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Inherited Autoinflammatory Syndromes

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Abstract

Autoinflammation describes a collection of diverse diseases caused by indiscriminate activation of the immune system in an antigen-independent manner. The rapid advancement of genetic diagnostics has allowed for the identification of a wide array of monogenic causes of autoinflammation. While the clinical picture of these syndromes is diverse, it is possible to thematically group many of these diseases under broad categories that provide insight into the mechanisms of disease and therapeutic possibilities. This review covers archetypical examples of inherited autoinflammatory diseases in five major categories: inflammasomopathy, interferonopathy, unfolded protein/cellular stress response, relopathy, and uncategorized. This framework can suggest where future work is needed to identify other genetic causes of autoinflammation, what types of diagnostics need to be developed to care for this patient population, and which options might be considered for novel therapeutic targeting.

INTRODUCTION

Autoinflammation represents a rapidly growing subset of immune dysregulation disorders characterized by excessive activation of immune cells independent of antigen trigger. This is in distinction to autoimmune diseases, which are typically characterized by immune activation as a result of antigen receptor stimulation due to a loss of tolerance to self-antigen. As with most attempts to define categories within complex syndromes, these distinctions are often blurred, as autoinflammation can be a setup that promotes loss of tolerance, and autoimmunity often leads to the release of mediators that activate nonantigen receptor–driven immune cells. Thus, many immune dysregulation syndromes are often a combination of autoinflammation and autoimmunity.

However, the rapid advances in genetic diagnostics have allowed for the identification of an ever-growing number of monogenic syndromes of autoinflammation that are more pure in their pathogenesis. While individually any one of these inherited autoinflammatory syndromes may represent a small number of patients, collectively as a group they represent a significant population with continued unmet needs both diagnostically and therapeutically. The study of these diseases provides an opportunity for better understanding of the fundamental function of the immune system, which in turn provides for more powerful and rapid diagnostics and for targeted precision therapeutics. This review attempts to provide a framework for the various categories of inherited autoinflammatory diseases and considers what these genetic lesions teach us about immune function in health and disease.

In the simplest terms, autoinflammation is thought of as dysregulation of the innate immune system, and autoimmunity is thought of as dysregulation of the adaptive immune system. While most examples follow this paradigm, this need not be the case, and examples of autoinflammation from adaptive immune cell defects are covered in this review. Rather than being defined as a defect in any particular type of cell, autoinflammation is best thought of as a defect in antigen-independent immune pathways that results in either gain-of-function activation of effector molecules or loss of function of repressive molecules. The net result of either situation is the constitutive activation of immune functions, most commonly cytokine release, that lead to shared clinical features such as fever, rash, arthritis, gastrointestinal dysfunction, and other end-organ damage. Given that there is often a nodal cytokine that seems to dominate the pathogenesis in many of these genetic syndromes, and that there is now a wide array of cytokine-neutralizing therapeutics available to treat them, understanding of the basic mechanisms of disease frequently leads to an immediate ability to translate to a targeted therapeutic intervention. This rapid bedside-to-bench-to-bedside cycle underscores the importance of immune dysregulation research in general and in particular for our understanding of the molecular mechanisms that drive inflammation in inherited diseases of autoinflammation.

This review is not intended to be an encyclopedic review of every genetic discovery in autoinflammation. Rather, we attempt to describe broad categories of disease and review the canonical genetic examples that support the concept of these categories. Consideration is given to how these categories may relate to each other and how that framework might provide clues about yet-to-be-discovered mechanisms that might explain the still large burden of disease that does not have a clear molecular definition. There are always problems with any attempt to categorize a heterogeneous group of diseases into a classification schema. The outline below should not be considered as the sole defining system for considering the inherited autoinflammatory syndromes; indeed, there will be overlap between groups, and boundaries between certain classes may be blurry. However, it is to be hoped that a structured approach toward thinking about the current state of knowledge will lead to continued refinement of our understanding of these syndromes and may help to shed light into where additional investigation is most needed. **Table 1** contains a more complete list of genetic entities and associated references for readers who wish to learn more about a particular area.

Table 1 List of inherited autoinflammatory syndromes

Disease	Gene(s)	Brief description	Reference(s)
Inflammasomopathy			
Familial Mediterranean fever (FMF)	*MEFV*	Fever, serositis, arthritis	9
Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA)	*PSTPIP1*	Pyogenic arthritis, pyoderma gangrenosum, acne	13
Cryopyrin-associated periodic syndrome (CAPS)	*NLRP3*	Fever, rash, bony lesions, central nervous system inflammation	15, 16
Blau syndrome	*CARD15*	Early onset sarcoidosis, rash, arthritis, uveitis	86
Deficiency of interleukin-1 receptor antagonist (DIRA)	*IL1RN*	Pustular skin rash, bony inflammation	18
Autoinflammation with infantile enterocolitis (AIFEC)	*NLRC4*	Inflammatory bowel disease, hemophagocytic lymphohistiocytosis	22, 23
Familial cold autoinflammatory syndrome 4 (FCAS4)	*NLRC4*	Cold-induced fever, rash	26, 27
X-linked proliferative disease type 2 (XLP2)	*XIAP*	Hemophagocytic lymphohistiocytosis, uveitis, inflammatory bowel disease	28
CDC42 mutation	*CDC42*	Hemophagocytic lymphohistiocytosis, central nervous system inflammation, urticaria	31, 32
Interleukin-18 binding protein deficiency	*IL18BP*	Fulminant viral hepatitis	87
Familial cold autoinflammatory syndrome 2 (FCAS2)	*NLRP12*	Cold-induced fever, rash	88
Majeed syndrome	*LPIN2*	Sterile osteomyelitis, anemia	89
Autoinflammatory periodic fever, immunodeficiency, and thrombocytopenia (PFIT)	*WDR1*	Periodic fevers with immunodeficiency and thrombocytopenia	90
Interferonopathy			
Aicardi-Goutières syndrome	*TREX1*, *SAMHD1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *ADAR1*, *IFIH1*, *USP18*, *ISG15*	Leukodystrophy/encephalopathy, liver inflammation, skin rash	38
Singleton-Merten syndrome (SMS)	*IFIH1*, *DDX58*	Dental dysplasia, aortic calcification, skeletal abnormalities, glaucoma, psoriasis	44, 45
Stimulator of interferon genes–associated vasculopathy with onset in infancy (SAVI)	*TMEM173*	Vasculopathy, fever, interstitial lung disease	47
Familial chilblain lupus	*TREX1*	Severe chilblain/pernio	91

(*Continued*)

Table 1 (*Continued*)

