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## Monogenic autoinflammatory disorders: conceptual overview, phenotype, and clinical approach

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### Abstract

Autoinflammatory diseases are conditions in which pathogenic inflammation arises primarily through antigen-independent hyperactivation of immune pathways. First recognized just over two 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 NF $\kappa$ 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.

### Keywords

autoinflammation; innate immunity; inflammasome; interferon; NF $\kappa$ B

### Introduction: Autoimmunity vs. 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 employed the now-famous phrase “horror autotoxicus” to describe what he presumed to be an absolute aversion to such self-targeting.<sup>1</sup> However, evidence in favor of immune mistakes emerged rapidly,

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and by the 1950s disease-causing autoantibodies had been clearly demonstrated.<sup>2-4</sup> Autoimmunity is now recognized as a core mechanism of human disease, arising when antigen-specific components of adaptive immunity – T cells, B cell 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.<sup>5</sup> 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 (Figure 1).<sup>6</sup> 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, NK 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 two 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.<sup>7, 8</sup> 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.<sup>9</sup> Daniel Kastner and colleagues 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.<sup>9</sup>

Since its introduction in 1999, the term “autoinflammation” has been employed 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 while 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. While 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 (Figure 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.<sup>10</sup> The first autoinflammatory disease recognized, FMF, is an inflammasomopathy; other autoinflammatory diseases arise through defects affecting interferon, NF $\kappa$ B and/or aberrant TNF activity, and miscellaneous mechanisms (Table 1). New categories of autoinflammatory disease will no doubt emerge over time.

### 1. 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-1 $\beta$  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 pro-inflammatory 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 that 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.<sup>11</sup> 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.<sup>12-14</sup> 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-1 $\beta$ . Overactivity of these inflammasomes therefore manifests as widespread immunopathology mediated primarily through IL-1 $\beta$ . By contrast, the NLRC4 inflammasome is expressed in the gut lining (among other locations), where its substrate pro-IL-18 predominates over pro-IL-1 $\beta$ , contributing to severe colitis mediated in part by IL-18, although IL-1 $\beta$  also plays a role. Mutations affecting the NLRP3 inflammasome inhibitor CARD8 (also called Cardinal) can manifest as inflammatory bowel

disease.<sup>15</sup> 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).<sup>16</sup> No AIM2-driven inflammasomopathy has yet been reported.

**Pyrin inflammasomopathies.**—*Familial Mediterranean fever* 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, since most affected patients carry two 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 one detectable mutation, and evidence from *Mefv* mutant mice indicating that causal mutations are gain-of-function.<sup>17, 18</sup> 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*.<sup>19, 20</sup> Patients typically present in childhood with episodes lasting 2–3 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 Dermatitis (PAAND)* is a dominantly-inherited disease due to unique activating mutations in *MEFV*.<sup>21</sup> 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 two related disorders, although PAAND often responds only partially. IL-1-targeted therapies can be effective, and TNF inhibitor response is also reported.<sup>21–23</sup>

*Mevalonate Kinase Deficiency (MKD)*, also called *Hyper IgD Syndrome (HIDS)*, is classified as a pyrin inflammasomopathy because disease pathophysiology is mediated by dysregulation of the pyrin regulatory factor RhoA.<sup>24</sup> 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 5–7 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.<sup>22</sup>

*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.<sup>25</sup> PAPA usually presents in childhood with sterile arthritis and systemic inflammation, while 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.<sup>26</sup>

**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* (MWS), and *neonatal onset multisystem inflammatory disease* (NOMID). The lines between these sub-phenotypes are blurry. Most CAPS patients 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 *F12* (Factor 12).<sup>27, 28</sup> For most CAPS patients, 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 sub-phenotype include cold sensitivity in FCAS, AA amyloidosis in MWS, and significant CNS and bone disease in NOMID. IL-1 blockade is the standard of care and most patients respond when dosed adequately.<sup>27</sup>

**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* (AIFEC) characterized by early-onset hyperinflammation (discussed elsewhere in this issue) involving rash, joint symptoms, severe intestinal disease, and hepatosplenomegaly.<sup>29, 30</sup> 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 support a central role for IL-18.<sup>31</sup>

