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Essay

Autoinflammatory Disease Reloaded: A Clinical Perspective

Daniel L. Kastner,[1,*] Ivona Aksentijevich,[1] and Raphaela Goldbach-Mansky[1]
[1]Laboratory of Clinical Investigation, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health, Bethesda, MD 20892, USA
*Correspondence: kastnerd@mail.nih.gov
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Our understanding of the etiology of autoinflammatory disease is growing rapidly. Recent advances offer new opportunities for therapeutic intervention and suggest that the definition of what constitutes an autoinflammatory disease should be reassessed.

Introduction

The term "autoinflammatory" appeared in the pages of *Cell* in the spring of 1999 to denote an emerging family of clinical disorders characterized by episodes of seemingly unprovoked inflammation without high-titer autoantibodies or antigen-specific T lymphocytes (McDermott et al., 1999). This proposed nomenclature was inspired by the discovery of dominantly inherited missense mutations in *TNFRSF1A*, the gene encoding the 55 kDa tumor necrosis factor receptor, in several families with prolonged fevers and severe localized inflammation. Patients with this illness, now known as the TNF receptor-associated periodic syndrome (TRAPS), present with dramatic, sometimes month-long bouts of fever with sterile peritonitis, pleurisy, arthritis, migratory erythema, or periorbital edema. In some cases, renal failure develops due to the deposition of an acute-phase reactant, serum amyloid A (SAA), in the kidneys. Although TNF has pleiotropic effects on immune function, inducing leukocyte activation and cytokine secretion, expression of adhesion molecules, and host resistance to intracellular pathogens, TRAPS patients do not usually manifest the self-reactive antibodies or T cells that are the hallmarks of autoimmunity.

The discovery of TRAPS followed close on the heels of the positional cloning of another gene that when mutated causes familial Mediterranean fever (FMF), the first-recognized and still most common hereditary recurrent fever syndrome (International FMF Consortium, 1997; French FMF Consortium, 1997). FMF presents with a constellation of serosal, synovial, and cutaneous inflammation similar to TRAPS and also lacks the cardinal features of autoimmunity seen in diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. The autoinflammatory terminology sought to provide a unifying concept for a newly recognized group of illnesses clinically distinct from the more well-studied autoimmune diseases.

This formulation has proven to be a useful construct over the last decade, with the recognition of an ever-growing list of illnesses falling under the autoinflammatory rubric (Table 1) (Galon et al., 2000; Masters et al., 2009). Four recurrent fever syndromes have been added to the list, including the recessively inherited hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) and a spectrum of three illnesses of varying severity all caused by dominant or de novo mutations in a gene, *NLRP3/CIAS1*, encoding a critical activator of IL-1β originally termed cryopyrin (now NLRP3). At the milder end of the cryopyrinopathies, familial cold autoinflammatory syndrome (FCAS) is characterized by cold-induced episodes of fever and hives, whereas the most severe phenotype, neonatal-onset multisystem inflammatory disease (NOMID; also known as chronic infantile neurologic cutaneous and articular syndrome, or CINCA), manifests nearly continuous fevers, with a hive-like rash, overgrowth of the epiphyses of the long bones, and chronic aseptic meningitis that can cause blindness, progressive hearing loss, and mental retardation. The concept of autoinflammation has been extended to a number of clinical entities beyond the confines of the hereditary recurrent fever syndromes, including several Mendelian diseases, as well as disorders with a more complex (polygenic) mode of inheritance. The clinical scope of autoinflammatory conditions is now broad, encompassing syndromes that variously present with, among other things, serositis, pyogenic arthritis, pyoderma gangrenosum, granulomatous uveitis, crystalline arthritis, and certain forms of vasculitis.