Disease	Gene(s)	Brief description	Reference(s)
Unfolded protein response/endoplasmic reticulum stress syndrome			
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE)/ proteasome-associated autoinflammatory syndromes (PRAAS)	*POMP8*, *PSMB4*, *PSMB9*, *PSMA3*, *POMP*	Fever, neutrophilic dermatosis, lipodystrophy	54–57
Tumor necrosis factor receptor–associated periodic syndrome (TRAPS)	*TNFRSF1A*	Fever; joint, muscle, and abdominal pain; rash	59
Vibratory urticaria	*ADGRE2*	Vibration-induced urticaria	92
Relopathy			
Haploinsufficiency of A20 (HA20)	*TNFAIP3*	Oral and genital ulcers, arthritis, ocular inflammation, fever	65, 66
Otulipenia	*OTULIN*	Fever, nodular or pustular rash, lipodystrophy, joint/muscle pain, lymphadenopathy	67
HOIP1 deficiency	*RNF31*	Autoinflammation, immunodeficiency, subclinical amylopectinosis, systemic lymphangiectasia	68, 69
Receptor interacting protein kinase 1 (RIPK1) deficiency	*RIPK1*	Recurrent infections, early onset inflammatory bowel disease, arthritis	70, 71
RELA haploinsufficiency	*RELA*	Chronic mucocutaneous ulceration	93
Uncategorized			
Deficiency of adenosine deaminase 2 (DADA2)	*CERC1*	Vasculopathy/vasculitis	72
Autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation (APLAID)	*PLCG2*	Blistering skin lesions, bronchiolitis, arthralgia, ocular inflammation, enterocolitis	74
Hyper IgD syndrome (HIDS)	*MVK*	Fever, arthritis, abdominal pain	76
Deficiency of the IL-36 receptor antagonist (DITRA)	*IL36RN*	Generalized pustular psoriasis	94
Sideroblastic anemia with B cell immunodeficiency, periodic fevers, and developmental delay (SIFD)	*TRNT1*	Fever, recurrent infection, anemia	95

INFLAMMASOMOPATHIES

The concept of the inflammasome broadly refers to macromolecular structures within the cytoplasm of the cell that sense molecular motifs associated with danger, whether these be of pathogen origin or from tissue damage. Inflammasome sensing of danger leads to activation of caspase-1, which in turn cleaves the proinflammatory cytokines interleukin (IL)-1β and IL-18 into their active forms (1), and additionally activates gasdermin D (GSDMD) (2), resulting in cell death by pyroptosis. The ultimate outcome is the release of IL-1β and IL-18 into the extracellular space, where they are sensed by a number of immune cells to promote inflammation.

A number of different inflammasomes have been described, each of which has different ligand sensing capabilities (3). Additionally, negative regulators of inflammasomes act to tune activity,

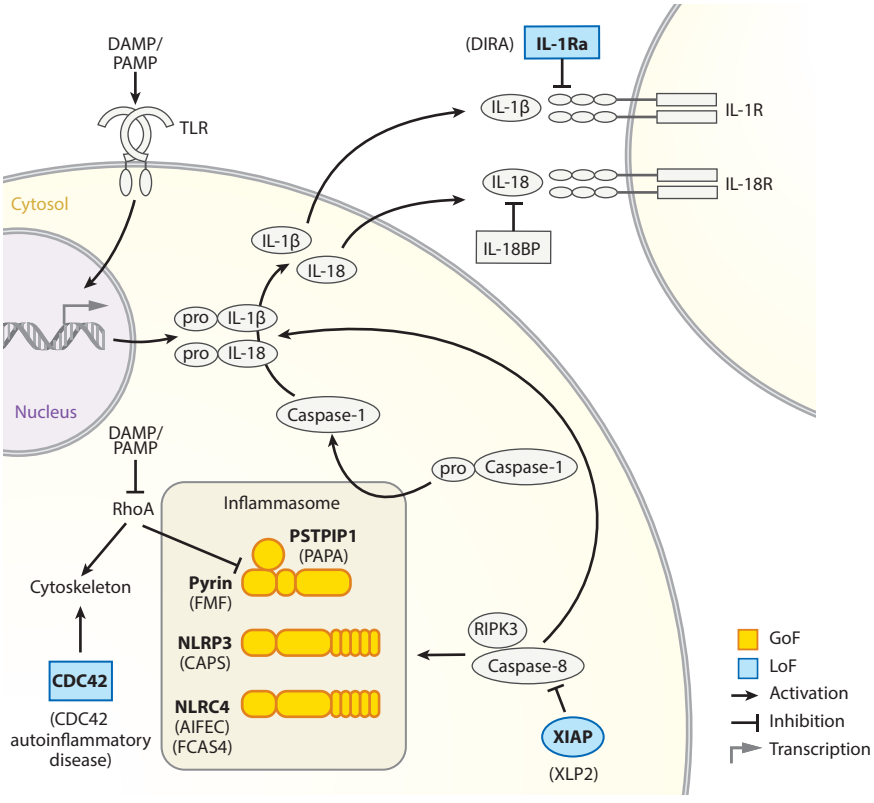

Figure 1

Inflammasomopathies. In response to danger signals, various inflammasomes (e.g., pyrin, NLRP3, and NLRC4) are activated to cleave pro-caspase-1 into caspase-1, which in turn cleaves pro-IL-1β and pro-IL-18 into their active forms. IL-1β and IL-18 are then secreted and signal via IL-1R and IL-18R, respectively. GoF mutations in inflammasome components or LoF mutations in regulatory proteins in this pathway lead to disorders of autoinflammation mediated by IL-1 and/or IL-18. Abbreviations: AIFEC, autoinflammation with infantile enterocolitis; CAPS, cryopyrin-associated periodic syndrome; DAMP, danger-associated molecular pattern; DIRA, deficiency of interleukin-1 receptor antagonist; FCAS4, familial cold autoinflammatory syndrome 4; FMF, familial Mediterranean fever; GoF, gain of function; IL, interleukin; IL-1R, IL-1 receptor; IL-1Ra, IL-1 receptor antagonist; IL-18BP, IL-18 binding protein; IL-18R, IL-18 receptor; LoF, loss of function; PAMP, pathogen-associated molecular pattern; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; TLR, Toll-like receptor; XLP2, X-linked proliferative disease type 2.

and both IL-1β and IL-18 have naturally occurring antagonist molecules that are capable of binding their respective receptors and inhibiting signaling (4–6). Defects in each of these types of molecules have been described and are outlined below. Inflammasomopathies can be broadly thought of as being more IL-1β driven or more IL-18 driven, and we consider each of these classes separately (**Figure 1**).

Interleukin-1-Opathies

IL-1β is first translated as a proprotein from mRNA, the transcription of which is induced by danger sensors other than the inflammasome such as Toll-like receptors (7). This initial priming step results in the production of pro-IL-1β protein, which is inactive and remains intracellular.

Upon inflammasome activation by an additional danger signal, caspase-1 is cleaved and activated, which in turn cleaves pro-IL-1β into its active form, which is subsequently released from the cell via pyroptosis (8). Monocytes, neutrophils, macrophages, and dendritic cells are the major source of IL-1β. The cytokine is responsible for fever induction, the skewing of $CD4^+$ T cell responses toward Th17 lineage, and a number of other inflammatory effects.

