Monogenic autoinflammatory disorders: Conceptual overview, phenotype, and clinical approach

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Activity Objectives:

1. To recognize distinguishing clinical patterns within the spectrum of autoinflammatory disorders.
2. To categorize and summarize the major categories of autoinflammatory disorders based on their molecular mechanisms.
3. To select targeted or empiric treatment options based on underlying molecular mechanisms and/or clinical phenotypic presentations of autoinflammatory disorders.

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Autoinflammatory diseases are conditions in which pathogenic inflammation arises primarily through antigen-independent hyperactivation of immune pathways. First recognized just over 2 decades ago, the autoinflammatory disease spectrum has expanded rapidly to include more than 40 distinct monogenic conditions. Related mechanisms contribute to common conditions such as gout and cardiovascular disease. Here, we review the basic concepts underlying the "autoinflammatory revolution" in the understanding of immune-mediated disease and introduce major categories of monogenic autoinflammatory disorders recognized to date, including inflammasomopathies and other IL-1–related conditions, interferonopathies, and disorders of nuclear factor kappa B and/or aberrant TNF activity. We highlight phenotypic presentation as a reflection of pathogenesis and outline a practical approach to the evaluation of patients with suspected autoinflammation. (J Allergy Clin Immunol 2020;146:925-37.)

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Abbreviations used
AGS: Aicardi-Goutières syndrome
AR: Autosomal recessive
CAPS: Cryopyrin-associated periodic syndrome
COPA: COPI Coat Complex Subunit Alpha
DITRA: Deficiency of IL-36 receptor antagonist
FMF: Familial Mediterranean fever
HA20: Haploinsufficiency of A20
JAK: Janus kinase
JAKinhibs: JAK inhibitors
MKD: Mevalonate kinase deficiency
NF-κB: Nuclear factor kappa B
PFAPA: Periodic fever, aphthous stomatitis, pharyngitis, adenitis
PLAID: Phospholipase C gamma 2–associated antibody deficiency and immune dysregulation
PRAAS: PRoteasome-associated autoinflammatory syndrome
STING: Stimulator of interferon genes
TRAPS: TNF receptor–associated periodic syndrome
USP18: Ubiquitin-specific protease 18

AUTOIMMUNITY VERSUS AUTOINFLAMMATION

In 1901, the German immunologist Paul Ehrlich recognized an important theoretical downside to the immune system's capacity to recognize specific targets—namely, the possibility that errors could translate into immune attack on self. He used the now-famous phrase "horror autotoxicus" to describe what he presumed to be an absolute aversion to such self-targeting.[1] However, evidence in favor of immune mistakes emerged rapidly, and by the 1950s disease-causing autoantibodies had been clearly demonstrated.[2-4] Autoimmunity is now recognized as a core mechanism of human disease, arising when antigen-specific components of adaptive immunity—T cells, B cells, and antibodies—mistakenly target autologous tissues as though they were foreign. Hundreds of autoimmune diseases are now recognized, impacting every organ system and affecting at least 3% of the population.[5] Allergic diseases similarly reflect aberrant antigen-directed immunity, albeit directed against innocuous targets from the environment.

However, adaptive immunity is only one arm of immune defense. From an evolutionary point of view, the ability to generate antigen specificity through genetic recombination was a late development, originating in distinct but related systems in the jawless and jawed vertebrates approximately 500 million years ago (Fig 1).[6,7] For the vast majority of species, immunity against pathogens is "hard-wired" into the organism's genetic code. In humans, innate immune mechanisms include lineages such as neutrophils, macrophages, mast cells, natural killer cells, and innate-like lymphocytes; cell-surface and intracellular pattern recognition mechanisms such as Toll-like receptors; and soluble defensive proteins such as C-reactive protein and complement. If inflammatory disease can arise through adaptive immune mistakes, it is plausible to suppose that it might also develop through dysfunction in these antigen-independent pathways.

Obvious as this possibility appears in retrospect, it is only in the last 2 decades that diseases originating through excesses of innate immunity have been recognized. This new understanding began with the discovery that familial Mediterranean fever (FMF) arose from mutations in *MEFV*, encoding pyrin, a protein expressed predominately by innate lineages.[8,9] Subsequent genetic dissection of a second heritable inflammatory disease, TNF receptor–associated periodic syndrome (TRAPS) arising from mutant *TNFRSF1A*, enabled the insight that FMF and TRAPS represented a new category of disease.[10] Daniel Kastner et al[10] originated the concept of *autoinflammatory disease* to denote inflammatory disorders that arise through mechanisms distinct from autoimmunity and distinguished by features such as absence of autoantibodies.

Since its introduction in 1999, the term "autoinflammation" has been used widely but variably. Here, we define an autoinflammatory disease as one in which *pathogenic inflammation arises primarily through antigen-independent hyperactivation of immune pathways*. The monogenic autoinflammatory diseases represent loss-of-function mutations in genes that suppress inflammation or gain-of-function mutations in genes that propagate inflammation, resulting in immune activation spontaneously or with minimal triggering. Broadly, autoinflammatory diseases reflect disorders of innate immunity, whereas autoimmune and allergic diseases represent disorders of adaptive immunity. However, this simplistic division is at best a first approximation. Innate and adaptive immunity are densely interconnected, and dysfunction in one often disturbs function in the other. For example, some diseases now considered autoinflammatory feature autoantibodies. T and B cells may mediate and theoretically even initiate autoinflammatory diseases, as long as activation does not reflect antigen-targeted misrecognition of self. Although the clearest examples of autoinflammation so far have been monogenic, it is likely that there are also autoinflammatory diseases that arise through defects in many genes (polygenic).

Autoinflammation represents one axis of immune dysfunction, together with autoimmunity/allergy and immunodeficiency (Fig 2). Allergists/immunologists are likely to encounter autoinflammation in the course of the evaluation of patients with fever, rash, lung disease, and other disease manifestations that can reflect aberrant immunity. Patients with primary immunodeficiencies may exhibit autoinflammation in addition to impaired immunocompetence, and patients with autoinflammation may paradoxically experience recurrent infections. For these reasons, as specialists in immune dysfunction, allergists and immunologists need to be prepared to provide a medical home to these complex patients.

CATEGORIES OF AUTOINFLAMMATORY DISEASES

Theoretically, there could be as many autoinflammatory diseases as there are immune pathways. Indeed, the last decade has witnessed an explosion of new autoinflammatory disorders, and more remain to be discovered. Many of these conditions engage multiple pathways and fit into several pathogenic categories.[11] The first autoinflammatory disease recognized, FMF, is an inflammasomopathy; other autoinflammatory diseases arise through defects affecting IFN, nuclear factor kappa B (NF-κB), and/or aberrant TNF activity, and miscellaneous mechanisms (Fig 3).[12-31] New categories of autoinflammatory disease will no doubt emerge over time.