The recognition of the distinction between autoimmune and autoinflammatory diseases has paralleled advances in our understanding of the molecular and cellular basis of innate immunity. In the traditional autoimmune diseases like SLE, the adaptive immune system, driven by lymphocytes with antigen receptors that somatically rearrange and mutate, plays a decisive role in pathogenesis. In contrast, the autoinflammatory diseases are defined by their relative lack of evidence for adaptive immunity. Not surprisingly, the innate immune system, with its myeloid effector cells and germline receptors for pathogen-associated molecular patterns and "danger signals," predominates in the pathogenesis of these illnesses. The recognition of disease-associated mutations in *NLRP3/CIAS1* (Hoffman et al., 2001; Aksentijevich et al., 2002; Feldmann et al., 2002) was particularly decisive in drawing the connection between autoinflammatory disease and innate immunity, given that the encoded protein is the linchpin of the NLRP3 inflammasome—a molecular engine of the

Table 1. Clinical Classification of Selected Autoinflammatory Diseases

Disease	Gene (Protein)	Proposed Mechanism[a]
Hereditary Recurrent Fevers		
Familial Mediterranean fever (FMF)	*MEFV* (pyrin)	Increased inflammasome activation
TNF receptor-associated periodic syndrome (TRAPS)	*TNFRSF1A* (TNFR1)	Protein misfolding
Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)	*MVK* (mevalonate kinase)	Increased inflammasome activation
Familial cold autoinflammatory syndrome (FCAS)	*NLRP3/CIAS1* (NLRP3/cryopyrin)	Intrinsic inflammasomopathy
Muckle-Wells syndrome (MWS)	*NLRP3/CIAS1* (NLRP3/cryopyrin)	Intrinsic inflammasomopathy
Neonatal-onset multisystem inflammatory disease (NOMID)	*NLRP3/CIAS1* (NLRP3/cryopyrin)	Intrinsic inflammasomopathy
Idiopathic Febrile Syndromes		
Systemic onset juvenile idiopathic arthritis (SoJIA)	Complex	Unknown
Adult-onset Still's disease	Complex	Unknown
Schnitzler syndrome	Sporadic?	Increased inflammasome activation
Pyogenic Disorders		
Pyogenic arthritis with pyoderma gangrenosum and acne (PAPA)	*PSTPIP1/CD2BP1* (PSTPIP1/CD2BP1)	Abnormal PSTPIP1 binding to pyrin causing increased IL-1β activation
Granulomatous Diseases		
Chronic granulomatous synovitis with uveitis and cranial neuropathy (Blau syndrome)	*NOD2/CARD15* (NOD2/CARD15)	NF-κB activation disorder
Crohn's disease	Complex (*NOD2*, *ATG16L1*, *IRGM)*	NF-κB activation disorder
Autoinflammatory Disorders of Skin and Bone		
Deficiency in IL-1 receptor antagonist (DIRA)	*IL1RN* (IL-1Ra)	Absence of negative regulator of IL-1α and IL-1β
Majeed syndrome	*LPIN2* (Lipin-2)	Unknown
Chronic recurrent multifocal osteomyelitis (CRMO)	Complex	Unknown
Synovitis acne pustulosis hyperostosis osteitis (SAPHO)	Complex	Unknown
Metabolic Disorders		
Gout (monosodium urate deposition)	Complex *(SLC2A9/GLUT9*, *ABCG2)*	Crystal-induced inflammasome activation
Pseudogout (calcium pyrophosphate dihydrate deposition)	Complex	Crystal-induced inflammasome activation
Type 2 diabetes mellitus	Complex	Hyperglycemia-induced inflammasome activation
Complement Disorders		
Atypical hemolytic-uremic syndrome (aHUS)	*CFH* (complement factor H), *MCP* (CD46), *CFI* (complement factor I), *CFB* (complement factor B)	Abnormal regulation of C3b
Age-related macular degeneration	Complex, *CFH*	Impaired inactivation of C3b
Vasculitis		
Behçet's disease	Complex	Unknown
Macrophage Activation Syndromes		
Familial hemophagocytic lymphohistiocytosis (HLH)	*UNC13D* (Munc13-4), *PRF1* (perforin 1), *STX11* (syntaxin 11)	Impaired efficacy of cytotoxic T lymphocytes with compensatory macrophage activation
Secondary HLH	Complex	Unknown
Storage Diseases		
Gaucher's disease	*GBA* (acid β-glucosidase)	Unknown
Atherosclerosis?	Complex	Unknown
Fibrosing Diseases		
Asbestosis/silicosis	Complex	Particle-induced inflammasome activation

[a]For details, see Masters et al., 2009. Intrinsic inflammasomopathies are disorders of proteins that are part of the inflammasome, whereas extrinsic inflammasomopathies are disorders of proteins upstream or downstream of the inflammasome in IL-1 activation. Complex genetics indicates multiple genetic loci interacting with environmental factors.

