and IL-1β in response to stimuli (Chae et al. 2003). Most mutations in patients with FMF affect the B30.2 domain, which is responsible for protein–protein interactions. Recent data that common mutations in pyrin result in impaired binding of pyrin to caspase-1 imply that these mutations may lead to clinical disease by impairing pyrin's antiinflammatory interactions with caspase-1 (Chae et al. 2006). However, the impact of mutations in the B30.2 domain has been variable (Papin et al. 2007).

A net positive effect of pyrin on IL-1β levels is suggested by data that fresh human monocytes have elevated pyrin protein and mRNA compared to monocyte-derived macrophages, a finding that parallels their ability to release active IL-1β in response to lipopolysaccharide (LPS) stimulation (Seshadri et al. 2007). In contrast to the competitive binding described previously, it has been suggested that pyrin's interaction with ASC modulates the formation of the "pyroptosome," a protein complex involved in "pyroptosis," a recently described caspase-1-dependent form of inflammatory cell death. The adaptor protein ASC contains an N-terminal PYD and C-terminal CARD. In response to various stimuli, including LPS and potassium flux, ASC self associates via its PYD domain, and forms a supramolecular assembly, termed the pyroptosome (Fernandes-Alnemri et al. 2007). This ASC supramolecular assembly activates caspase-1, thus leading to elevated IL-1β. This process is independent of the recently described inflammasomes formed by members of the NALP family. Moreover, data using THP-1 human monocytic cell lines suggest that PSTPIP1 binding to pyrin may lead to PYD interaction with ASC, pyroptosome assembly, and procaspase-1 activation (Yu et al. 2006, 2007).

Colchicine has been the mainstay in the therapy of FMF since the 1970s (Goldfinger 1972). Clinical trials support the role of colchicine in the treatment of

acute episodes, in the prevention of FMF attacks (Zemer et al. 1974), and in reducing the risk of AA amyloidosis. The induction of *MEFV* mRNA by the addition of a combination of colchicine and interferon (IFN)-α suggests a role for *MEFV* in the antiinflammatory actions of these agents (Centola et al. 2000). Pyrin's close association with actin filaments and microtubules suggests a role for pyrin in directed migration that can be modulated by colchicine (Mansfield et al. 2001). Colchicine displays a dose responsive effect on microtubule function and structure. At high concentrations colchicine disrupts microtubules by inhibiting polymerization at the "plus" or growing terminus. Low concentrations inhibit tubulin exchange at microtubule ends without affecting polymerization. High doses of colchicine inhibit the processing of caspase-1, a finding replicated with nocodazole, a compound with microtubule-inhibiting properties (Yu et al. 2007). The low concentrations resulting from the usual doses given to patients with FMF, however, are insufficient to disrupt microtubule arrangement patterns, but may instead affect microtubule dynamics, resulting in defective trafficking of cell adhesion molecules. As not all patients benefit from colchicine, in some, adjunctive therapy with anakinra, an IL-1 receptor antagonist, has proved beneficial, supporting the role of IL-1β in the pathogenesis of FMF (Calligaris et al. 2007; Chae et al. 2006).

Cryopyrin-Associated Periodic Syndromes

The cryopyrinopathies or cryopyrin-associated periodic syndromes (CAPS) correspond to a spectrum of dominantly inherited disorders. They include familial cold autoinflammatory syndrome (FCAS)/familial cold urticaria, Muckle–Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular syndrome (CINCA). All three may present with fever and urticaria-like skin rash and varying degrees of joint and neurologic involvement. FCAS (OMIM 120100) is generally considered the mildest, with distinct cold-induced episodic attributes. NOMID (OMIM 607115) is typically the most severe, with nearly continuous symptoms that may fluctuate in severity. Persistent central nervous system inflammation may result in intellectual impairment and loss of vision. NOMID is associated with a deforming arthropathy (Prieur 2001). MWS (OMIM 191900) is intermediate, with urticarial rash that is not cold-induced, and some patients develop sensorineural hearing loss. The clinical boundaries of these conditions have become blurred and a greater degree of overlap is now recognized. Patients with CAPS may develop AA amyloidosis and subsequent renal failure.