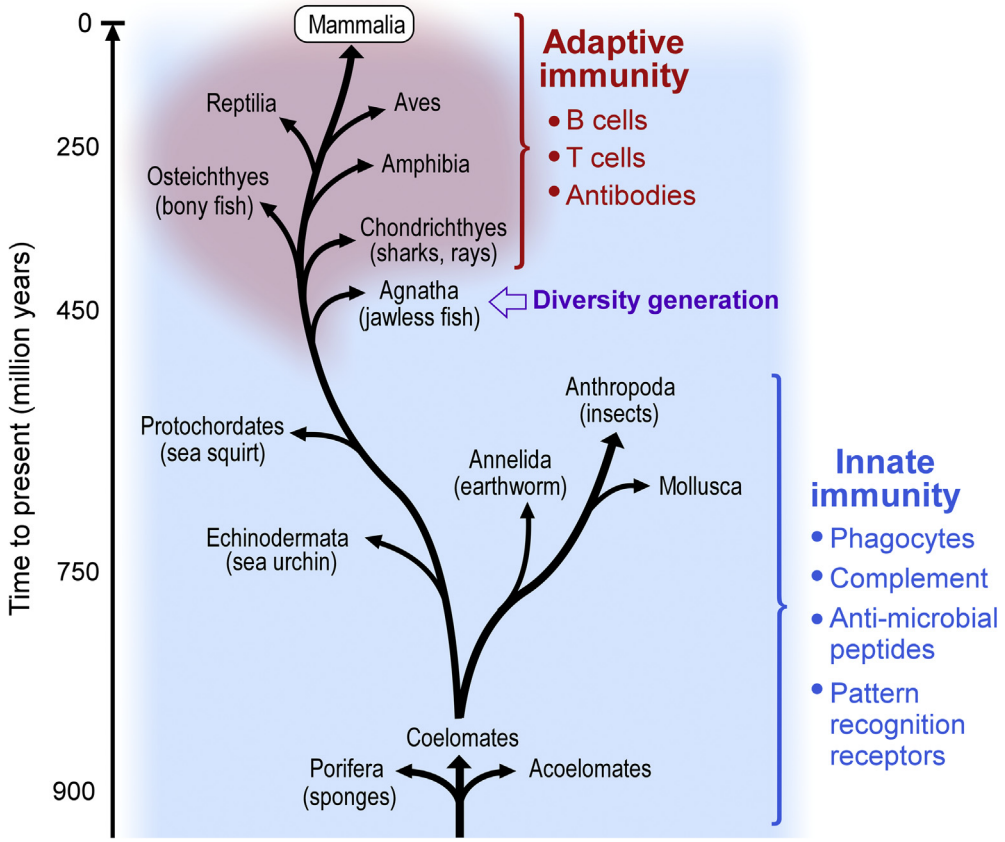

FIG 1. Innate and adaptive immunity in evolution. Simplified evolutionary tree of animal phyla depicting the development of adaptive immunity at the stage of jawless fishes. Adapted with permission from Porcelli.[6]

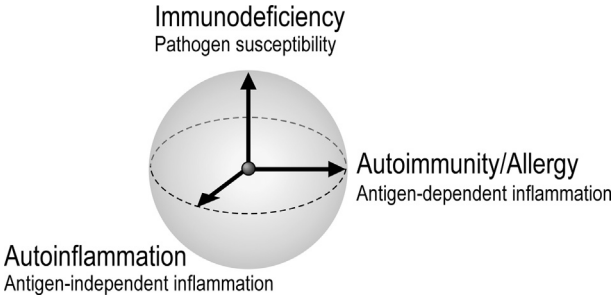

FIG 2. Three axes of immune dysfunction. Schematic representation of conceptually orthogonal ways in which dysregulated immunity leads to human disease: autoinflammation (aberrant antigen-independent immune activation), autoimmunity/allergy (aberrant antigen-dependent immune activation), and immunodeficiency (defects in innate or adaptive immunity resulting in inadequate defense against pathogens). For simplicity, the axes are depicted as beginning at a common origin reflecting normal immune function. However, some immune states might potentially cross this origin, as for example enhanced resistance to plague in individuals bearing mutant *MEFV*.

Inflammasomopathies and other diseases arising through IL-1-family cytokines

The inflammasomes are a family of protein complexes that activate caspase-1, also called IL-1–converting enzyme, leading to proteolytic activation of IL-1β and IL-18. Caspase-1 also cleaves gasdermin D, which then forms membrane pores that release these cytokines into the extracellular milieu and allow solute entry to trigger a proinflammatory form of cell death termed pyroptosis. The inflammasome forms when a core nucleating protein changes conformation in response to a cytoplasmic danger signal, resulting in prion-like assembly of ASC (Apoptosis-associated Speck like protein containing a Caspase recruitment domain) proteins, which in turn coordinate reciprocal activation of multiple caspase-1 molecules. Multiple inflammasomes are well established, defined by their nucleating proteins including pyrin, cryopyrin (NLRP3/NALP3), NLRC4, NLRP1, and AIM2. Inflammasomopathies arise from mutations in these genes or in genes encoding direct or indirect inflammasome regulators, leading to inappropriate nucleation of the inflammasome complex.[32] The molecular mechanisms underlying the activation of different inflammasomes in the setting of disease may include cytoskeletal dysregulation for pyrin or redox stress or phosphorylation for cryopyrin.[33-35] Clinical differences among the inflammasomopathies reflect the nature and severity of the genetic defect, as well as the cellular distribution of a particular inflammasome and its substrates, helping to determine the predominant downstream mediator. For example, pyrin and cryopyrin are expressed widely in innate immune lineages, as is their substrate pro–IL-1β. Overactivity of these inflammasomes therefore manifests as widespread immunopathology mediated primarily through IL-1β. In contrast, the NLRC4 inflammasome is expressed in the gut lining (among other locations), where its substrate pro–IL-18 predominates over pro–IL-1β, contributing to