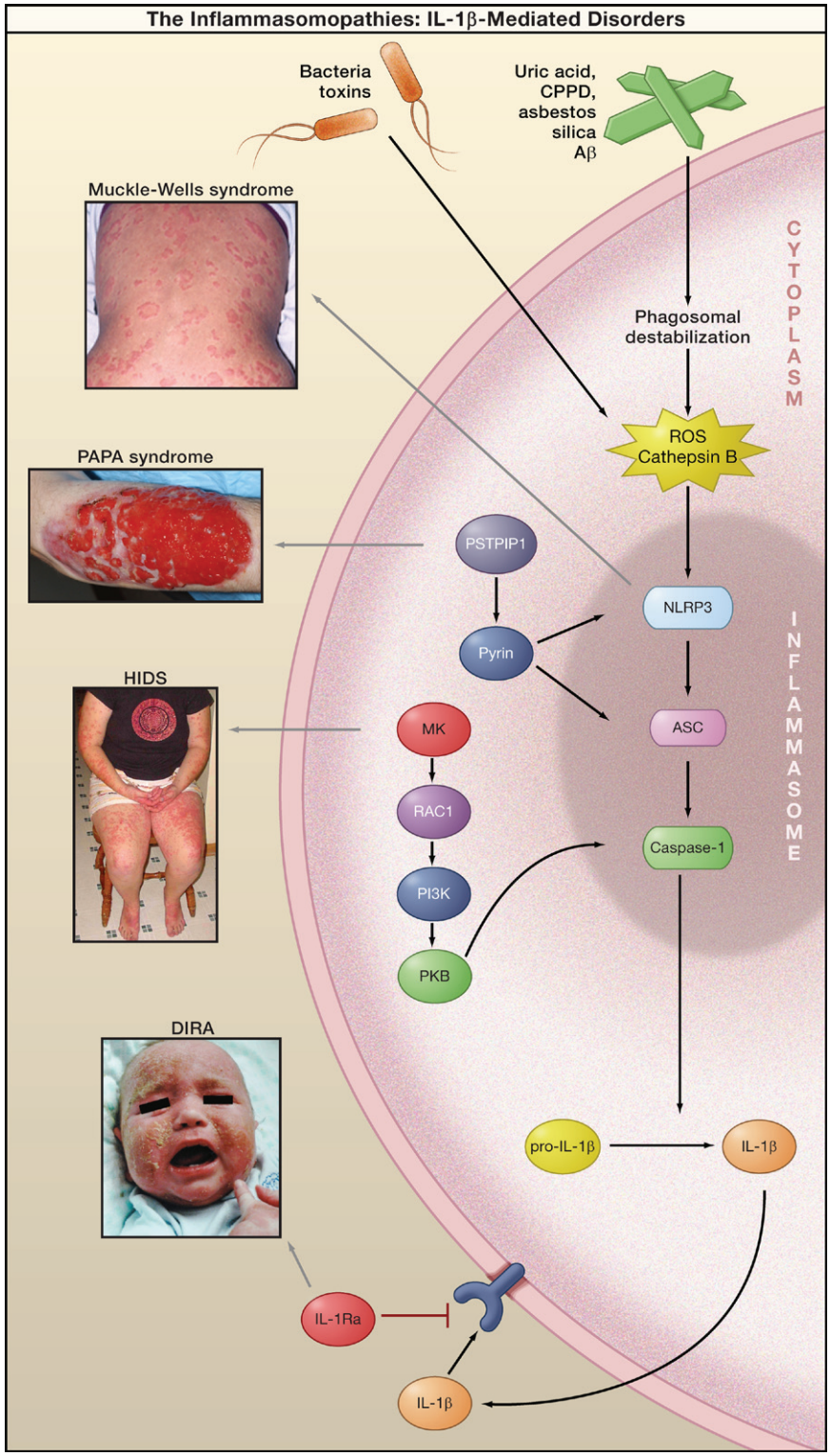

Figure 1. IL-1β-Mediated Disorders

Several Mendelian autoinflammatory diseases are caused by mutations in genes encoding proteins that directly or indirectly regulate interleukin-1β (IL-1β), an important mediator of fever and inflammation. The NLRP3 inflammasome is one of the macromolecular complexes by which IL-1β is activated in monocytes and is comprised of NLRP3, ASC, and caspase-1. Several endogenous "danger signals," such as monosodium urate or calcium pyrophosphate dihydrate crystals, asbestos, silica, amyloid β, and ATP, as well as bacterial toxins, activate the NLRP3 inflammasome through pathways that have not been well defined but may involve reactive oxygen species (ROS) and cathepsin B. With inflammasome activation, caspase-1 (IL-1β-converting enzyme) cleaves pro-IL-1β into its biologically active form. Secreted IL-1β can act in an autocrine or paracrine fashion through the IL-1 receptor. The IL-1 receptor antagonist (IL-1Ra) is a naturally occurring antagonist of the binding of IL-1β to its receptor. Through mechanisms that have not been thoroughly elucidated, PSTPIP1 and pyrin may influence inflammasome activity (Shoham et al., 2003; Chae et al., 2006; Yu et al., 2007). Mevalonate kinase may also modulate inflammasome activity through the Rac1/PI3K/PKB pathway (Kuijk et al., 2008). Muckle-Wells syndrome is caused by activating mutations in NLRP3 itself and manifests a hive-like skin rash. The syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA) is caused by missense mutations in PSTPIP1. A typical lesion of pyoderma gangrenosum is shown. The hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) is caused by inactivating mutations in mevalonate kinase. Patients with HIDS have episodes of fever and a diffuse macular papular rash. The deficiency of the IL-1 receptor antagonist (DIRA) is caused by recessive loss-of-function mutations in IL-1Ra and presents in infancy with diffuse pustular skin lesions. Image from Aksentijevich et al. (2009), copyright ©2009 Massachusetts Medical Society. All rights reserved. Mutations in pyrin cause familial Mediterranean fever (not illustrated here).