Independent linkage studies placed the susceptibility locus for both MWS and FCAS on chromosome 1q (Cuisset et al. 1999; Hoffman et al. 2000). In 2001, mutations in a 9-exon gene were identified in both FCAS and MWS families (Hoffman et al. 2001); the next year mutations in the same gene were identified in patients with NOMID (Aksentijevich et al. 2002; Feldmann et al. 2002). The gene named *CIAS1* (for cold-induced autoinflammatory syndrome-1) (NALP3/PYPAF1/NLRP3, OMIM

606416) encodes the protein cryopyrin. Cryopyrin is composed of an N-terminal pyrin (PYD) domain, a NACHT/nucleotide-binding oligomerization domain (NOD) and a leucine-rich repeat (LRR) domain. Cryopyrin is expressed in the cytoplasm of non-keratinized epithelial cells, uroepithelial cells, granulocytes, dendritic cells, and both T and B cells. It is also weakly expressed in monocytes (Kummer et al. 2007). Cryopyrin is a member of the CATERPILLER family (Ting et al. 2006) and is also called NALP3 (for NACHT domain-, Leucine-rich-repeat-, and Pyrin domain-containing protein 3) (Tschopp et al. 2003). Cryopyrin bears homologies with the extended NALP family of proteins, the plant cytosolic resistance (R) proteins, which mediate resistance to a variety of fungi, viruses, and bacteria, and the NOD family, a member of which, NOD2/CARD15, is mutated in patients with Crohn's disease and Blau syndrome (Miceli-Richard et al. 2001; Rosé et al. 2006).

The PYD of cryopyrin is involved in cognate interactions with other proteins containing a PYD. The NACHT domain is thought to regulate oligomerization. The LRR domain, which is found in a number of proteins including the Toll-like receptors (TLRs), may mediate interactions with numerous intracellular and extracellular potential pathogens.

Stimulation of cryopyrin leads to the formation of a macromolecular complex called the "NALP3 inflammasome." This inflammasome is formed by homotypic interactions between the PYD domain of cryopyrin and ASC, which in turn interacts via its CARD domain with caspase-1. Cryopyrin also interacts with another adaptor protein CARDINAL, which recruits additional caspase-1. The resultant homo-oligomerization of procaspase-1 is thought to facilitate autocatalytic activation to caspase-1. Active caspase-1 cleaves pro-IL-1β into mature proinflammatory IL-1β (Tschopp et al. 2003).

The demonstration that the NALP3 inflammasome activates IL-1β release in response to gram-negative bacteria in the absence of cell surface TLR4 (Kanneganti et al. 2007) strongly suggests a role for cryopyrin in the intracellular control of infectious agents. Cryopyrin's role as an intracellular sensor of so-called PAMPs has expanded greatly recently. Other activators of the inflammasome include bacterial RNA, imidazoquinoline compounds and the gram-positive bacterial toxins nigericin and maitotoxin (Kanneganti et al. 2006; Mariathasan et al. 2006). Knockout models suggest that cryopyrin plays a central role in the robust inflammatory response to both uric acid and calcium pyrophosphate (CPPD) crystals (Martinon et al. 2006). These findings suggest that both gout (uric acid) and pseudogout (CPPD) are, at least in part, autoinflammatory diseases. The means by which cryopyrin senses PAMPs remains unclear; homologies to the LRR domain present in both TLRs and NOD2/CARD15, however, may suggest a role for this domain in pathogen sensing.

The inflammasome complex alone does not appear to be sufficient for the IL-1β-mediated inflammatory response since knockout experiments implicate SGT1 and HSP90 as being essential for inflammasome activity (Mayor et al. 2007). The precise role of these proteins in modulating the inflammatory response remains uncertain. Cryopyrin may also induce cell death upon stimulation with bacteria or other pathogens independent of ASC and IL-1β (Willingham et al. 2007).