Familial Mediterranean fever. Familial Mediterranean fever (FMF) was the first genetically described inflammasomopathy, being associated with the *MEFV* gene that encodes the pyrin inflammasome protein product in 1997 (9). FMF presents as sporadic but recurrent episodes of inflammation characterized by fever and inflammation at serosal surfaces resulting in pericarditis, pleuritis, arthritis, and peritonitis. Episodes may last for a few days, with complete resolution of symptoms in between. Patients most often only exhibit a subset of these symptoms, with some only presenting with fever. Chronic inflammation, suggested by elevations in the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), may lead to amyloidosis and organ failure if not adequately treated.

The pyrin inflammasome is activated by RhoA activity, which acts to suppress pyrin function. Pathogens that inhibit RhoA activity release this repression, leading to activation of the pyrin inflammasome (10). Accordingly, mutations in *MEFV* that allow an active conformation of the pyrin inflammasome independent of RhoA activity result in FMF. Typically, these mutations are inherited in an autosomal recessive manner, although a few variants do show autosomal dominant inheritance. It has been recently postulated that there may be a survival benefit to having a more active pyrin inflammasome for some pathogens such as *Yersinia pestis* (11), explaining why these disease-causing variants have a higher frequency in the population than what one might expect from a pathogenic allele.

Colchicine, long the empiric mainstay of therapy for FMF, has as one of its mechanisms of action the activation of RhoA (12), which may explain its efficacy in this disease. Blockade of IL-1β is another rational approach to therapy and is approved by the US Food and Drug Administration for this indication.

Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome. Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is caused by mutations in the *PSTPIP1* gene, which has been shown to be a binding partner of pyrin (13). PAPA-syndrome-causing mutations in *PSTPIP1* confer a greater binding capacity with pyrin. Accordingly, IL-1β blockade also seems to be effective for these patients (14).

Cryopyrin-associated periodic syndrome. Mutations in the *NLRP3* gene (encoding the NLRP3 protein, also known as cryopyrin) result in a set of three related syndromes that are known collectively as cryopyrin-associated periodic syndrome (CAPS): neonatal onset multisystem inflammatory disease, Muckle-Wells syndrome, and familial cold autoinflammatory syndrome (FCAS) (15, 16). These syndromes exist along a spectrum and present with fever, central nervous system (CNS) and ocular inflammation, rash, arthritis, and bony inflammation. Symptoms are often precipitated by cold exposure; however, up to half of patients experience daily symptoms. Mutations in *NLRP3* result in ligand-independent constitutive activation of the NLRP3 inflammasome and IL-1β release with some genotypic-phenotypic association (17). As with FMF, IL-1β blockade is therapeutically efficacious for CAPS, and long-term uncontrolled disease may lead to amyloidosis. While there is some overlap between the clinical symptoms of FMF and CAPS, there is clearly a difference as well, with greater CNS and bone disease in CAPS.

Deficiency of interleukin-1 receptor antagonist. Mutations in the gene *IL1RN*, which encodes for the IL-1 receptor antagonist protein IL-1Ra, lead to a syndrome consisting of pustular skin rash; bony inflammation and overgrowth including periosteal elevation, epiphyseal ballooning, and lytic lesions; and elevated ESR and CRP (18). Interestingly, fever does not seem to be a significant feature. Mutations consist of frameshifts, nonsense point mutations, or chromosomal deletions that all result in the loss of IL-1Ra protein. IL-1Ra is a naturally occurring antagonist of IL-1β that competitively inhibits IL-1β activity by binding to the IL-1 receptor. Accordingly, treatment with recombinant IL-1Ra is effective in stopping symptoms. Since IL-1Ra prevents the binding of both IL-1β and IL-1α, some of the phenotypic differences between deficiency of interleukin-1 receptor antagonist and the other inflammasomopathies may be related to IL-1α activity.

Interleukin-18-Opathies

IL-18 biology mirrors that of IL-1β in that it is initially translated as a proprotein that is then cleaved by the inflammasome to its active form. Regulation of IL-18 transcription and translation is different than that of IL-1β. IL-18 is constitutively expressed in mononuclear cells (19) and is also expressed in gut epithelium (20). IL-18, in conjunction with IL-12, induces interferon gamma (IFN-γ) responses in T cells and natural killer cells. Therefore, unlike IL-1β, IL-18 may not require a priming step from signals other than the inflammasome. Much like IL-1Ra is the naturally occurring antagonist of IL-1β, IL-18 binding protein (IL-18BP) is the naturally occurring antagonist of IL-18, by binding to the IL-18 molecule itself and preventing it from binding to its receptor. IL-18BP is induced by IFN-γ, creating a natural feedback inhibition that regulates its function (21). Recent descriptions of diseases that are associated with excessive levels of IL-18 demonstrate some common phenotypes of the combination of hemophagocytic lymphohistiocytosis (HLH) and gastrointestinal inflammation. This is perhaps not surprising, given the connection between IL-18 and IFN-γ, the latter of which is well associated with HLH. Noting that the intestinal epithelium is a major source of IL-18, it is also perhaps not surprising to find this organ involved as well.

Autoinflammation with infantile enterocolitis. Heterozygous gain-of-function mutations in the *NLRC4* gene result in a syndrome of HLH, severe intestinal inflammation, skin rash, and fever (22, 23). Patients with these gain-of-function mutations demonstrate high serum levels of IL-18. Treatment with recombinant IL-18BP in combination with IL-1β blockade resulted in complete resolution of symptoms in one patient, with a decrease in the IFN-γ gene signature (24). Autoinflammation with infantile enterocolitis (AIFEC) patients do have elevated IL-1β in the serum, with levels similar to those seen in CAPS patients; however, the IL-18 levels seen in these patients far exceed those of CAPS patients. This may be related to intrinsic differences in the biochemistry of the NLRC4 inflammasome, differences in the cellular expression of NLRC4 versus NLRP3, or both. *NLRC4* mutations causing AIFEC affect the autoinhibitory domain of the protein, allowing for constitutive activation of the molecule (25). This results in ligand-independent, spontaneous activation of caspase-1 in cells transduced with mutant protein (23).

Familial cold autoinflammatory syndrome 4. H443P and S445P mutations in *NLRC4* give rise to a phenotype that is milder than AIFEC and consists of cold-induced urticaria and arthralgias (26, 27). Patients with the S445P mutation also develop uveitis. These mutations are in a different domain of the protein (the WHD domain) than the autoinhibitory domain mutations associated with AIFEC. IL-18 levels were also high in patients with the S445P mutation, and rather than the

neutrophilic rash of the FCAS/NLRP3 disease, these patients had a lymphohistiocytic infiltrate (27).

X-linked proliferative disease type 2. Loss-of-function mutations in the X-linked gene X-linked inhibitor of apoptosis protein (*XIAP*, also referred to as *BIRC4*) lead to a syndrome of X-linked proliferative disease type 2 (XLP2) characterized by hypogammaglobulinemia, lymphoproliferation/leukemia, HLH, uveitis, and inflammatory bowel disease (28). Patients may exhibit one or all of these symptoms. XIAP is a negative regulator of RIP3-induced IL-1β release and cell death, suggesting that it does regulate inflammasome activity; however, this appears to be a caspase-1-independent mechanism (29). This mechanism is dependent on tumor necrosis factor alpha (TNF-α) signaling. Interestingly, IL-18 levels are constitutively high in patients with XLP2 and increase further with disease exacerbations, suggesting yet another link to inflammasome regulation by XIAP (30).