**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 *familial cold autoinflammatory syndrome 2* (FCAS2).<sup>32</sup> Despite similar domain structure and cell expression patterns of *NLRP12* and *NLRP3*, the function of these proteins may be different. While reliable reports suggest that *NLRP12* can form an active inflammasome, *NLRP12* also regulates NFκB, 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 since disease-associated mutations in *NLRP12* are generally loss of function.<sup>32–34</sup> 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 (IL-1ra, available in recombinant form as anakinra) and a similar receptor antagonist for IL-36 termed IL-36ra. Deficiency of either protein results in an autoinflammatory disease. *Deficiency of IL-1ra* (DIRA), due to biallelic mutation of *IL1RN*, results in neonatal-onset pustulosis, multifocal

osteomyelitis and periostitis due to excess IL-1 signaling.<sup>35, 36</sup> As expected, DIRA is managed effectively by anakinra.<sup>35, 37</sup> *Deficiency of IL-36ra* (DITRA) from mutations in *IL36RN* causes generalized pustular psoriasis, since IL-36 receptor is expressed primarily in the skin and other epithelial cells in contact with the environment.<sup>38</sup> Some of the original DIRA patients also had DITRA due to large deletions involving these contiguous genes.<sup>35, 36, 39</sup> DITRA flares are accompanied by fever, malaise, neutrophilia and elevated inflammatory markers.<sup>40</sup> Although recombinant IL36ra is not yet available, DITRA can be effectively managed by biologics that target TNF, IL-17, or IL-12/23.<sup>41</sup> The efficacy of IL-1 inhibition is variable.<sup>41, 42</sup> IL-18 has two antagonists, circulating IL-18 binding protein (IL-18bp) and the anti-inflammatory IL-1-family cytokine IL-37; diseases arising from defects in these mechanisms are not yet described.

## 2. Interferonopathies

Interferons (IFN) are a family of cytokines involved in immune defense. Three IFN families are recognized. *Type I interferons* encompass IFN $\alpha$ , IFN $\beta$  and other members, involved in antiviral defense and signaling through the type I IFN receptor and its signal transduction kinases JAK1 and TYK2. *Type II interferons* are limited to IFN $\gamma$ , 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 interferons*, termed IFN $\lambda$ , 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 interferon – 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 interferon axis is aberrantly activated.<sup>43</sup> IFN $\alpha/\beta$  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 interferon 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 (Table 1). 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.<sup>44</sup> Vasculopathy manifesting as cold-induced chilblains and livedo reticularis are common skin manifestations.<sup>45</sup> 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 based on the causative genes: *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR1* and *IFIH1*.<sup>46</sup> 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 AGS patients 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.<sup>47</sup>

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.<sup>48–50</sup> 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 AGS patients, especially those with RNASEH-complex mutations.<sup>51</sup>

**Disorders of enhanced nucleic acid sensing.**—MDA5 (encoded by *IFIH1*) and RIG-I (encoded by *DDX58*) are members of the RIG-I-like receptor family that sense viral nucleic acids and activate type I IFN production.<sup>52</sup> 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.<sup>53, 54</sup> Other gain-of-function mutations in *IFIH1* and *DDX58* cause *Singleton-Merten syndrome*, a distinct interferonopathy characterized by aortic and valvular calcification, osteopenia, acroosteolysis and dental anomalies.<sup>55, 56</sup>

*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 interferon genes (STING).<sup>57</sup> While 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.<sup>49, 58</sup>

**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.<sup>59</sup> 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 Dermatitis with Lipodystrophy and Elevated temperature* (CANDLE) syndrome and *Proteasome-Associated Autoinflammatory Syndrome* (PRAAS).<sup>59–61</sup> Patients with CANDLE / PRAAS typically present during infancy with recurrent fever, annular violaceous plaques, violaceous eyelid swelling, hepatosplenomegaly, lipodystrophy and failure to

thrive; PRAAS patients 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.<sup>62</sup> The JAKinibs baricitinib and ruxolitinib can partially ameliorate clinical manifestations and laboratory abnormalities; corticosteroids and methotrexate are also employed.<sup>49, 63</sup>