Mutations in cryopyrin lead to constitutive activation, although the molecular mechanism is not clear. Modeling of the cryopyrin structure suggests that the LRR domain self-associates with the NACHT domain, thus preventing activation and interaction with the adaptor protein CARDINAL. Mutations in either the NACHT or LRR domains may prevent self-association, resulting in direct assembly of the inflammasome complex. Most of the described mutations are found in exon 3 of *CIAS1*, which encodes the NACHT domain. Current models of cryopyrin mutants inadequately explain the spectrum of disease seen in CAPS (Aksentijevich et al. 2007; Hentgen et al. 2005), reflecting the limitations of in silico techniques.

Early insights into the role of the inflammasome, supported by the findings that monocytes from patients with CAPS showed increased caspase-1 activation and increased IL-1β release, prompted clinical trials of IL-1 inhibition in patients with CAPS. The use of anakinra, an IL-1 receptor inhibitor, in the treatment of all three syndromes has been met with considerable success, consistent with the key role of IL-1β in CAPS (Hawkins et al. 2003). The use of anakinra in patients with NOMID, the most severe of these conditions, resulted in complete remission in both peripheral and central nervous system (CNS) inflammation in a majority of subjects. Discontinuation of therapy led to a rapid relapse in symptoms, supporting the need for continuous IL-1 blockade in this condition (Goldbach-Mansky et al. 2006). The use of IL-1 blockade represents a significant advance in the treatment of CAPS.

Syndrome of Pyogenic Arthritis, Pyoderma Gangrenosum and Acne

The syndrome of pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) was first described in a large family who attended the Mayo Clinic (Lindor et al. 1997); another family in Texas was later noted to have similar clinical features (Wise et al. 2000). From childhood, patients have episodic destructive arthritis that is sometimes triggered by minor trauma. Arthritis may lead to periosteal proliferation and ankylosis. Skin manifestations usually occur after puberty and range from severe cystic acne on the face, chest, or back to pyoderma gangrenosum, an ulcerating skin lesion that may be triggered by minor trauma.

Studies of both of the originally described families established linkage to chromosome 15q (Wise et al. 2000). Two different missense mutations were identified in the gene encoding PSTPIP1. This protein interacts with pyrin, the protein mutated in FMF, and is largely restricted to the hematopoietic tissues, being prominent in spleen and peripheral blood leukocytes (Li et al. 1998; Shoham et al. 2003).

PSTPIP1 protein contains an N-terminal CIP4 domain, a coiled-coil (CC) domain, and an SH3 domain. The coiled-coil and SH3 domains are important for protein interactions and both are necessary for PSTPIP1's interaction with pyrin's B-box domain (Shoham et al. 2003). PSTPIP1 also interacts via its CC domain with the C-terminal proline-rich homology domain of PTP-PEST (protein tyrosine phosphatase with a proline, glutamate, serine, threonine domain). The mutations

identified in PAPA patients affect the coiled-coil domain of PSTPIP1 and lead to decreased binding of PSTPIP1 to PTP-PEST, which in turn leads to hyperphosphorylation of PSTPIP1. The hyperphosphorylation of PSTPIP1 increases its avidity for pyrin (Shoham et al. 2003; Yu et al. 2007). Cell lines co-transfected with PAPA-associated PSTPIP1 mutants and with pyrin demonstrate elevated production of interleukin-1β (Shoham et al. 2003). While it is agreed that mutant PSTPIP1 binds pyrin with greater avidity, the precise mechanism by which increased IL-1β production results is unclear. It has been proposed that when mutant PSTPIP1 binds more avidly to pyrin, it results in the sequestration of an antiinflammatory pyrin resulting in a net increase in IL-1β production (Shoham et al. 2003). Alternatively, when mutant PSTPIP1 avidly binds pyrin it may permit the unfolding of pyrin to its proinflammatory state, permitting the interaction of PYD with ASC and subsequent pyroptosome-mediated caspase-1 activation (Yu et al. 2007).