CDC42 autoinflammatory disease. Two recent reports of patients with C-terminal mutations in CDC42 protein resulting in a syndrome of high IL-18, HLH, urticarial rash, and CNS disease have been published (31, 32). CDC42 does not have a direction connection to the inflammasome; rather, it is important in cytoskeletal organization and migration. It is interesting to note that, enzymatically, CDC42 is a Rho GTPase, recalling the connection between RhoA and the pyrin inflammasome. While CDC42 does not activate the pyrin inflammasome (10), it can act as a pathogen sensor in much the same way as RhoA, leaving open the possibility that it might connect to other inflammasomes as a bacterial sensor.

We have learned much from the study of the inflammasome both in health and in these genetic syndromes. Yet many questions remain, such as how these two cytokines, IL-1β and IL-18, can produce such a diversity of clinical presentations. It is particularly interesting to note that while the IL-18-opathies are clearly associated with HLH, diseases of IL-1β do not seem to have such a strong association. This may be related to the effects of IL-18 on the production of IFN-γ, a known central cytokine associated with HLH. Differential tissue location of the inflammasomes and their site of activation, and the tissue distribution in which the relevant cytokines act, may also be related to how different gene mutations present differently. Additionally, how the unique inflammasomes subtly differ from each other may be crucial to understanding how these different molecules perform their normal functions in health and their associated clinical presentations in disease. Structure/function studies, correlated with genotype/phenotype studies, have the potential to teach us how the inflammasomes operate at the molecular level and may potentially lead to targeted therapies.

INTERFERONOPATHIES

The type I interferons consist of the IFN-α family, IFN-β, and a number of other less-well-understood single family member IFNs, all of which signal though the type I IFN receptor. Initially described as a potential antiviral restriction factor (reviewed in 33), type I IFNs have now been implicated in the pathogenesis of a number of autoimmune diseases including systemic lupus erythematosus (34) and dermatomyositis (35) as well as in infections such as hepatitis C (36) and severe acute respiratory syndrome coronavirus 2 (37). An entire class of genetic syndromes that involve mutations resulting in constitutive production of type I IFNs has been described as the interferonopathies. These mutations typically result in the overactivation of cytosolic sensors of nucleic acids. These RNA or DNA sensors detect viral pathogens or the activation of genome integrated retroelements. These sensors are in balance with another set of proteins

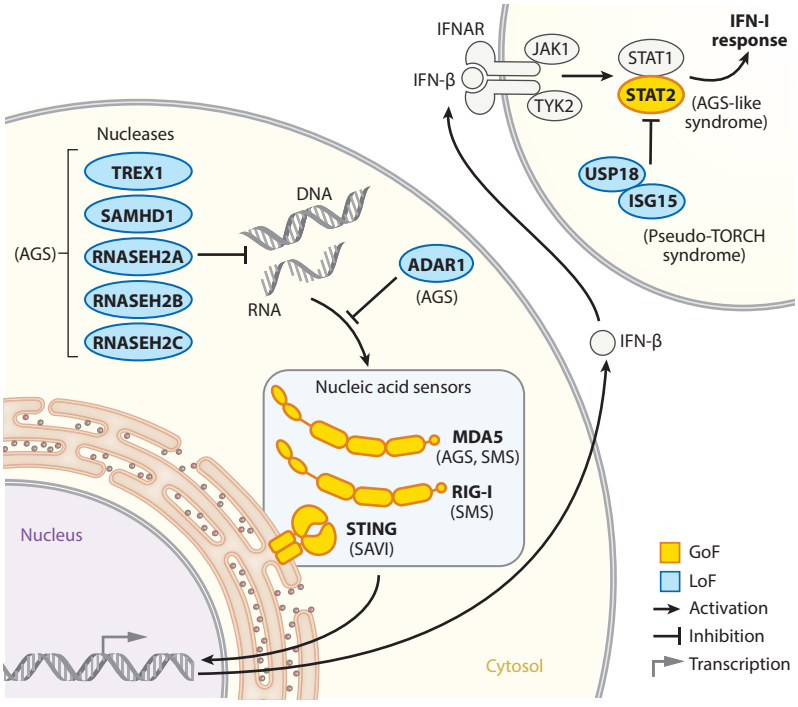

Figure 2

Interferonopathies. Specialized sensors such as MDA5, RIG-I, and STING detect the presence of nucleic acids in the cytosol and generate an IFN-I program in response. Secreted IFN-I such as IFN-β likewise activates an IFN-I response in adjacent cells via IFNAR through STAT1/2-mediated signaling. GoF mutations in these cytosolic sensors or downstream molecules in the IFN-I signaling pathway such as STAT2 lead to excess production of IFN-I and IFN-stimulated genes. LoF mutations in cytosolic nucleases or other inhibitory molecules lead to cytosolic accumulation of nucleic acids and overstimulation of this pathway. Abbreviations: AGS, Aicardi-Goutières syndrome; GoF, gain of function; IFN-I, type I interferon; IFNAR, IFN-α/β receptor; JAK1, Janus kinase 1; LoF, loss of function; SAVI, STING-associated vasculopathy with onset in infancy; SMS, Singleton-Merten syndrome; STING, stimulator of interferon genes; TORCH, toxoplasmosis, other, rubella, cytomegalovirus, and herpes simplex; TYK2, tyrosine kinase 2.

whose function is to degrade pathogenic nucleic acids in the cytosol. Thus, mutations that cause constitutive activation of the sensors, or mutations that cause loss of protective nuclease activity, result in overactivation of this system and the unbridled production of type I interferons. A number of different syndromes have been described with different genetic causes; in this review, we consider some archetypal examples (**Figure 2**).

Aicardi-Goutières Syndrome

Aicardi-Goutières syndrome (AGS) is primarily characterized by leukodystrophy/encephalopathy accompanied by a variety of other symptoms including liver inflammation and skin rash. AGS may present as an early onset disease, with poor feeding and jittery behaviors from birth, or as late onset, with symptoms developing months after birth. It has been observed that symptoms of AGS can mimic congenital infection syndromes, perhaps due to the type I IFNs that are produced with those infections as well. Conceptually, AGS genetics can be grouped into three classes of genes:

loss of function of nuclease/nucleotide editing activity, gain of function of nucleic acid sensors, and gain of function of interferon-α/β receptor (IFNAR) signaling.

Loss of function of nuclease genes including *TREX1*, *SAMHD1*, *RNASEH2A*, *RNASEH2B*, and *RNASEH2C* results in AGS (38). Nucleic acid products of DNA replication, cell death, DNA repair, and transcription all require breakdown and clearance for homeostasis. When these clearance functions are not operational, a buildup of nucleic acid products results; in turn, these nucleic acid products are sensed by the cytosolic sensors as pathogenic, and type I IFNs are produced. Similarly, loss of function of *ADAR1* results in the inability to edit adenosine bases in RNA to inosine by deamination. Typically, the activity of *ADAR1* on RNAs would prevent the RNA from binding to the RNA sensors. When this function is lost, there is an increased burden of RNAs able to be sensed and, therefore, increased type I IFN production. To date, the only gain-of-function nucleic acid sensor mutation in AGS includes *IFIH1*, which encodes the MDA5 protein, a cytosolic double-strand RNA (dsRNA) sensor (39).