	Mechanism	Disease	Gene	Inheritance	Clinical presentation	Targeted therapy
Inflammasomopathies and other IL-1 family conditions	Pyrin activation	FMF	*MEFV*	AR or AD	fever, pain, (abdominal, chest, joint), rash	IL-1, colch.
		PAAND	*MEFV*	AD	fever, myalgia, myositis, rash, abscesses	IL-1, colch.
		MKD	*MVK*	AR	fever, pain (abdominal, extremity), vomiting, rash	IL-1
		PAPA	*PSTPIP1*	AD	pyoderma gangrenosum, arthritis	IL-1, TNF
		Hz/Hc[12]	*PSTPIP1*	AD	rash, FTT, hepatosplenomegaly, neutropenia	IL-1, TNF
		PFIT[13]	*WDR1*	AR	fever, infection, oral inflammation, perianal ulceration	IL-18
	Cryopyrin activation	FCAS	*NLRP3*	AD	cold urticaria, extremity pain, conjunctivitis, fever	IL-1
		MWS	*NLRP3*	AD	urticarial rash, extremity pain, hearing loss, conjunctivitis, fever	IL-1
		NOMID	*NLRP3*	AD	CNS inflammation, urticaria, knee arthropathy, fever	IL-1
		Majeed's[14]	*LPIN2*	AR	osteomyelitis, fevers, rash, dyserythropoietic anemia	IL-1
	NLRC4 activation	AIFEC	*NLRC4*	AD	enterocolitis, rash, arthritis, fever	IL-1, IL-18
		FCAS/ NOMID	*NLRC4*	AD	cold urticaria, extremity pain, fever, CNS disease	IL-1
	NLRP12 activation	FCAS	*NLRP12*	AD	cold urticaria, extremity pain, fever	TNF, IL-1
	NLRP1 activation	NAIAD[15]	*NLRP1*	AD	Ocular, laryngeal, skin dyskeratosis, fever, arthritis	IL-1, TNF
	Receptor antagonist deficiency	DIRA	*IL1RN*	AR	pustular rash, osteomyelitis, periostitis, fever,	IL-1
		DITRA	*IL36RN*	AR	pustular psoriasis, fever, malaise	TNF, IL-17/12/23?
Type I Interferonopathies	Nucleic acid processing and degradation	Aicardi-Goutières syndrome	*TREX1, ADAR1, RNASEH2A/B/C, SAMHD1, IFIH1*	AR (AD: *IFIH1*)	fever, neurologic decline, encephalopathy, cerebral calcification, chilblains, autoantibodies	JAK, RTI?
		monogenic SLE	*DNASE1/2/1L3, complements*	AR (AD: *DNASE1*)	autoantibodies, cytopenias, glomerulonephritis, skin rash, oral ulcers, arthritis	JAK?
	Nucleic acid sensing	SMS	*IFIH1, DDX58a*	AD	calcification of aorta / cardiac valves, osteopenia, acro-osteolysis, dental anomalies	JAK?
		SAVI	*TMEM137*	AD	Chilblain's rash, small vessel vasculitis, arthritis, ILD	JAK
	Proteasome	CANDLE / PRAAS, PRAID[16]	*PSMB4, PSMA3, PSMB8, POMP, PSMG2,PSMB9, PSMB10*	Digenic, AR (AD: POMP)	fever, joint contractures, annular plaques, eyelid swelling, hepatosplenomegaly, lipodystrophy, FTT, developmental delay, anemia	JAK
	IFN signaling	AGS-like	*USP18, ISG15, STAT2*	AR	skin ulcerations, seizures, hydrocephalus, cerebral calcifications, respiratory failure	JAK
	other	SPENCD[17]	*ACP5*	AR	skeletal dysplasia, short stature, cerebral calcification, cytopenias, autoantibodies	?
NF-κB and/or aberrant TNF activity	dysregulation of NFκB signaling	HA20	*TNFAIP3*	AD	oral, gastrointestinal and genital ulcerations, fever, arthritis, recurrent infection	TNF, IL-1, JAK?
		RELA haploinsuf.[18]	*RELA*	AD	oral and gastrointestinal ulcerations, cytopenias, lymphoproliferative disease	TNF
		ORAS	*OTULIN*	AR	fever, panniculitis, diarrhea, arthritis, FTT	TNF
		LUBAC deficiency[19,20]	*HOIL1, HOIP*	AR	fever, recurrent infection, FTT, hepatosplenomegaly, amylopectin-like deposits in muscles	TNF?
	Dysregulation of TNF	Blau	*NOD2*	AD	granulomatous dermatitis, uveitis, polyarticular arthritis	TNF
		TRAPS	*TNFRSF1A*	AD	episodic fever, abdominal pain, headache, conjunctivitis, painful centrifugal rash	IL-1, TNF
		DADA2	*ADA2*	AR	systemic vasculitis, fever, rash, stroke, cytopenias, hypogammaglobulinemia	TNF, HSCT
		CRIA[21,22]	*RIPK1*	AD	fever, lymphadenopathy, hepatosplenomegaly	IL-6?

FIG 3. The monogenic autoinflammatory diseases. Presented are a simplified representation of disease mechanism classification, causative gene, heritability, major clinical manifestations, and typical treatment options for a representative range of monogenic autoinflammatory diseases. *AD,* Autosomal dominant; *AIFEC,* autoinflammation with infantile enterocolitis; *APLAID,* autoinflammation and PLAID; *AR,* autosomal recessive; *CANDLE,* Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature; *CNS,* central nervous system; *CRIA,* cleavage-resistant RIPK1-induced autoinflammatory syndrome;

	Mechanism	Disease	Gene	Inheritance	Clinical presentation	Targeted therapy
Other mechanisms	Golgi-ER transport	COPA	*COPA*	AD	arthritis, ILD, diffuse alveolar hemorrhage, autoantibodies	IL-17? JAK?
	Intracellular calcium signaling	PLAID	*PLCG2*	AD	cold urticaria, atopy, granulomatous dermatitis, hypogammaglobulinemia, infection, autoantibodies	?
		APLAID	*PLCG2*	AD	blistering skin lesions, ILD, bronchiolitis, eye inflammation, enterocolitis, immunodeficiency	?
	tRNA biogenesis	SIFD[23]	*TRNT1*	AR	fever, developmental delay, seizures, microcytic anemia hypogammaglobulinemia	TNF
	Lipid metabolism? ER stress?	LACC1 deficiency[24,25]	*LACC1/FAMIN*	AR	fever, systemic JIA, oligoarticular/polyarticular JIA	?
	Cytokine dysregulation	VEO-IBD[26,27]	*IL-10, IL10RA, IL10RB*	AR	Early-onset colitis, FTT	HSCT, IL-1?
	Actin assembly	ARPC1B deficiency[28, 29]	*ARPC1B*	AR	platelet abnormalities, bleeding, recurrent infection, small vessel vasculitis, eczema, arthritis	?
	Actin polymerization	CDC42 deficiency[30,31]	*CDC42*	AR	Neurodevelopmental defects, facial dysmorphism cytopenias, recurrent infection, fever, rash	IL-1

FIG 3. *(Continued).*

severe colitis mediated in part by IL-18, although IL-1β also plays a role. Mutations affecting the NLRP3 inflammasome inhibitor CARD8 (also called Cardinal) can manifest as inflammatory bowel disease.[36] NLRP1 is expressed mainly in skin, such that overactivity presents as primarily skin pathology (Multiple Self-healing Palmoplantar Carcinoma and Familial Keratosis Lichenoides Chronica, not discussed further here).[37] No AIM2-driven inflammasomopathy has yet been reported.