innate immune system—through which caspase-1 and thence IL-1β are activated (Martinon et al., 2009; see Review by K. Schroder and J. Tschopp in this issue). With TNF, IL-1β is one of the major mediators of fever and inflammation in man. Several other autoinflammatory diseases are caused by extrinsic perturbations of inflammasome activity. In addition to these so-called inflammasomopathies, there are five other provisional molecular categories of autoinflammatory disease (different from the clinical categories in Table 1), including NF-κB activation disorders, protein-misfolding disorders, complement disorders, cytokine signaling diseases, and macrophage activation syndromes (Masters et al., 2009).

The convergence of the clinical concept of autoinflammatory disease with the basic science of innate immunity has been mutually reinforcing. This Essay summarizes some of the important implications of the discoveries of the last decade for clinical medicine and will outline several challenges for the next decade. Finally, we will revisit the original concept of autoinflammatory disease to propose an updated definition that reflects the current state of knowledge.

Autoinflammatory Disease in Current Medical Practice

Advances in the diagnosis of autoinflammatory disease in the last decade have been nothing short of breathtaking, owing both to the availability of molecular genetic testing and to the greatly increased clinical awareness of these illnesses. Consequently, diagnoses have been established in patients who heretofore were clinical enigmas, in many cases ending years of fruitless testing and permitting evidence-based prognostication and targeted therapy. The case of FMF is illustrative, with the availability of molecular genetic testing having markedly expanded both the geographical and clinical boundaries of the disease. Prior to the identification of the causative gene, FMF was thought to affect North African (Sephardi) and Iraqi Jews almost to the exclusion of East European Ashkenazi Jews. It is now apparent that FMF is quite prevalent among Ashkenazi Jews but usually presents with milder (although often still debilitating) or less frequent attacks than seen in their Sephardi brethren, reflecting the relative frequencies of the V726A and M694V mutations in the respective populations (Aksentijevich et al., 1999). Genetic testing for *MEFV* mutations has also permitted the recognition of undiagnosed cases among Italian, Greek, and other "low-risk" Mediterranean populations and fewer but still significant numbers of cases in many other ethnic groups, including East Asians. Given the usually excellent responses of FMF patients to colchicine prophylaxis, such diagnoses are often life-altering. Genetic diagnosis is now possible for several monogenic autoinflammatory diseases (Table 1).