IFNAR signaling uses Jak1 and Tyk2 as its proximal kinases to phosphorylate STAT1 and STAT2. Mutations that affect this pathway can also result in interferonopathy. STAT2 gain-of-function mutations present with an AGS-like syndrome (40). USP18 and its positive regulator ISG15 act to limit IFNAR signaling through as-yet-unclear mechanisms (41). Loss-of-function mutations of these molecules also lead to an AGS-like syndrome, which in the case of USP18 is known as pseudo-TORCH syndrome due to its similarity in presentation to the TORCH (toxoplasmosis, other, rubella, cytomegalovirus, and herpes simplex) congenital infections (42, 43).

Singleton-Merten Syndrome

Singleton-Merten syndrome (SMS) is another rare interferonopathy presenting as dental dysplasia, aortic calcification, skeletal abnormalities, glaucoma, and psoriasis. The disease is caused by gain-of-function mutations in *IFIHI1* (44) as well as in the gene *DDX58*, which encodes the dsRNA sensor RIG-I (45). Both MDA5 and RIG-I signal through mitochondrial antiviral signaling (MAVS) protein (46). It remains unclear how different mutations in *IFIH1* might result in different phenotypes.

STING-Associated Vasculopathy with Onset in Infancy

Gain-of-function mutations in *TMEM173*, which encodes the protein stimulator of interferon genes (STING), result in a syndrome of early onset cutaneous vasculopathy, fever, and interstitial lung disease known as STING-associated vasculopathy with onset in infancy (SAVI) (47). STING is a cytosolic DNA sensor, which induces a type I IFN response upon activation. Gain-of-function mutations lead to hyperactivation of this function and excessive type I IFN production. It is interesting to note that although this is a nucleic acid sensor defect, just as in AGS, different organs are primarily involved, with the lungs being the predominant organ in SAVI and the brain in AGS. The mechanism that results in these differences remains unclear.

Understanding the fundamental molecular mechanism of the interferonopathies, that is, excessive type I IFN signaling, usually by nucleic acid sensors, has led to targeted therapies for these diseases. Targeting signaling of the type I IFN receptor via Janus kinase blockade has been described to have efficacy (48). Targeting the burden of nucleic acids in patients with loss of function of nucleases has also been attempted with success. Suppressing endogenous retroelements by inhibiting their reverse transcription using the same types of drugs used to treat human immunodeficiency virus infection has shown promise as an approach (49). The number of different phenotypes that can result from defects in regulation of these overlapping pathways raises the

question of how this heterogeneity arises. Clearly, additional work is needed to understand how these different sensors and their regulators generate these differential effects.

There remains a large number of patients with what appear to be molecularly undefined interferonopathy-like diseases, on the basis of systemic inflammation and evidence of excessive interferon response by measurement of interferon-inducible gene expression. Whether these cases are defects in genes in the three classes outlined above or whether additional classes of defects exist that can result in interferonopathies remains an open question. As a highly regulated system, type I IFN biology has an enormous surface area of interactions that could potentially contribute to disease. Furthermore, it is interesting to consider how polygenic IFN-associated inflammatory diseases such as systemic lupus erythematosus or dermatomyositis might have variants in these same genes that may contribute to risk.

UNFOLDED PROTEIN RESPONSES/ENDOPLASMIC RETICULUM STRESS SYNDROMES

Normal handling of misfolded proteins in the endoplasmic reticulum (ER) is crucial to homeostasis (50). A major pathway for this process is the ER-associated protein degradation pathway that shuttles misfolded proteins that would have been destined for secretion or the plasma membrane instead to the proteasome for degradation (51). When this system is stressed by overload, ER sensors can detect the accumulation of misfolded products and generate the unfolded protein response (UPR). The UPR is a complex system of signaling, with three different branches, each of which is capable of intersection with multiple immune regulators including inflammasomes (52) and type I IFNs (53). It is therefore not surprising that gene defects that either result in excessive accumulation of unfolded proteins or make their breakdown less efficient result in autoinflammation. Because the UPR intersects with many of the inflammatory pathways described above, it is also not surprising that the clinical presentation of these conditions would mimic either inflammasomopathies or interferonopathies. We consider a few archetypal examples in this section (**Figure 3**).

Proteasome-Associated Autoinflammatory Syndromes

Proteasome-associated autoinflammatory syndromes (PRAAS) represent a collection of gene mutations in the 20S proteasome that share a similar clinical phenotype. The literature contains a number of alternate names for these syndromes depending on the group that described the syndrome or particular gene mutation. These include chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; Nakajo-Nishimura syndrome; POMP-related autoinflammation and immune dysregulation disease; and joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy (54–57). We consider these conditions as a group and refer to them as PRAAS from here forward. PRAAS is traditionally considered under the group of interferonopathies, given the observation of increased interferon-inducible gene signatures in these conditions. Yet, clinically, PRAAS appears quite different from the syndromes described above, with the absence of leukodystrophy and the presence of neutrophilic skin inflammation and lipodystrophy as prominent features. While it seems that type I IFN almost certainly contributes to inflammation in this setting, PRAAS may not represent a pure interferonopathy, as the UPR intersects with many other immune effector functions as well. The exact mechanisms by which the UPR in PRAAS causes IFN-dependent and -independent inflammation remain an area of active research (58).