Pyrin inflammasomopathies. *FMF* is the most common of the monogenic autoinflammatory disorders, due to the high carrier frequency of *MEFV* mutations in specific populations from the Mediterranean region. FMF is classically considered autosomal recessive, because most affected patients carry 2 mutations; however, it is perhaps better regarded as autosomal dominant with limited penetrance, on the basis of families with clear autosomal-dominant inheritance, affected patients (up to 30%) with only 1 detectable mutation, and evidence from *Mefv* mutant mice indicating that causal mutations are gain of function.[38,39] Multiple founder mutations and high prevalence reflect enhanced resistance to pathogens that evolved mechanisms to neutralize conventional pyrin inflammasome assembly, including the agent of plague, *Yersinia pestis*.[40,41] Patients typically present in childhood, with episodes lasting 2 to 3 days of fever, abdominal and/or chest pain, occasional erysipelas-like lower extremity rash, monoarticular arthritis, neutrophilia, and elevated inflammatory markers. The primary long-term morbidity is amyloidosis, most frequently affecting the kidneys. *Pyrin-associated autoinflammation with neutrophilic dermatosis* is a dominantly inherited disease due to unique activating mutations in *MEFV*.[42] Patients present in childhood with recurrent episodes lasting weeks and characterized by rashes including sterile skin abscesses, but also fever, myalgia, myositis, and elevated acute-phase reactants similar to FMF. Some patients exhibit abdominal pain. Maintenance colchicine therapy is the standard of care for these 2 related disorders, although pyrin-associated autoinflammation with neutrophilic dermatosis often responds only partially. IL-1–targeted therapies can be effective, and TNF inhibitor response is also reported.[42-44]

Mevalonate kinase deficiency (MKD), also called *hyper-IgD syndrome*, is classified as a pyrin inflammasomopathy because disease pathophysiology is mediated by dysregulation of the pyrin regulatory factor RhoA.[45] MKD is autosomal recessive, consistent with mutations in *MVK* being loss of function. A founder mutation in northern Europe accounts for its prevalence in the Netherlands and northern France. Patients often present in childhood (usually infancy), with episodes lasting 5 to 7 days of fever, abdominal pain, vomiting, rash, and elevated inflammatory markers. Vaccines are frequent triggers for these episodes. Serum IgD and IgA levels are often elevated, and urine mevalonate may be elevated. IL-1 inhibitors are somewhat effective but may require aggressive dosing.[43]

DADA2, deficiency of adenosine deaminase 2; *DIRA*, deficiency of IL-1 receptor antagonist; *ER*, endoplasmic reticulum; *FAMIN*, fatty acid metabolism-immunity nexus; *FTT*, failure to thrive; *Haploinsuf.*, haploinsufficiency; *HSCT*, hematopoietic stem cell transplant; *HOIL1*, heme-oxidized IRP2 ubiquitin ligase 1; *HOIP*, HOIL1-interacting protein; *Hz/Hc*, hyperzincemia/hypercalprotectinemia; *ILD*, interstitial lung disease; *JIA*, juvenile idiopathic arthritis; *LACC1*, Laccase Domain Containing 1; *MWS*, Muckle-Wells syndrome; *NOMID*, neonatal-onset multisystem inflammatory disease; *ORAS*, OTULIN-related autoinflammatory syndrome; *PAAND*, pyrin-associated autoinflammation with neutrophilic dermatosis; *PAPA*, Pyogenic Arthritis, Pyoderma gangrenosum and Acne; *PFIT*, periodic fever, immunodeficiency, and thrombocytopenia; *PLAID*, PLCG2-associated antibody deficiency and immune dysregulation; *PLCG2*, phospholipase C gamma 2; *PRAAS*, PRoteasome-associated autoinflammatory syndrome; *PRAID*, POMP-related autoinflammation and immune dysregulation disease; *RTI*, reverse-transcriptase inhibitor; *SAVI*, STING-associated vasculopathy of infancy; *SIFD*, sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay; *SLE*, systemic lupus erythematosus; *SMS*, Singleton-Merten syndrome; *SPENCD*, spondyloenchondrodysplasia; *tRNA*, transfer ribonucleic acid; *VEO-IBD*, very early onset inflammatory bowel disease.

Pyogenic Arthritis with Pyoderma gangrenosum and Acne (PAPA) is an autosomal-dominant disorder due to mutations in *PSTPIP1*, encoding a protein that binds and likely activates pyrin.[46] It usually presents in childhood with sterile arthritis and systemic inflammation, whereas cutaneous features develop in adolescence or young adulthood. Patients typically respond to IL-1 or TNF blockade, although some may require aggressive dosing or a combination therapy.[47]

Cryopyrin (NLRP3) inflammasomopathies. *Cryopyrin-associated periodic syndrome* (CAPS) is a continuum of previously defined autoinflammatory syndromes of increasing severity including *familial cold autoinflammatory syndrome* (FCAS), *Muckle-Wells syndrome*, and *neonatal-onset multisystem inflammatory disease*. The lines between these subphenotypes are blurry. Most patients with CAPS possess heterozygous germline or somatic gain-of-function mutations in *NLRP3,* with a fairly consistent genotype-phenotype correlation such that specific mutations predict clinical features and severity along the disease continuum. Patients with very similar clinical presentations but without easily defined *NLRP3* mutations may either have *NLRP3* mutations that are difficult to detect due to somatic mosaicism or mutations in genes with related function including *NLRP12, NLRC4*, and *factor 12*.[48,49] For most patients with CAPS, symptoms begin within the first year of life, although rarely presentation is delayed until adulthood. Common symptoms include urticaria-like rash, fever, arthralgia, myalgia, headache, and conjunctivitis, usually in the context of persistent systemic inflammation indicated by neutrophilia and elevated acute-phase reactants. At the severe end of the spectrum, chronic sterile meningitis results in cognitive impairment and hearing loss. Features that may distinguish each subphenotype include cold sensitivity in FCAS, amyloid A amyloidosis in Muckle-Wells syndrome, and significant central nervous system and bone disease in neonatal-onset multisystem inflammatory disease. IL-1 blockade is the standard of care, and most patients respond when dosed adequately.[48]

NLRC4 inflammasomopathy. Patients with *NLRC4* gain-of-function mutations may present with CAPS-like symptoms, but the classic presentation is a disease termed *autoinflammation with infantile enterocolitis* characterized by early-onset hyperinflammation (discussed elsewhere in this issue) involving rash, joint symptoms, severe intestinal disease, and hepatosplenomegaly.[50,51] Patients exhibit systemic inflammation including hyperferritinemia, cytopenias, and laboratory evidence of liver and kidney injury, resembling macrophage activation syndrome. IL-1 inhibitors may be helpful, but accumulating evidence supports a central role for IL-18.[52]

NLRP12-related disease. The initial description of patients with heterozygous mutations in *NLRP12* resembled the *NLRP3*-associated FCAS phenotype, resulting in this disease being referred to as *FCAS2*.[53] Despite similar domain structure and cell expression patterns of NLRP12 and NLRP3, the function of these proteins may be different. Although reliable reports suggest that NLRP12 can form an active inflammasome, NLRP12 also regulates NF-κB, placing this condition at a border with disorders discussed further below and potentially explaining a lack of complete response to IL-1 blockade, in particular because disease-associated mutations in *NLRP12* are generally loss of function.[53-55] Expanded access to genetic sequencing has seen the phenotype of *NLRP12* mutations broaden to include other autoinflammatory phenotypes as well as immunodeficiency and autoimmunity, implying diverse roles for NLRP12.