Equally important, the advances of the last decade have dramatically improved our understanding of disease pathogenesis. One major theme that has emerged is the importance of excessive IL-1 signaling in Mendelian autoinflammatory diseases. FCAS, NOMID/CINCA, and Muckle-Wells syndrome (MWS) are all caused by autosomal-dominant or de novo activating mutations in cryopyrin/NLRP3, a key inflammasome protein. Relative to healthy controls, peripheral blood mononuclear cells from mutation-positive MWS and NOMID patients produce increased amounts of IL-1β in response to lipopolysaccharide (LPS), even in the absence of the second signal ATP (Gattorno et al., 2007), and peripheral blood leukocytes from FCAS patients spontaneously release IL-1β when cultured at 32°C (Brydges et al., 2009), providing a dramatic in vitro correlate of the cold sensitivity these patients exhibit. In contrast, patients with the recently described deficiency in the IL-1 receptor antagonist (DIRA) have recessive loss-of-function mutations in *IL1RN*, encoding the IL-1 receptor antagonist (IL-1Ra), a physiologic inhibitor of IL-1 signaling (Aksentijevich et al., 2009; Reddy et al., 2009). Whereas patients with NOMID present with fever, urticarial rash, epiphyseal overgrowth of the long bones, and chronic aseptic meningitis, patients with DIRA often do not present with fever or central nervous system inflammation but do manifest a diffuse pustular rash and multifocal sterile osteomyelitis. It is at once intellectually satisfying to see two different molecular lesions in the same pathway causing autoinflammation and intriguing that the clinical phenotypes differ as much as they do. Possibly, the nuances could be due to other molecules, such as IL-18, that are activated by the inflammasome in the cryopyrinopathies, or to the fact that the IL-1Ra fails to inhibit signaling by both IL-1α and IL-1β in DIRA. Other autoinflammatory disorders with a likely IL-1 connection include FMF (Chae et al., 2003, 2006), HIDS (Kuijk et al., 2008), and the syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA) (Shoham et al., 2003; Yu et al., 2007). Figure 1 draws attention to the common thread of IL-1 signaling among illnesses that, at first glance, appear quite different.

Positional cloning and candidate gene analyses of patients have provided important insights into the monogenic autoinflammatory diseases, and these discoveries have had immediate and dramatic impact on current therapy (Goldbach-Mansky et al., 2006; Hoffman et al., 2008; Dinarello, 2009; Lachmann et al., 2009). Largely through the analysis of mice deficient in *Nlrp3*, a number of other genetically complex conditions appear also to share an autoinflammatory pathophysiology. Prime examples are gout and pseudogout, which are caused by deposition of, respectively, monosodium urate (MSU) and calcium pyrophosphate dihydrate (CPPD) crystals in the joints and adjacent tissues. Whereas both MSU and CPPD crystals elicit substantial caspase-1 activation and IL-1β release by normal mouse macrophages primed with LPS, this response is almost completely abrogated in *Nlrp3* knockout mice (Martinon et al., 2006). MSU-induced inflammation is also reduced in mice deficient in another inflammasome component, Asc, or in the IL-1 receptor, or in the IL-1 signal transducer MyD88, but not in mice deficient for various Toll-like receptors (Chen et al., 2006). Several other particulates, including asbestos, silica, and alum, are also activators of the inflammasome in mouse models and human leukocytes (Dostert et al., 2008; Eisenbarth et al., 2008; Hornung et al., 2008). Although the predisposing factors identified to date in human gout appear to be primarily metabolic and renal (Choi et al., 2010), early clinical trials of both anakinra (recombinant IL-1 receptor antagonist) and rilonacept (an IL-1 receptor fusion protein) support an important role for IL-1β in the pathophysiology of gouty arthritis (So et al., 2007; Terkeltaub et al., 2009). Because of the burden that common diseases like gout impose on the general population, studies such as these assume a high priority with potentially broad therapeutic application.