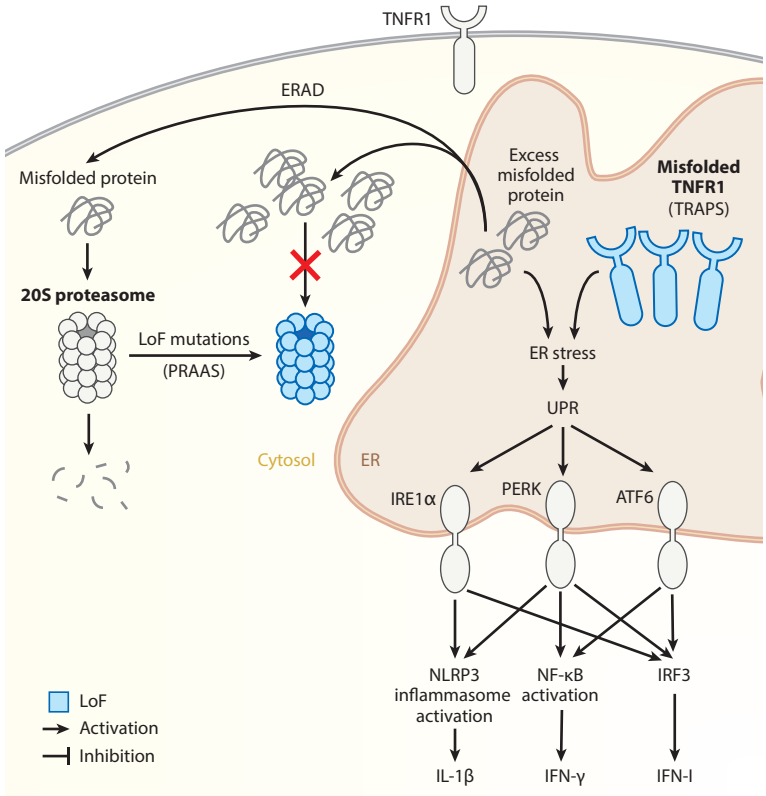

Figure 3

UPR/ER stress syndromes. ERAD normally eliminates misfolded proteins from the ER by targeting them for degradation in the proteasome. Misfolded proteins may accumulate in the ER due to LoF mutations in subunits of the 20S proteasome inhibiting ERAD or, in the case of TRAPS, TNFR1 mutations causing protein oligomerization within the ER. This ER stress activates the three arms of the UPR: IRE1α, PERK, and ATF6. These in turn lead to activation of the NLRP3 inflammasome and transcription factors NF-κB and IRF3, resulting in production of proinflammatory cytokines. Abbreviations: ATF6, activating transcription factor 6; ER, endoplasmic reticulum; ERAD, endoplasmic-reticulum-associated protein degradation; IFN-I, type I interferon; IL, interleukin; IRE1α, inositol-requiring enzyme 1-α; IRF3, interferon regulatory factor 3; LoF, loss of function; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PERK, protein-kinase-R-like ER kinase; PRAAS, proteasome-associated autoinflammatory syndromes; TNFR1, tumor necrosis factor receptor 1; TRAPS, tumor necrosis factor receptor–associated periodic syndrome; UPR, unfolded protein response.

Tumor Necrosis Factor Receptor–Associated Periodic Syndrome

Mutations in *TNFRSF1A*, the gene encoding tumor necrosis factor receptor 1 (TNFR1), result in a periodic fever syndrome associated with joint, muscle, and abdominal pain and rash known as TNF receptor–associated periodic syndrome (TRAPS). Amyloidosis occurs with long-standing uncontrolled disease. This is an autosomal dominant disorder, and causative mutations lie exclusively in the extracellular domain of the receptor (59). The mechanisms by which these mutations cause disease have been a matter of controversy over the two decades during which this syndrome has been described. Work demonstrating that a common feature of nine different TRAPS mutations

is that the receptor is abnormally oligomerized and is retained in the ER suggests that perhaps a UPR response to this protein may also be induced (60). Importantly, the low penetrance/noncausal R121Q (R92Q) variant of *TNFRSF1A* does not show this intracellular retention in the ER, suggesting that severity of disease is related to improper folding and ER retention. Peripheral blood mononuclear cells from TRAPS patients do show some evidence of a UPR, although they are not complete responses, suggesting a nontraditional activation (61). Only 30% of patients treated with etanercept (a TNFR decoy receptor) show a complete response (62). Treatment with TNF-α blocking monoclonal antibodies does not seem to help and may in fact worsen disease (63). In contrast, IL-1β blockade seems to have significant efficacy; a large body of literature supporting this finding culminated in a successful phase III trial (64). This suggests that TNF-α may not be playing a direct role in pathogenesis, despite the mutation in its receptor. Rather, an unrelated downstream event, such as a UPR inducing inflammasome-directed IL-1β release, may be driving inflammation.

It is quite possible that there are many other UPR-related autoinflammatory diseases that are as of yet unrecognized. While defects in the UPR machinery itself may be easier to detect from genetic screens, individual cases of misfolded proteins may be harder to recognize on the basis of genotype alone. TRAPS provides an interesting example where the first inclination, because of the immune nature of the gene involved, is to invoke immune pathways related to the gene itself. Yet, further study reveals that the defect may not be due to altered function of the TNF pathway but rather due to a UPR induced by the abnormal protein. These types of mutations may be hard to screen for on a purely informatic basis. Therefore, it may be prudent to consider functional UPR screens in the assessment of autoinflammatory syndromes where identified genetic lesions may not make immediate immunologic sense. Developing such assays for clinical use remains an unmet need.

RELOPATHIES

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a family of transcription factors responsible for controlling the transcription of a large number of inflammatory mediators. There are a large number of upstream positive and negative regulators of NF-κB activity, and their dysfunction in turn can lead to excessive function and transcription of NF-κB regulated genes and autoinflammation. Because of the fact that NF-κB family members have a Rel homology domain in their N terminus, diseases resulting from NF-κB hyperactivation are termed relopathies. Many of these genetic defects are in deubiquitinases, as linear ubiquitination is an activating modification of the NEMO protein complex that lead to NF-κB activation. These diseases do not necessarily share overlapping clinical phenotypes between different genetic lesions, likely owing to the very complex signaling network of NF-κB activation; however, they often share some combined element of immunodeficiency and autoinflammation (**Figure 4**).

Haploinsufficiency of A20

TNF alpha-induced protein 3 (TNFAIP3) encodes the deubiquitinase known as A20. Nonsense or truncating mutations in TNFAIP3 lead to a clinical syndrome known as haploinsufficiency of A20 (HA20) that consists of oral and genital ulcers, arthritis, ocular inflammation, and fevers (65, 66). Interestingly, patients also develop signs of immunodeficiency with recurrent infections as well as autoimmunity in the form of antinuclear antibodies and even immune complex glomerulonephritis, demonstrating the heterogeneity of disease even within a single genetic entity. Treatment with IL-1, TNF-α, and IL-6 blockade has been described (65).