Deficiency of IL-1-family cytokine antagonists. A common feature of the IL-1 cytokine family (including IL-1α, IL-1β, IL-18, and IL-36) is the presence of endogenous circulating antagonists. These include IL-1 receptor antagonist (available in recombinant form as anakinra) and a similar receptor antagonist for IL-36 termed IL-36 receptor antagonist. Deficiency of either protein results in an autoinflammatory disease. *Deficiency of IL-1 receptor antagonist*, due to biallelic mutation of *IL1RN,* results in neonatal-onset pustulosis, multifocal osteomyelitis, and periostitis due to excess IL-1 signaling.[56,57] As expected, deficiency of IL-1 receptor antagonist is managed effectively by anakinra.[56,58] *Deficiency of IL-36 receptor antagonist* (DITRA) from mutations in *IL36RN* causes generalized pustular psoriasis, because IL-36 receptor is expressed primarily in the skin and other epithelial cells in contact with the environment.[59] Some of the original patients with deficiency of IL-1 receptor antagonist also had DITRA due to large deletions involving these contiguous genes.[56,57,60] DITRA flares are accompanied by fever, malaise, neutrophilia, and elevated inflammatory markers.[61] Although recombinant IL-36 receptor antagonist is not yet available, DITRA can be effectively managed by biologics that target TNF, IL-17, or IL-12/23.[62] The efficacy of IL-1 inhibition is variable.[62,63] IL-18 has 2 antagonists, circulating IL-18 binding protein and the anti-inflammatory IL-1–family cytokine IL-37; diseases arising from defects in these mechanisms are not yet described.

Interferonopathies

IFNs are a family of cytokines involved in immune defense. Three IFN families are recognized. *Type I IFNs* encompass IFN-α, IFN-β, and other members, involved in antiviral defense and signaling through the type I IFN receptor and its signal transduction kinases Janus kinase (JAK) 1 and TYK2. *Type II IFNs* are limited to IFN-γ, a cytokine implicated in multiple aspects of adaptive and innate immunity that signals via the type II IFN receptor and its kinases JAK1 and JAK2. *Type III IFNs*, termed IFN-λ, are less well understood and signal through a distinct receptor that shares kinases with the type I IFN receptor. To date, autoinflammatory diseases related to IFN—commonly known as the interferonopathies—reflect aberrant activation of type I pathways, though in the future type II and type III interferonopathies may be recognized.

The (type I) interferonopathies represent conditions in which the type I IFN axis is aberrantly activated.[64] IFN-α/-β production is triggered by viral DNA or RNA, and correspondingly interferonopathies often arise through defects in nucleic acid sensing or through accumulation of host nucleic acid or other intracellular debris that mimic chronic viral infection. Alternately, mutations may aberrantly amplify type I IFN receptor signaling. Clinically, patients with interferonopathies often exhibit fever (type I IFNs are potent endogenous pyrogens), rash, and systemic inflammation, frequently together with skin vasculitis and basal ganglia calcifications (Fig 3). Interestingly, many of these diseases feature autoantibodies, highlighting the lack of a sharp divide between autoinflammatory and autoimmune disorders.

Disorders of degradation or processing of endogenous nucleic acids. Recognition of type I IFN-mediated autoinflammation originated with studies of *Aicardi-Goutières*

syndrome (AGS), a group of inherited disorders characterized by early-onset neurologic decline, encephalopathy, cerebral calcification, and sometimes fevers and systemic inflammation.[65] Vasculopathy manifesting as cold-induced chilblains and livedo reticularis are common skin manifestations.[66] Patients with AGS display variable features of autoimmunity, ranging from low-titer autoantibodies and mild cytopenias to the full clinical spectrum of systemic lupus erythematosus. Seven types of AGS have been defined on the basis of causative genes: *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR1*, and *IFIH1*.[67] With the exception of *IFIH1*, which amplifies IFN signaling (see below), these genes participate in nucleic acid processing, and loss of function translates into accumulation of endogenous nucleic acids. Most patients with AGS present early in life, but asymptomatic individuals (incomplete penetrance) and delayed presentation with milder disease are well recognized, suggesting a role for modifier genes and environmental factors. Additional genes implicated in type I interferonopathy through aberrant nucleic acid handling include DNA-degrading enzymes (DNAse1, DNAse2, and DNAse1L3) that are associated with monogenic forms of lupus, potentially reflecting constitutive recognition of accumulated intracellular host DNA triggering pathways engaged by DNA viruses.[68]

JAK inhibitors (JAKinibs) disrupt JAK signaling downstream of the IFN receptor complex. JAKinibs that preferentially target JAK1/2 (ruxolitinib and baricitinib) or JAK1/3 (tofacitinib) have shown therapeutic efficacy in AGS, with improvement in quality of life, growth, inflammatory markers, autoimmune manifestations, and corticosteroid dependency.[69-71] Neurologic damage in AGS is likely irreversible, but early treatment may attenuate decline. Intriguingly, one source of stimulatory nucleic acid for some AGS subtypes may be activation of endogenous retroviral elements; a recent study demonstrated successful use of nucleoside analogue reverse-transcriptase inhibitors to suppress the IFN signature in patients with AGS, especially those with RNASEH-complex mutations.[72]

Disorders of enhanced nucleic acid sensing. Melanoma differentiation antigen 5 (encoded by *IFIH1*) and retinoic acid–inducible gene I (encoded by *DDX58*) are members of the retinoic acid–inducible gene I–like receptor family that sense viral nucleic acids and activate type I IFN production.[73] Gain-of-function mutations in *IFIH1* cause an autosomal-dominant form of AGS (type VII), characterized in some patients by psoriasis and pulmonary hypertension in addition to the classic AGS findings.[74,75] Other gain-of-function mutations in *IFIH1* and *DDX58* cause *Singleton-Merten syndrome*, a distinct interferonopathy characterized by aortic and valvular calcification, osteopenia, acro-osteolysis, and dental anomalies.[76,77]

STING-associated Vasculopathy of Infancy (SAVI) is a syndrome of vasculitis rash, arthritis, and interstitial lung disease caused by gain-of-function mutations of *TMEM137*, which encodes stimulator of IFN genes (STING).[78] Although the vasculopathy of SAVI can resemble AGS, interstitial lung disease distinguishes STING from most other interferonopathies, likely reflecting tissue-specific effects of STING expression in the lung. JAKinibs can be effective, but their impact on the IFN signature is variable, corresponding generally to an incomplete clinical response.[70,79]

Disorders of proteasome function. The proteasome is a multimeric protein complex that degrades ubiquitinated proteins both in steady-state and with cell activation. Production of type I IFN by immune cells can be driven by proteasome dysfunction, as shown by experiments using proteasome inhibitors.[80] Mutations that disrupt proteasome subunits or chaperone proteins involved in proteasome assembly, either recessive or digenic affecting different components, are associated with the diseases *Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature* (CANDLE) syndrome and *PRoteasome-Associated Autoinflammatory Syndrome* (PRAAS).[80-82] Patients with these syndromes typically present during infancy with recurrent fever, annular violaceous plaques, violaceous eyelid swelling, hepatosplenomegaly, lipodystrophy, and failure to thrive; patients with PRAAS may also have panniculitis. A strong type I IFN signature is present in the peripheral blood, but unlike AGS, clinical features of autoimmunity are uncommon.[83] The JAKinibs baricitinib and ruxolitinib can partially ameliorate clinical manifestations and laboratory abnormalities; corticosteroids and methotrexate are also used.[70,84]