Autoinflammation 2010: Challenges for a New Decade

Progress in the study of autoinflammatory diseases appears to be in an exponential growth phase, as today's discoveries pose tomorrow's questions, many of which have direct clinical relevance. For the monogenic autoinflammatory diseases, three genetic questions stand out as particularly important to the clinician because of the frequency with which they arise. The first concerns the interpretation of positive genetic testing for several polymorphic variants of the periodic fever loci, including E148Q and P369S/R408Q at *MEFV*, R92Q and P46L at *TNFRSF1A*, and Q703K and V198M at *CIAS1.* All of these variants are present at an allele frequency of greater than 1% in certain populations—for *MEFV* E148Q the allele frequency may be as high as 23% among the Japanese (Sugiura et al., 2008), and for *NLRP3/CIAS1*

Q703K 6.5% among Swedes (Verma et al., 2008)—and are commonly reported among patients with undiagnosed autoinflammatory phenotypes. For each of these variants, the jury is still out, based on either careful epidemiologic data or in vitro functional studies, as to whether they actually confer a distinct phenotype, act as modifiers for other inflammatory loci, or are simply coincidental bystanders. Because of their frequency, the implications are substantial.

The second "frequently asked question" concerns FMF in particular and is based on the fact that many of the patients with colchicine-responsive clinical FMF have only a single demonstrable *MEFV* mutation, despite thorough scrutiny (Booty et al., 2009; Marek-Yagel et al., 2009; Ozen, 2009). Although this widely confirmed observation is based on a clinical definition of FMF that includes milder cases than were appreciated 20 years ago, it suggests a more complex pattern of inheritance than the simple recessive model of the textbooks. It also argues that solitary *MEFV* mutations may confer a biochemical or clinical phenotype by mechanisms yet to be elucidated, perhaps in the presence of as yet unidentified modifier loci.

A third major genetic issue for the clinician is finding an explanation for the approximately 60% of patients with various autoinflammatory phenotypes who do not have mutations in any of the known genetic loci. The recent examples of DIRA (Aksentijevich et al., 2009; Reddy et al., 2009) and IL-10 receptor deficiencies (Glocker et al., 2009) raise the possibility that at least some of these individuals will eventually be found to have mutations in currently unrecognized autoinflammatory genes. An important initiative currently undertaken at the NIH is to apply whole-genome single-nucleotide polymorphism (SNP) analyses to search for areas of homozygosity in patients from consanguineous families or isolated populations who are more likely to have recessive mutations and to perform directed candidate gene screening or whole-exome sequencing in selected other cases. Overall, in the NIH cohort alone there are over 1000 unrelated patients with genetically unexplained autoinflammatory phenotypes who may be a rich source of yet additional loci that may deepen our understanding of the human innate immunome.

Another important and largely untouched area is the identification of susceptibility loci for complex (polygenic) autoinflammatory diseases. There are a number of such disorders, including Behçet's disease (Gül, 2005), systemic onset juvenile idiopathic arthritis (SoJIA) (Allantaz et al., 2007), and the syndrome of periodic fever with aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) (Feder and Salazar, 2009). These illnesses are much more common than the monogenic autoinflammatory diseases, at least in certain parts of the world. Current thinking among human geneticists is that, for many of the common complex diseases, the etiology derives from permutations and combinations of common variants, each of which alone may only confer a small risk. Such variants can be detected by genome-wide association studies (GWAS). Based on the experience with GWAS conducted thus far for the classic autoimmune diseases, it is likely that the clinical implications of such studies will be more relevant to identifying pathways that may be amenable to targeting with small molecules or biologics than to establishing parameters to diagnose or predict disease (Gregersen and Olsson, 2009). Alternatively, at least some of these genetically complex diseases may be due to high-penetrance rare mutations that only account for a few cases each (Frazer et al., 2009), in which case screening or prediction would be possible. Of course, the most likely scenario is that many of these complex autoinflammatory diseases are due to a combination of the two models, with some cases due to low-penetrance common variants and others caused by rare high-penetrance mutations.