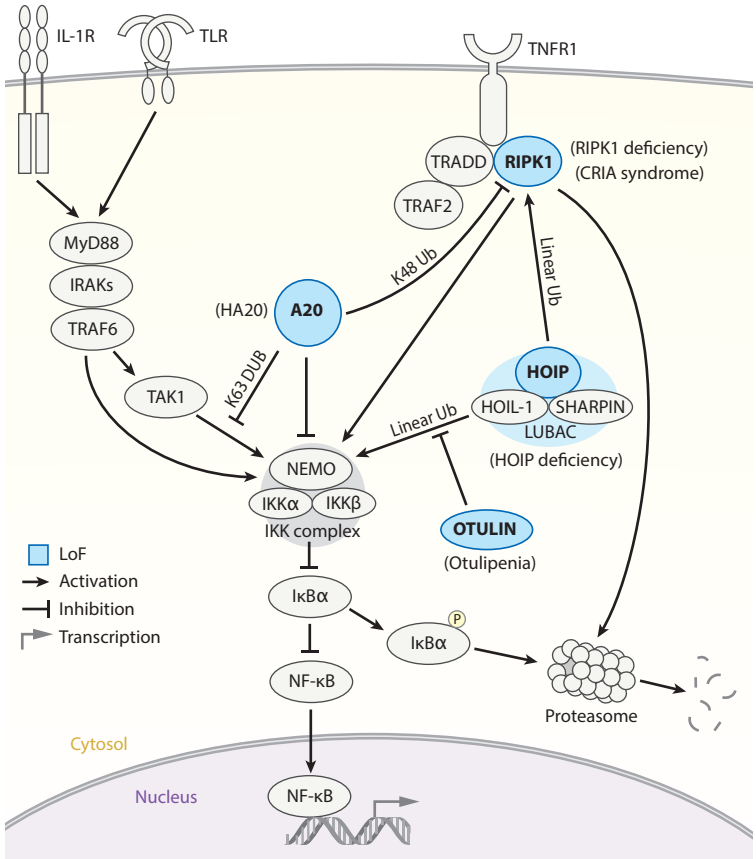

Figure 4

Relopathies. NF-κB is activated through the canonical pathway via activation of the IKK complex, which phosphorylates IκBα, thereby targeting it for proteasomal degradation and releasing NF-κB to translocate to the nucleus. IKK can be activated by a number of cytokine and pathogen recognition receptors. LoF mutations in negative regulators of this pathway lead to excess NF-κB activation and transcription of proinflammatory genes. Abbreviations: CRIA, cleavage-resistant RIPK1-induced autoinflammatory; DUB, deubiquitinase; HA20, haploinsufficiency of A20; IKK, IκB kinase; IL-1R, interleukin-1 receptor; LoF, loss of function; LUBAC, linear ubiquitination chain assembly complex; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; P, phosphorylation; RIPK1, receptor interacting protein kinase 1; TLR, Toll-like receptor; TNFR1, tumor necrosis factor receptor 1; Ub, ubiquitination.

Otulipenia

Loss-of-function mutations in *FAM105B*, which encodes the protein Otulin, another deubiquitinase capable of acting on the NEMO complex, lead to a syndrome known as otulipenia (67). Clinical features include fever, nodular or pustular rash, lipodystrophy, joint/muscle pain, and lymphadenopathy. In general, the inflammation is more severe than what is seen in HA20. Reported experience with treatment has been limited, with steroids being the mainstay of therapy with the addition of cytokine blockade.

HOIP Deficiency

Biallelic missense mutations in the *RNF31* gene encoding the protein HOIP, a component of the linear ubiquitination chain assembly complex responsible for ubiquitination of NEMO (68, 69), lead to HOIP deficiency. Patients exhibit autoinflammation, immunodeficiency, subclinical amylopectinosis, and systemic lymphangiectasia. Studies from patient fibroblasts suggest that the mutations result in a loss of function of linear ubiquitination, pointing out the complexity of the relopathies, where both loss and gain of ubiquitination result in inflammation.

Receptor Interacting Protein Kinase 1 Mutations

RIPK1 is a kinase that intersects with multiple immune pathways downstream of Toll-like receptors and the TNF-α receptor. It is an important mediator of activation of the linear ubiquitination complex that activates NEMO. Biallelic mutations in RIPK1 that result in loss of function have been reported to cause a syndrome of recurrent infections, early onset inflammatory bowel disease, and progressive polyarthritis (70). In these patients, a combination of immunodeficiency and autoinflammation occurs, likely due to a complex phenotype of decreased mitogen-activated protein kinase activation and NF-κB activation, resulting in decreased lipopolysaccharide (LPS)-induced TNF-α and IL-6 but increased IL-1β production. This highlights the complex nature of many of these diseases, where patients can present with a mixed picture of immune dysregulation.

Heterozygous mutations at amino acid position D324 in RIPK1 that prevent its cleavage by caspase-8 result in a syndrome of early onset periodic fevers and intermittent lymphadenopathy that has been termed cleavage-resistant RIPK1-induced autoinflammatory syndrome (71). In mice bred homozygously, these same mutations led to fetal demise (71). In heterozygous mice, the mutation leads to resistance to TNF-α-induced cell death and results in increased TNF-α, IL-6, and IL-1β production after LPS stimulation. Interestingly, patients did not respond to TNF-α inhibition but did show a good response to IL-6 blockade.

UNCATEGORIZED SYNDROMES

There are other important examples of monogenic autoinflammatory diseases that do not yet seem to belong to a larger category. These may be suggestive of other related mutations yet to be found or may simply represent single entities by themselves. There are a large number of examples of these uncategorizable inflammatory syndromes, which grows yearly. A few interesting and illustrative examples are provided here, as covering the entire spectrum of these genetic disorders is beyond the scope of this review.

Deficiency of Adenosine Deaminase 2

Patients presenting with a syndrome of early onset stroke, systemic vasculopathy, organomegaly, and livedoid rash were discovered to have homozygous mutations in the *CERC1* gene that encodes adenosine deaminase 2 (ADA2) (72). This syndrome, known as deficiency of ADA2, was noted to have similarity to polyarteritis nodosa and therefore represents an interesting example of inherited vasculitis, although the neurologic events did not appear to be vasculitic and rather were hemorrhagic. The pathogenic mechanism remains an area of intense study. ADA2 is an extracellular enzyme that converts adenosine into inosine. Effects on endothelial cell function and leukocyte development have been shown (72). Interestingly, treatment with TNF-α blockade had a dramatic effect on reducing stroke (73).

Autoinflammation and PLCγ2-Associated Antibody Deficiency and Immune Dysregulation

A family affected by blistering skin lesions, bronchiolitis, arthralgia, ocular inflammation, enterocolitis, and mild immunodeficiency in a dominant inheritance pattern was discovered to harbor a variant in PLCγ2, an important signaling molecule downstream of the B cell receptor (74). Not surprisingly, these patients had defects in class-switched memory B cells. These patients' symptoms and mutations were distinct from those described for PLCγ2-associated antibody deficiency and immune dysregulation (PLAID) (75). The mutations in PLAID are thought to result in a loss of autoinhibition by complete deletion of the SH2 domain of PLCγ2, which paradoxically results in negative feedback inhibition and decreased signaling through PLCγ2 during physiologic homeostasis. In contrast, autoinflammation and PLAID (APLAID) mutations are point mutations thought to compromise autoinhibition partially but not enough to induce negative feedback, therefore resulting in increased PLCγ2 signaling in homeostasis. PLAID patients do suffer from cold-induced urticaria, an autoinflammatory-like symptom, but otherwise have a phenotype more related to B cell/antibody dysfunction. In APLAID, patients did not have significant autoantibodies, suggesting that the inflammation in APLAID is in line with autoinflammatory, not autoimmune, pathology. APLAID is an important example of a defect in the adaptive immune system that can lead to autoinflammation, breaking down the paradigm that autoinflammation must result from innate immune defects.

Hyper IgD Syndrome

Mutations in mevalonate kinase (MVK) are associated with hyper IgD syndrome (HIDS), an autosomal recessive syndrome of periodic fever, abdominal pain, arthralgia/arthritis, and elevated IgD levels (76). MVK is important in the biosynthesis of isoprenoids, which are cholesterol-based lipids that can influence many different inflammatory pathways. Complete loss of MVK results in the metabolic disease of mevalonic aciduria, the symptoms of which are predominantly related to the metabolic defect but can also come with febrile crises (77). Pathogenic mechanisms remain undetermined; however, one explanation may be that the mutations render the enzyme more susceptible to temperature (78). Thus, incidental fevers lead to loss of enzymatic activity, further dysregulation of isoprenoids, and therefore more inflammation and fever in a feed-forward cycle. Blockade of IL-1 has reported efficacy in many HIDS patients, suggesting a connection between this isoprenoid metabolism and inflammasome activation (62, 79). HIDS remains an important example of a metabolic defect translating into autoinflammatory disease.