Disorders of amplified IFN receptor signaling. Ubiquitin-specific protease 18 (USP18) is an endogenous inhibitor of type I IFN signaling that binds to one of the type I IFN receptor chains, IFNAR2, to block JAK1 activation. Deficiency of USP18 causes an aggressive interferonopathy with severe brain inflammation.[85] ISG15 is a stabilizer of USP18, such that ISG15 deficiency causes a related interferonopathy characterized by brain calcifications and seizures through insufficiency of USP18.[86] The recruitment of USP18 to IFNAR2 requires a binding site on STAT2, and severe early-onset interferonopathy arises from *STAT2* mutations that disrupt the interaction with USP18.[87,88] JAK inhibition with ruxolitinib led to remarkable improvement in 1 patient with USP18 deficiency.[89]

Disorders of NF-κB and/or aberrant TNF activity

The NF-κB complex is a central signaling hub within the cytoplasm, integrating signals from multiple cell surface and intracellular danger sensors, upon which one of several transcription factors is freed to move to the nucleus where it triggers coordinated expression of proinflammatory genes. Regulation of NF-κB is correspondingly complex, involving a set of sensor proteins, inhibitory proteins, and ubiquitin-dependent functional modifications.[90,91] Defects in any of these pathways can lead to aberrant activation of NF-κB. Hallmark clinical features of the "NFκBopathies" (sometimes termed the Relopathies, because RelA and RelB are key components of the NF-κB complex) are fever, systemic inflammation, and sometimes granuloma formation.[92] Key upstream activators of NF-κB activation include receptors in the TNF family, which engage this pathway both via canonical (degradation of the NF-κB inhibitor IκBα) and noncanonical (variant NF-κB complex formation) pathways.[93] NF-κB activation also results in TNF production. Thus, NF-κB and TNF are closely intertwined, helping to define a subgroup of autoinflammatory diseases that often respond at least partially to TNF blockade (Fig 3).

Haploinsufficiency of A20. *TNFAIP3* encodes the protein A20, a ubiquitin-editing enzyme that functions as a negative regulator of NF-κB. *Haploinsufficiency of A20* (HA20) causes recurrent oral and genital ulcers that mimic Behcet disease with relapsing and remitting disease.[94] Other phenotypes include early-onset autoimmunity and immunodeficiency including a presentation similar to autoimmune lymphoproliferative syndrome.[95] PBMCs from patients with HA20 show overproduction of TNF and IL-1β, and biologics targeting these cytokines are

often used in severe cases. Although NF-κB and type I IFN are nonredundant pathways, patients with HA20 may exhibit elevated expression of IFN signature genes that parallels disease activity, potentially reflecting a regulatory role of A20 in IFN signaling as well as the induction of IFN-β by TNF.[96,97] Importantly, the presence of a type I IFN signature predicted a good response to JAKinib treatment in HA20 cases that were resistant to anticytokine treatment.[98]

Blau syndrome. Gain-of-function mutations in the cytoplasmic sensor *NOD2* result in *Blau syndrome,* an autosomal-dominant disease characterized by arthritis, uveitis, and granulomatous dermatitis.[99] Patients usually present early in life (before age 5 years) with skin rash as the initial manifestation. The arthritis associated with Blau syndrome is typically symmetric, with marked synovitis but not always erosions, and affecting wrists, ankles, knees, and fingers.[100] Additional manifestations of Blau syndrome are central nervous system inflammation, interstitial pneumonitis, liver inflammation, and vasculitis. TNF inhibitors can be highly effective, whereas response to IL-1 blockade is inconsistent.[101]

TNF receptor–associated periodic syndrome. TRAPS is a dominantly inherited recurrent fever disorder due to mutations in *TNFRSF1A*, encoding TNF receptor 1.[10] Usually beginning in childhood, patients experience episodes lasting 2 to 4 weeks, which include fever, abdominal and muscle pain, headache, and conjunctivitis, without response to colchicine. Hallmark features are a tender centrifugal rash and periorbital edema. Chronic elevation of inflammatory markers corresponds to an increased risk of systemic amyloidosis. The mechanism of disease remains incompletely understood. Although failure to shed TNF receptor was initially suspected, aberrant trafficking or signaling of mutant TNF receptor 1 leading to inflammasome activation appears to be a more accurate disease mechanism. Etanercept (soluble TNF receptor 1) therapy can be successful in some patients, but efficacy is frequently lost and—paradoxically—anti-TNF antibodies such as infliximab can worsen disease.[10,102,103] IL-1 blockade is more consistently effective and has become standard of care, suggesting a role for the inflammasome in disease pathophysiology.[48]

Deficiency of adenosine deaminase 2. Biallelic mutations in *ADA2* result in a syndrome that variably features systemic vasculitis, early-onset stroke, cytopenias, and immunodeficiency.[104,105] Vasculitis in deficiency of adenosine deaminase 2 (ADA2) can resemble the medium vessel vasculitis polyarteritis nodosa. TNF is the predominant driver of inflammation, because TNF inhibitors are strikingly effective at treating vasculitis and preventing stroke.[106] Mutations with residual ADA2 function tend to be associated with stroke and other inflammatory manifestations responsive to TNF inhibition, whereas mutations that abrogate gene function manifest as profound immunodeficiency and hematologic compromise, often not responsive to TNF inhibitors; bone marrow transplant should be considered for this subset of patients.[107] The physiologic function of ADA2 is not clear, but appears to be different from that of ADA1 and ADAR (double-stranded RNA-specific adenosine deaminase) based on the unique biochemical properties and clinical consequences of mutations in these genes.[108]

Autoinflammation mediated by other mechanisms

The mechanisms by which disordered immune function can lead to inflammatory pathology are potentially as numerous as the list of genes involved in immune function. Some autoinflammatory diseases have yet to fall into an established pathogenic category, or to establish a category of their own (Fig 3).