The molecular pathophysiology of the autoinflammatory diseases is a topic of growing clinical interest. Particularly for diseases where a genetic approach has been taken, we may know the genes and mutations, and we may know the clinical phenotypes, but in many cases there is a black box between the two. Understanding this connection can have important implications for how clinicians think about human disease. There are many examples. FMF has long been a source of fascination because of the extraordinarily high carrier frequencies of multiple different mutations in Mediterranean and Middle Eastern populations, strongly suggesting a heterozygote advantage for a pathogen endemic to that part of the world (Masters et al., 2009). Such speculation is further fueled by the fact that disease-associated mutations tend to cluster around a pocket in the C-terminal domain of pyrin, the FMF protein, that may be a binding site for such a putative pathogen (Weinert et al., 2009). Although purely conjectural at this point, the smallpox virus appears a particularly attractive candidate binding partner, both because of the fact that this disease probably arose in Africa and was common in the ancient Mediterranean basin where there was a sufficient population density to maintain human-human spread of the disease (Hopkins, 1983) and because poxviruses produce proteins with the canonical N-terminal pyrin domain (an interaction motif named after the FMF protein) that are thought to subvert the host innate immune response (Johnston et al., 2005). The recent development of pyrin knockin mice by our laboratory may help to investigate the interaction between pyrin and various pathogens, although of course not the smallpox virus itself.

There are many other questions with clinical relevance regarding the pathophysiology of autoinflammatory disease, some of which relate to single diseases, and others that are more broadly applicable. In the case of TRAPS, it appears that the impaired TNF receptor ectodomain cleavage initially described in these pages (McDermott et al., 1999) may have less of a proinflammatory effect than more recently described activation due to abnormal receptor trafficking (Lobito et al., 2006), and this may have important implications for treatment. One major issue that cuts across many of these illnesses is understanding what may provoke or exacerbate the autoinflammatory phenotype and why. Although the original definition alluded to "seemingly unprovoked" inflammation, we now know that frequently there are triggers. Examples include cold exposure in FCAS, childhood immunizations in HIDS, physical trauma in TRAPS and PAPA syndrome, mechani-

cal trauma to the skin and gastrointestinal tract in DIRA, strenuous physical exertion in FMF, and psychological stress and menstrual cycles in several of these illnesses. Longer-term gene-environment interactions are just beginning to be appreciated. One important example is the apparent relationship between country of origin and susceptibility to systemic amyloidosis in FMF, with much higher risks observed for individuals who have spent their early lives in countries with high infant mortality rates (Touitou et al., 2007). For example, Armenians with FMF living in Armenia have a much higher risk of developing amyloidosis than Armenian-Americans. Although there are many possible explanations, one attractive possibility is that frequent, untreated exposure to bacterial infection in early childhood may predispose to amyloid deposition upon repeated inflammatory episodes later in life. Similar geographic variability in susceptibility to AA amyloidosis has been observed in a number of other conditions, including juvenile idiopathic arthritis.

Also still a mystery is why the autoinflammatory diseases exhibit a relative paucity of the usual markers of adaptive immunity. Of course, just as we are now aware that there are triggers for the "seemingly unprovoked" episodes of autoinflammation, so too is it clear that the adaptive immune system is not totally quiescent, as evidenced, for example, by the polyclonal hyperglobulinemia that is frequently seen in the hereditary recurrent fevers. Nevertheless, antinuclear antibodies and rheumatoid factors are notably absent in patients with autoinflammatory disease, despite the recent demonstration that the vaccine adjuvant alum stimulates antibody production through its activation of the inflammasome and innate immunity (Eisenbarth et al., 2008). Perhaps the absence of some essential second signal, such as the presentation of intracellular antigens on apoptotic blebs in SLE (Suber and Rosen, 2009), explains the relative lack of adaptive immunity in the autoinflammatory diseases. Finally, there is a brave new world of human biology that is just emerging as genetic analysis begins to uncover the loci that underlie the complex autoinflammatory diseases and the host of disorders, such as ankylosing spondylitis and psoriasis, that reside at the interface between autoinflammatory and autoimmune (McGonagle and McDermott, 2006).