As denoted by its alternative name CD2-binding protein 1 (CD2BP1), PSTPIP1 interacts not only with CD2 but also Wiskott–Aldrich syndrome protein (WASp). WASp co-localizes with actin to form the immunologic synapse in natural killer (NK) cells (Orange et al. 2002). Thus, PSTPIP1 may play a role in the adaptive immune system through both CD2 binding and WASp-induced polymerization with actin, with potential effects on the formation of immunologic synapses in antigen recognition (Badour et al. 2003).

Therapeutic strategies have been informed by evidence that LPS-induced IL-1β secretion is markedly increased in cells from PAPA patients compared to controls (Shoham et al. 2003). In contrast, cytokines such as IL-2, IL-5, and IFN-γ were undetectable. Anecdotal reports suggest that anakinra, an IL-1 receptor antagonist, is beneficial (Dierselhuis et al. 2005); however, both the variable natural history and rarity of this condition suggest that definitive clinical trials of targeted therapies will prove difficult.

TNF Receptor-Associated Periodic Syndrome

Clinical descriptions of families of individuals with prolonged fever and localized inflammation were the first hints of an autosomal-dominant recurrent fever syndrome. Early clinical reports highlighted the Celtic ethnicity of affected individuals, resulting in the term “familial Hibernian fever” (McDermott et al. 1997), while smaller family series described a broader North European ancestry and used the term “autosomal-dominant recurrent fever syndrome.” Now known as tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), patients typically have episodes lasting at least 1 week and sometimes as long as 6–8 weeks. Characteristic manifestations include migratory erythema which may occur on the torso or limbs and spreads distally, with myalgia in the underlying muscle group. Ocular involvement with conjunctivitis or periorbital edema is common. TRAPS is associated with an increased risk of AA amyloidosis in up to 15% of affected individuals.

In 1998, linkage studies placed the susceptibility locus of a subset of these individuals to a region of chromosome 12p13 (McDermott et al. 1998; Mulley et al. 1998). Within a year *TNFRSF1A* (OMIM entry 191190) was identified as the causative gene (McDermott et al. 1999). Dominantly inherited mutations were identified in families of diverse ancestry, and the term TRAPS (OMIM entry 142680) is used to describe all patients with mutations in *TNFRSF1A* irrespective of ancestry.

TNFRSF1A encodes a 55-kDa receptor (TNFR1/p55) for the cytokine TNF. This receptor has four extracellular cysteine-rich domains, a transmembrane domain, and an intracellular death domain. TNFR1 is expressed on a wide range of cell types and can mediate apoptosis and function as a regulator of inflammation. Of the initial six mutations that were described, five were single-nucleotide substitutions resulting in amino acid substitutions in highly conserved extracellular cysteine domains (McDermott et al. 1999). These cysteine residues are required to maintain the stability of the extracellular domain by forming disulfide bonds. A further mutation disrupted a highly conserved intrachain hydrogen bond in the extracellular domain. Mutations in the intracellular or transmembrane domains have not been identified.

Initial studies of affected families suggested that disease-associated mutations are highly penetrant. Not all mutations, however, are associated with such high penetrance or typical disease. Two substitutions occur in over 1% of the Caucasian (R92Q) and African-American (P46L) populations, and one substitution occurs in up to 9% of selected African (P46L) populations. While these substitutions may lead to a proinflammatory phenotype, patients typically do not appear to have typical TRAPS (Tchernitchko et al. 2005).