COPI Coat Complex Subunit Alpha syndrome. Coatomer protein subunit α, encoded by COPI Coat Complex Subunit Alpha (*COPA*), is a part of coat protein complex I, which regulates retrograde transport from the Golgi to the endoplasmic reticulum. Mutations in *COPA* cause an autosomal-dominant syndrome of autoimmunity, inflammatory arthritis, interstitial lung disease, and diffuse alveolar hemorrhage.[109] Endoplasmic reticulum stress from disrupted intracellular trafficking skews effector T cells toward a T_H17 phenotype. Patients with COPA may also have a type I IFN signature, raising the possibility that it is an interferonopathy.[110] Consistent with this finding, COPA has been found to regulate normal trafficking of STING.[111,112] However, a murine model implicated autoreactive T cells derived through abnormal thymic function, suggesting that COPA might be a monogenic autoimmune disease in addition to (or rather than) a monogenic autoinflammatory condition, illustrating the challenge of distinguishing unambiguously between categories of immune dysfunction.[113] Numerous immunosuppressive agents have been trialed in COPA syndrome with variable success.[114] JAKinib treatment was effective in 1 patient with COPA with severe arthritis, although the type I IFN signature was not assessed.[115]

Phospholipase C gamma 2–associated antibody deficiency and immune dysregulation/autoinflammation and phospholipase C gamma 2–associated antibody deficiency and immune dysregulation. *Phospholipase C gamma 2–associated antibody deficiency and immune dysregulation* (PLAID) further exemplifies the intersection of autoinflammation, autoimmunity/allergy, and immunodeficiency (Fig 2). Phospholipase C gamma 2 hydrolyzes phosphatidylinositol-4,5-bisphosphate into diacylglycerol and inositol trisphosphate, triggering calcium release from the endoplasmic reticulum to mediate cell activation.[116] In PLAID, heterozygous genomic deletions in the autoinhibitory domain of phospholipase C gamma 2 cause constitutive enzyme activation and enhanced signaling at cold temperatures. Clinical features include cold urticaria, atopy, granulomatous dermatitis, hypogammaglobulinemia, recurrent sinopulmonary infection, and variable manifestations of autoimmunity.[117] A constellation of autoinflammatory features was later found in patients with heterozygous missense mutations in these autoinhibitory regions. This combined phenotype of autoinflammation and PLAID is characterized by recurrent blistering skin lesions, interstitial pneumonitis and bronchiolitis, eye inflammation, enterocolitis, cellulitis, and immunodeficiency.[118,119] Treatment for PLAID includes cold avoidance, antihistamines, and antibiotic prophylaxis and/or intravenous immunoglobulin for immunodeficiency.[120] Experience with autoinflammation and PLAID is limited, but corticosteroids, hydroxychloroquine, and IL-1 inhibitors have not shown sustained efficacy.[119]

Disorders of complement. Complement is a system of plasma proteins and related cell-surface regulators that serves multiple functions in innate immunity, including recognition and clearance of pathogens. Coordinated closely with adaptive immunity, the complement system plays a key role in antibody-dependent pathogen targeting and in clearance of immune complexes. Defects in complement or its surface inhibitory proteins result in pathogenic conditions including immunodeficiency, early-onset systemic lupus erythematosus, and age-

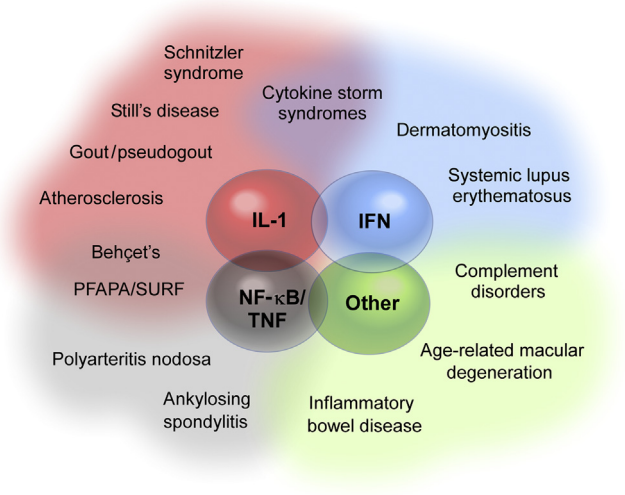

FIG 4. The autoinflammatory penumbra. Major families of autoinflammatory disorders include the inflammasome/IL-1 diseases, the interferonopathies, the NF-κB/TNF disorders, and autoinflammation mediated by other mechanisms. Many other human diseases exhibit clinical and/or mechanistic overlap with these disease families without perhaps being best conceptualized as primarily autoinflammatory; some of these are depicted in a shaded zone (penumbra) surrounding the monogenic autoinflammatory diseases. *SURF*, Syndrome of undifferentiated recurrent fever.

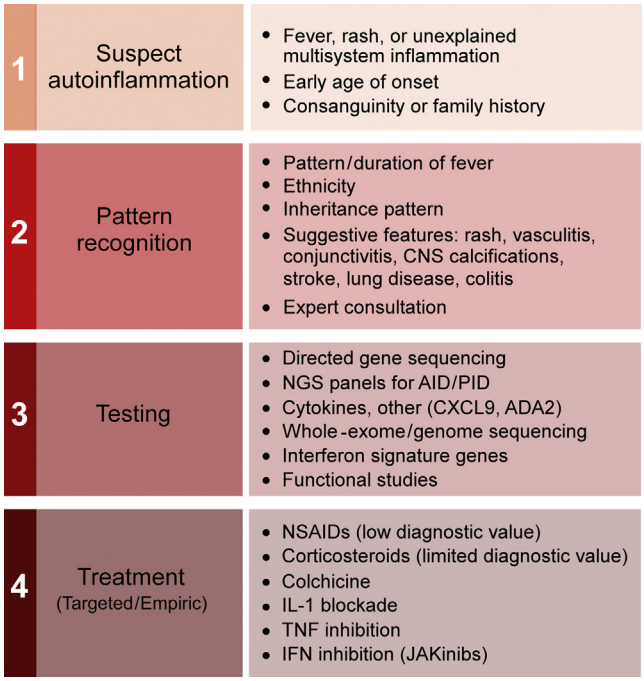

FIG 5. Clinical approach to patients with suspected autoinflammation. Please see text for discussion of each step. *AID*, Autoinflammatory disease; *ADA2*, adenosine deaminase 2; *CNS*, central nervous system; *CXCL9*, chemokine (C-X-C motif) ligand 9; *NSAID*, nonsteroidal anti-inflammatory drug; *PID*, primary immunodeficiency disease.

related macular degeneration. In some cases, these conditions represent inflammatory consequences of antigen-independent hyperactivation of immune pathways, fulfilling the definition of autoinflammatory diseases. Complement activation and its implications have been reviewed extensively and are not considered further here.[121]

THE "AUTOINFLAMMATORY PENUMBRA"

Diseases such as FMF, TRAPS, MKD, and CAPS seem at this point clearly autoinflammatory, but for some conditions the situation is less straightforward. Antigen-independent immune activation contributes to initiation or propagation of tissue injury in multiple diseases. Some diseases present with clinical features resembling those of autoinflammatory diseases, but understanding of pathogenesis remains too limited to draw firm conclusions. These conditions belong to the "autoinflammatory penumbra" (Fig 4).