Although nearly any topic regarding the treatment of autoinflammatory disease is clinically relevant, there are two that are particularly exciting, the first concerning IL-1 and the second relating to all of the other possible therapeutic targets (See also Review by C.A. Dinarello in this issue). As previously noted, the spectrum of disorders in which the inflammasome plays some role has grown rapidly in the last 10 years, and perhaps one of the most interesting is type 2 diabetes mellitus. By mechanisms that have not been completely elucidated, hyperglycemia may induce IL-1β production by pancreatic islet cells, leading to islet cell death, decreased insulin production, and a diabolical resonance between hyperglycemia and IL-1β production (Maedler et al., 2002). A recent paper by Monath and colleagues suggests a possible role for anakinra, the recombinant IL-1 receptor antagonist, in maintaining glycemic control (Larsen et al., 2007), which, if confirmed, could have a far-reaching impact on the practice of clinical medicine. On the other hand, despite the incontrovertible importance of IL-1 in both monogenic and complex autoinflammatory diseases, other pathways are already apparent (Masters et al., 2009; Glocker et al., 2009), and it is very likely that additional yet-to-be-discovered cytokines and pathways will also be established in the next 10 years. A recent treatment of the current state of the art suggested five molecular categories of autoinflammation besides the inflammasomopathies (Masters et al., 2009), and preliminary data from a recently completed Behçet's disease GWAS at the NIH suggest even further heterogeneity. Of course, the attraction of approaching these inherited diseases from the standpoint of patient cohorts with genes to be discovered is that such an approach maximizes clinical relevance while minimizing investigator bias.

Autoinflammatory Disease Reconsidered: Time for a New Definition?

The initial definition of autoinflammatory disease was predicated on two negatives, the lack of apparent provocation for inflammation and the absence of high-titer autoantibodies or antigen-specific T cells. It is now clear that neither criterion is consistently valid, and it seems inevitable that more counterexamples will appear as time goes on.

For example, given the fact that the molecular lesion in FCAS, MWS, and NOMID lowers the threshold for inflammasome activation, and given the proliferation of agents now known to stimulate the inflammasome, it is likely that the list of factors known to precipitate attacks of the cryopyrinopathies will continue to grow. Of course, this is really no different from the classic autoimmune diseases, where such factors as sun exposure in SLE and cigarette smoking in RA are increasingly recognized as contributory. Similarly, with the growing appreciation of crosstalk between the innate and adaptive immune systems, it is likely that as autoinflammatory diseases are further scrutinized, autoantibodies will be found within the hyperglobulinemia already documented in some of these illnesses.

In contrast, during the last 10 years the association between the autoinflammatory diseases and the innate immune system has only strengthened, and it is thus reasonable to propose a revised definition that recognizes this connection. Simply put, the autoinflammatory diseases are clinical disorders marked by abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant host predisposition. Such a definition is broad enough still to include the Mendelian diseases that initially stimulated the conception of the autoinflammatory terminology, as well as the complex disorders currently under investigation. "Significant host predisposition" might include both hereditary factors and proclivities that are the result of gene-environment interactions, and such a definition would also recognize that there is a continuum between the autoinflammatory and the autoimmune.

In medicine as in other branches of science, terminology evolves with our understanding of underlying causes, and thus clinging to the initially proposed definition of autoinflammation in 2010 would make no more sense than lumping all renal disorders together as "Bright's disease." Given that our conceptualization of disease is constrained by the words

that we use and how we define them, it is critical that our clinical terminology keep pace with our science. In this way we can continue to recognize and understand new patients in the clinic with bona fide autoinflammatory phenotypes that may be a long way from the recurrent fevers that first inspired the term.

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