DIAGNOSTICS IN AUTOINFLAMMATORY DISEASE

The categorization above is not meant to be the only possible means to group together these diverse syndromes. Nor is the assignment of individual syndromes meant to be definitive, as there is overlap in mechanisms in many of these syndromes. However, the construct of broader groups of genetic autoinflammatory syndromes can be particularly useful in considering how the field might advance in diagnostics for these conditions. Whole-exome sequencing (WES) and now whole-genome sequencing (WGS) have revolutionized the care of these patients, since given the phenotypic overlaps, it is difficult to make a diagnosis on clinical presentation alone. WES has allowed for the rapid identification of mutations for patients suffering from autoinflammatory symptoms, leading in turn to more rapid initiation of targeted therapy. Yet, there remain a significant number of patients clearly suffering from autoinflammation for whom clinical WES does

not provide a genetic diagnosis. There is an urgent need to expedite answers for these patients. The difficulty of identifying variants of unknown significance and assigning causality to them is an impediment to the process. The search space is large, and often there are many variants to consider. By using a framework such as the one presented in this review, the search space may be made more manageable. That is, looking specifically for defects in inflammasome, NF-κB, UPR, or interferon regulatory pathways in the correct clinical contexts may help guide discovery. More importantly, continuously expanding and refining these categories will make this task even higher yield, making continued research in this area critical.

Perhaps the most pressing need is the availability of clinical-grade functional immunologic testing to probe the pathways related to autoinflammation. Even if a genetic variant is unknown in a particular patient, functional demonstration of dysregulation in a pathway can guide both diagnosis and treatment. For instance, the ability to detect excessive type I IFN production through assessment of IFN-responsive gene signatures, or UPRs, or to detect excessive NF-κB signaling at baseline and with stimulation, could suggest a disorder in these pathways even without a genetic diagnosis. Indeed, such findings might prompt closer inspection using WES/WGS to find such types of genetic defects. Many such assays remain available only as research-based testing to clinicians who are connected to a research apparatus. This situation makes these tests inaccessible to many patients who are unable to receive care at these institutions, a particular concern as we consider equity issues in healthcare accessibility and delivery. Functional immunologic testing is technical, requires interpreted tests, and often involves specialized laboratories or equipment. All of these features make setting up an assay challenging and expensive. However, considering the costs of the diagnostic odysseys and empiric therapeutic trials that patients endure, from a systems perspective it makes sense to figure out how we can better bring this type of testing to patients to deliver more efficient care.

From a therapeutic perspective, the array of immune-modulatory and immunosuppressive medications is growing at a dizzying pace. A large number of cytokines or their receptors may be inhibited with monoclonal antibodies, decoy receptors, or receptor antagonists, including IL-1, IL-2, IL-4, IL-5, IL-6, IL-12, IL-17, IL-23, TNF-α, and IFN-γ, among others. Small-molecule inhibitors of immune signaling pathways such as Jak, Syk, calcineurin, and mTOR are available. Cell-depleting therapies against B cells, T cells, and various subsets are available. This opens up the possibility of a precision medicine approach for autoinflammatory diseases if the patient's immune phenotype is understood. Even in the absence of a defined genetic diagnosis, diagnostics to assess either levels of or response to cytokines in the form of cytokine-inducible gene products can be used to guide the choice of therapy as well as the response. Flow cytometric–based assays of immune cell population number, as well as fate choice (e.g., Th1 versus Th17), also bear the potential to direct precision medicine approaches.

COMPARISON BETWEEN MONOGENIC AUTOINFLAMMATORY DISEASE AND POLYGENIC INFLAMMATION

While the focus of this review is on inborn errors of immunity that lead to inflammation, there are clearly many immune diseases that are not monogenic. Etiologic lessons from inherited autoinflammatory diseases may also apply to our understanding of polygenic or noninherited immune diseases. The spondyloarthropathies, a disease cluster that can include axial arthritis, enthesitis, psoriasis, and inflammatory bowel disease, may have UPRs driving some element of inflammation due to their association with HLA-B27 (80). Both systemic lupus erythematosus (81) and dermatomyositis (82) are associated with type I IFN activation. The NLRP3 inflammasome has been linked to pathogenesis in both gout and type 2 diabetes as a sensor of metabolic derangement that

leads to inflammation (83). Indeed, IL-1β blockade has been demonstrated to be efficacious in reducing gouty flares (84). Elevated IL-18 is associated with systemic juvenile idiopathic arthritis and may be a disease activity marker (85). Monogenic inborn errors of immunity present a unique opportunity to dissect mechanisms for immune diseases in general, and therapies that may work for these rare entities may well find use in more common noninherited diseases of immune dysregulation.

CONCLUSION

Inherited autoinflammatory diseases encompass a wide array of symptoms, many of which overlap with each other, making precise clinical recognition difficult. Advances in molecular diagnostics, including WES and WGS, have made identification of described genetic conditions more rapid and accurate. Mechanistic research into how such genetic defects lead to autoinflammation has allowed for categorization into syndromes of similar etiology. These categories also often have overlap, such as the fact that mutations of the proteasome, leading to ER stress responses, result in a type I IFN response that is similar to the interferonopathies. Thus, not only symptoms but also molecular mechanisms may overlap, highlighting the continued need to advance molecular diagnostics, which are the final arbiter of categorization. While exome analysis has become increasingly advanced, much remains to be done to make complete genome analysis reliably sensitive as we work to understand how to interpret the noncoding elements of the genome. Likewise, challenges remain in interpreting missense mutations, particularly in the case of possible unfolded protein syndromes such as TRAPS. Advances in bioinformatics will continue to increase the speed at which we can become successful in those endeavors.

On the other hand, continued refinement of the basic biology of autoinflammation can also give us clues on where to look for genetic answers. By narrowing the search space to the common etiologic themes of autoinflammation, we may be able to more rapidly identify additional genetic causes of disease. This makes understanding the entirety of the broad categories of autoinflammatory disease all the more important. Surely, the categories presented in this review are not exhaustive, and more categories remain to be elucidated. Overlaps with other categories of disease, such as the cytotoxic defects of hyperinflammatory syndromes, must also be considered. Pairing this conceptual framework with actionable assays of immune function is essential. Assays for inflammasome dysfunction; ubiquitination dysfunction; UPRs; cytokine levels and responsive signatures; and cell differentiation, development, and effector functions would all represent significant advances that would also narrow the search space for molecular diagnoses for patients. While there has been some increased availability of such tests, these assays still remain out of reach for most patients and represent an important unmet clinical need for the field. Continued research across the spectrum of modalities, including fundamental mechanisms of inflammation, genotype/phenotype correlations, and clinical presentation and treatment response, will be important in advancing the care of patients suffering from autoinflammatory disease.

DISCLOSURE STATEMENT

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