Several examples illustrate the scope of this penumbra. Gout and pseudogout are mediated through activation of the cryopyrin inflammasome by monosodium urate and calcium phosphate dihydrate crystals.[122] Cholesterol crystals activate the same inflammasome, conferring an autoinflammatory element to atherosclerosis, consistent with the (modest) efficacy of IL-1β blockade in cardiovascular disease.[123-125] Ankylosing spondylitis is strongly associated with the MHC class I allele HLA-B27; this association may reflect the propensity of HLA-B27 to misfold and thereby trigger the unfolded protein response rather than its antigen specificity.[126] The pediatric disorders *Periodic fevers with aphthous stomatitis, pharyngitis, and adenopathy* (PFAPA) and *syndrome of undifferentiated recurrent fever* (SURF, an increasingly recognized group of patients who meet some but not all criteria for PFAPA), as well as the adult-onset *Schnitzler syndrome*, are commonly regarded as autoinflammatory because of their presentation with episodic fever.[127] For these conditions, the lack of a molecular understanding renders classification only provisional. For example, a recent study made the surprising observation that PFAPA exhibits genetic associations with the HLA region as well as other loci associated with T-cell function, findings that implicate antigen-directed immunity.[128] Systemic juvenile idiopathic arthritis and its adult counterpart adult-onset Still's disease are characterized by fever, rash, arthritis, and in many patients a brisk response to IL-1β blockade. These features resemble those of other autoinflammatory diseases, but an HLA association and characteristic changes in T cells suggest that (like PFAPA) this phenotype is unlikely to be "purely" autoinflammatory.[129-131] Inflammatory bowel disease likely reflects both immune hyperresponsiveness and defects in mucosal barrier function.[132]

The autoinflammatory penumbra is to be expected. Immune function is complicated, and it is not surprising that aberrant immune activity can manifest with varying combinations of autoinflammation, autoimmunity/allergy, and immunodeficiency. For example, FMF-associated mutations in *MEFV* are associated with an increased risk of rheumatoid arthritis and a higher prevalence of ankylosing spondylitis and vasculitis.[133-135] Patients with CDC42 deficiency, ARPC1B deficiency, or homozygous mutations in *WDR1* present with not only recurrent infections but also clinical features of autoinflammation (Fig 3). Most primary immune defects can be expected to yield a phenotype that resides somewhere within the autoinflammatory-autoimmunity/allergy-immunodeficiency spectrum rather than adhering tightly to a single axis alone (Fig 2).

CLINICAL APPROACH TO THE AUTOINFLAMMATORY DISEASES

Given the complexity of the autoinflammatory family, how can clinicians proceed to diagnosis and management without having to master each disease? We suggest a 4-step approach (Fig 5).

First, consider autoinflammation in the differential diagnosis. Several clinical features of inflammation facilitate disease recognition. Fever is common, albeit not invariable, as is elevation in inflammatory markers such as C-reactive protein and the erythrocyte sedimentation rate. Many patients have skin involvement, including evanescent or persistent rashes, sometimes with vasculitis. Inflammation typically affects many organ systems, sometimes including lungs and the gastrointestinal tract. Disease often begins early in life, and close relatives may have similar disease, suggesting a genetic etiology. Broadly, autoinflammation should be suspected in any patient—especially a child—with persistent or recurrent inflammatory episodes that fail to fit the pattern of other established diseases.

Second, recognize hallmarks of particular autoinflammatory diseases. Clinical history, physical examination, and laboratory/imaging studies remain essential to diagnosis. For example, recurrent episodes of fevers and abdominal pain lasting less than 48 hours in a patient with Middle Eastern heritage suggests FMF. An acral vasculitic rash and basal ganglia calcifications suggest an interferonopathy. Childhood-onset stroke with livedo suggests deficiency of adenosine deaminase 2. Where possible, clinicians with limited exposure to this disease family should seek help from colleagues with more experience recognizing clinical patterns within the autoinflammatory spectrum. For the more common periodic fever syndromes, validated classification criteria are available and provide useful guidance for diagnosis.[136]

Third, cast a broad net. Not all autoinflammatory diseases manifest in their canonical form. The therapeutic implications of correct diagnosis support a broad screen for autoinflammation-associated genetic mutations early in the evaluation of unexplained multisystem inflammation, using any of a range of commercial services that test a large panel of immune-related genes. Genetic findings require cautious interpretation because many variants of unknown significance will be irrelevant, whereas some described as likely benign could still represent low-penetrance causal variants. Commercial screens will miss noncoding mutations, copy number variants, complex chromosomal rearrangements, mutations in novel disease genes, and states of mosaicism in which the mutation affects only a subset of cells.[137] Genetic testing guidelines for the autoinflammatory diseases are available, and an updated list of variants and associated phenotypes is provided at Infevers, an online database of autoinflammatory mutations, at https://infevers.umai-montpellier.fr/.[138,139]

Clinical tests can suggest or in some cases establish a diagnosis. Examples include circulating serum cytokines such as IL-6 and IL-18, serum IgD and IgA, or urine organic acids in MKD, ADA2 activity, and stable proxies for cytokines that are difficult to measure directly, such as the chemokine CXCL9 as a proxy for IFN-γ.[140,141] Further tests are available largely on a research basis, such as assessment of peripheral blood for cytokine release or expression of type I IFN-stimulated genes.[11] Whole-exome or whole-genome sequencing, potentially together with sequencing of affected and unaffected family members, can provide definitive guidance but requires specialized expertise and can miss large deletions and mutations affecting noncoding regions such as promoters and enhancers.

Fourth, consider empiric therapy. Many autoinflammatory diseases operate through pathways or mediators for which inhibitors are available. Nonsteroidal anti-inflammatory drugs and corticosteroids are anti-inflammatory but have little value as therapeutic diagnostics. The exception is PFAPA, in which abrogation of fever with a single dose of corticosteroids strongly supports the diagnosis.[142] In contrast, response to colchicine supports an autoinflammatory etiology, because it can attenuate assembly of the pyrin inflammasome and thus treat FMF as well as an appreciable fraction of suspected autoinflammatory syndromes that defy molecular diagnosis.[143-145] Response to the recombinant IL-1 receptor antagonist anakinra establishes the role of IL-1 in an inflamed patient. The short half-life of this agent (4-6 hours) and documented safety even in patients with severe bacterial illness render a therapeutic trial feasible and safe in many clinical contexts.[146] Another option is empiric canakinumab (anti–IL-1β antibody), although this drug has a considerably longer half-life (26 days).[43] JAKinibs such as tofacitinib, baricitinib, and ruxolitinib can be used to explore the role of IFN signaling, albeit with caution because of their broad immunosuppressive reach and uncertain safety in bacterial and viral infection.[11,70] IL-18 blockade can establish the causative contribution of this cytokine, as exemplified by experience in NLRC4-related disease.[52] Careful utilization of targeted immunomodulators provide a diagnostic and therapeutic path forward for the more than 50% of patients with presumed autoinflammatory disease who defy diagnosis despite genetic testing and expert evaluation.[144,145]

Conclusions: Autoinflammation in immune-mediated diseases

Like the primary immunodeficiencies, the monogenic autoinflammatory disorders provide a window into human immunity in action, illustrating the degree to which precise regulation of inflammatory pathways is essential to health. Autoinflammation is not all-or-none. Related mechanisms contribute to classic autoimmune diseases as well as to diseases not usually considered primarily immune-mediated, including the crystalline arthropathies and atherosclerosis. Improved understanding of autoinflammation has both illuminated new immune pathways and provided novel diagnostic and therapeutic possibilities for our patients.

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