The pathophysiology of TRAPS remains unclear. In healthy subjects, TNF stimulates TNFR1, which recruits several proteins to form a complex resulting in the activation of nuclear factor-κB (NF-κB), while an alternate pathway leads to apoptosis (Chen and Goeddel 2002). TNFR1 stimulation results in cleavage of the extracellular domains of the receptor following activation. Cleaved soluble TNFR1 (sTNFR1) acts as a decoy receptor for TNF. In patients with TRAPS, low levels of cleaved soluble TNFR1 led to the hypothesis that mutations lead to impaired cleavage of the extracellular domain of TNFR1 by matrix metalloproteinases following stimulation. Thus, the usual regulatory processes in terminating TNF signaling were impaired, with insufficient sTNFR1 to act as a TNF blocker in serum and excess activated TNFR1 remaining on the cell surface. This was supported by early laboratory studies (McDermott et al. 1999); subsequent reports, however, demonstrated variable rates of cleavage across disease-associated mutations, and thus did not fully explain the pathophysiology of this disease. Defective intracellular processing of mutant TNFR1 has also been identified. Following synthesis, mutant TNFR1 is unable to traffic appropriately from the endoplasmic reticulum to the cell surface (Lobito et al. 2006; Todd et al. 2007). It has been postulated that mutant TNFR1 is retained in the endoplasmic reticulum resulting in the proinflammatory unfolded protein response. Thus, inflammation may occur without direct ligand interactions with TNFR1. Alternatively, mutant receptors may be retained within the cell, autoaggregate, and inappropriately activate proinflammatory cascades

(Rebelo et al. 2006). Collectively this is termed the "ligand-independent" hypothesis. Mutant TNFR1 may also result in prolonged survival of inflammatory cells, since neutrophils from patients with TRAPS demonstrate impaired TNF-mediated apoptosis (D'Osualdo et al. 2006).

The initial "defective shedding" hypothesis, whereby the decoy receptor for TNF, cleaved soluble TNFR1, is decreased in patients with TRAPS, led to efforts to restore the balance in favor of inhibition of TNF using etanercept. Etanercept is a p75 TNF receptor fusion protein that binds serum TNF and prevents its engagement with cell surface TNFR1. Use of this agent has been beneficial in terms of clinical and laboratory parameters (Hull et al. 2002). In keeping with the alternative "ligand-independent" hypothesis, in which inflammation results from non-TNF-mediated pathways, the use of anakinra, an IL-1 receptor antagonist, has also been reported to be of benefit (Simon et al. 2004).

Hyperimmunoglobulinemia D with Periodic Fever Syndrome

In 1984 a Dutch group described six patients with periodic fever and elevations in immunoglobulin D (van der Meer et al. 1984). In 1999 two independent Dutch groups identified the gene responsible for Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), an autosomal-recessive condition. Traditional linkage analysis enabled one group to localize the causative gene (Drenth et al. 1999), while the other group identified elevated mevalonate in the urine of patients with HIDS and decreased enzyme activity in skin fibroblasts (Houten et al. 1999). The causative gene, *MVK*, encodes an enzyme involved in the isoprenoid biosynthesis pathway, and this unanticipated finding suggested a new role for this pathway in regulating inflammatory responses. The isoprenoid metabolism pathway generates a wide variety of important compounds for cell function. Branches of the pathway synthesize over 20,000 compounds including sterols, which includes cholesterol, and the nonsterol isoprene compounds. Two isoprenoid moieties, farnesyl or geranylgeranyl, are added to proteins during posttranslational modification, thus promoting membrane association.

HIDS episodes usually start in infancy, and may be triggered by immunizations. Episodes may occur once or twice per month and typically last 3–7 days. Typical episodes are characterized by initial chills and headache with subsequent fevers and diffuse tender lymphadenopathy. Diarrhea frequently occurs and a number of cutaneous manifestations have been described including painful erythematous macules. Joint symptoms include arthralgia and polyarticular large joint arthritis. Episodes typically occur less frequently in adulthood and are usually less severe (Drenth et al. 1994).

Mutations in *MVK* that result in complete loss of mevalonate kinase (MK) enzymatic activity cause the related condition mevalonic aciduria, a rare metabolic disease with mental retardation, failure to thrive, and early death, in addition to the features seen in HIDS. In contrast, HIDS-associated *MVK* mutations result in

residual MK enzymatic activity, in the range of 1%–8% of normal (Mandey et al. 2006a). Interestingly, in vitro experiments demonstrate that MK enzymatic activity is temperature-sensitive, with decreased activity at higher temperatures (Houten et al. 2002).

Mutations in *MVK* are found throughout the gene, and most HIDS patients are compound heterozygotes for missense mutations. A number of mutations are more strongly associated with either HIDS or MA. Mutations resulting in a base pair change at position 377 (V377I) are most commonly associated with HIDS, and result in modest decreases in enzymatic activity, in contrast to predictions that this mutation would not affect enzymatic activity based on modeling studies (Mandey et al. 2006b). This mutation exhibits a founder effect in the Dutch population, and likely explains the higher prevalence of HIDS in this population. Population-based studies indicate that 0.6% of Dutch people carry the V377I mutation. Given the marked underrepresentation of homozygote V377I patients in HIDS cohorts, it has been suggested that the homozygous state results in either a milder phenotype or none at all (Houten et al. 2003).

The activity of the isoprenoid pathway is tightly controlled. An early rate-limiting step, undertaken by HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase, has been extensively studied. The identification of this enzyme, and use of the "statin" group of HMG-CoA reductase inhibitors, has been a major advance in the treatment of hypercholesterolemia. The next step in isoprenoid synthesis is MK, resulting in the phosphorylation of mevalonate to 5-phosphomevalonate. MK deficiency results in an increase in HMG-CoA reductase activity, which may increase mevalonate concentrations.

In HIDS there is no general deficiency in isoprenoid end products, and serum cholesterol levels are only slightly decreased. Mevalonate levels are increased to detectable levels in urine during attacks.

Manipulation of the isoprenoid pathway with statins, in an effort to reduce mevalonate levels, has been considered to have antiinflammatory effects, although contradictory reports have emerged. The use of statins in patients with MA resulted in acute flares in two patients within weeks of commencement of a statin; in contrast, six HIDS patients treated for 6 months did show a decrease in symptoms (Simon et al. 2004).

Peripheral blood mononuclear cells (PBMCs) from patients with HIDS show excess IL-1β production in response to LPS stimulation, a finding that can be reversed by the addition of geranylgeranyl, an isoprenoid deficient in HIDS (Mandey et al. 2006a). In contrast, the addition of mevalonate, which is elevated in HIDS, also reduced IL-1β production, suggesting that it is not central to the proinflammatory phenotype. Apoptosis of activated cells is a key mechanism in the termination of the inflammatory response and, in keeping with the protracted inflammatory response seen in HIDS, defective apoptosis has been observed in PBMCs from patients with HIDS (Bodar et al. 2007).

Therapeutic options in HIDS are limited. As stated earlier, there are conflicting results regarding the usefulness of statins. Manipulation of the isoprenoid biosynthesis pathways to augment the production of nonsterol isoprenoids has been

suggested as a potential therapeutic option based on in vitro studies (Schneiders et al. 2006). Elevations in urinary leukotrienes during HIDS episodes led to the trial of oral leukotriene receptor antagonism, using montelukast, with anecdotal reports suggesting clinical benefit. The demonstration of elevated serum TNF led to a pilot study involving the use of etanercept, the p75 TNF receptor fusion protein, which demonstrated clinical benefit (Takada et al. 2003).

Future Directions

The study of rare autoinflammatory syndromes has informed us of novel proteins involved in the innate immune response. These proteins provide further evidence for the complexity of this ancient host defense system. Many of these recently described proteins are involved in intracellular pathogen sensing, a previously under-recognized role for the innate immune system. Despite the progress made in recent years, there remain a significant number of patients with recurrent fevers in whom the previously described gene defects cannot be found. Efforts are ongoing to identify new genes. Regarding the known genes and their products, the accumulating evidence highlights the difficulties encountered in unraveling their interactions. Further information regarding the roles of these proteins should in time allow clear elucidation of their complex interplay with the cell and host environment.

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