**Disorders of amplified IFN receptor signaling.**—Ubiquitin specific protease (USP)-18 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.<sup>64</sup> ISG15 is a stabilizer of USP18, such that ISG15 deficiency causes a related interferonopathy characterized by brain calcifications and seizures through insufficiency of USP18.<sup>65</sup> 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.<sup>66, 67</sup> JAK inhibition with ruxolitinib led to remarkable improvement in one patient with USP18 deficiency.<sup>68</sup>

### 3. Disorders of NF $\kappa$ B and/or aberrant TNF activity

The NF $\kappa$ B 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 pro-inflammatory genes. Regulation of NF $\kappa$ B is correspondingly complex, involving a set of sensor proteins, inhibitory proteins, and ubiquitin-dependent functional modifications.<sup>69, 70</sup> Defects in any of these pathways can lead to aberrant activation of NF $\kappa$ B. Hallmark clinical features of the “NF $\kappa$ Bopathies” (sometimes termed the Relopathies, since RelA and RelB are key components of the NF $\kappa$ B complex) are fever, systemic inflammation, and sometimes granuloma formation.<sup>71</sup> Key upstream activators of NF $\kappa$ B activation include receptors in the TNF family, which engage this pathway both via canonical (degradation of the NF $\kappa$ B inhibitor I $\kappa$ B $\alpha$ ) and non-canonical (variant NF $\kappa$ B complex formation) pathways.<sup>72</sup> NF $\kappa$ B activation also results in TNF production. Thus, NF $\kappa$ B and TNF are closely intertwined, helping to define a subgroup of autoinflammatory diseases that often respond at least partially to TNF blockade (Table 1).

**Haploinsufficiency of A20.**—*TNFAIP3* encodes the protein A20, a ubiquitin-editing enzyme that functions as a negative regulator of NF $\kappa$ B. *Haploinsufficiency of A20* (HA20) causes recurrent oral and genital ulcers that mimics Behcet’s disease with relapsing and remitting disease.<sup>73, 74</sup> Other phenotypes include early onset autoimmunity and immunodeficiency including an presentation similar to autoimmune lymphoproliferative syndrome.<sup>75</sup> Peripheral blood mononuclear cells from HA20 patients show overproduction of TNF and IL-1 $\beta$ , and biologics targeting these cytokines are often used in severe cases. Although NF $\kappa$ B and type I IFN are non-redundant pathways, HA20 patients may exhibit elevated expression of IFN signature genes that parallels disease activity, potentially reflecting a regulatory role of A20 on IFN signaling as well as the induction of IFN $\beta$  by TNF.<sup>76, 77</sup> Importantly, the presence of a type I IFN signature predicted a good response to JAKinib treatment in HA20 cases that were resistant to anti-cytokine treatment.<sup>78</sup>



**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.<sup>79</sup> Patients usually present early in life (prior to age 5) 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.<sup>80</sup> 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.<sup>81</sup>

**Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS).**—TRAPS is a dominantly-inherited recurrent fever disorder due to mutations in *TNFRSF1A*, encoding TNF receptor 1 (TNFR1).<sup>9</sup> Usually beginning in childhood, patients experience episodes lasting 2–4 weeks that 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. While failure to shed TNF receptor was initially suspected, aberrant trafficking or signaling of mutant TNFR1 leading to inflammasome activation appears to be a more accurate disease mechanism. Etanercept (soluble TNFR1) therapy can be successful in some patients, but efficacy is frequently lost and – paradoxically – anti-TNF antibodies such as infliximab can worsen disease.<sup>9, 82, 83</sup> IL-1 blockade is more consistently effective and has become standard of care, suggesting a role for the inflammasome in disease pathophysiology.<sup>27</sup>

**Deficiency of adenosine deaminase 2 (DADA2).**—Biallelic mutations in *ADA2* result in a syndrome that variably features systemic vasculitis, early-onset stroke, cytopenias and immunodeficiency.<sup>84, 85</sup> Vasculitis in DADA2 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.<sup>86</sup> Mutations with residual ADA2 function tend to be associated with stroke and other inflammatory manifestations responsive to TNF inhibition, while 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.<sup>87</sup> 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.<sup>88</sup>

#### 4. 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 (Table 1).

**COPA syndrome.**—Coatomer protein subunit  $\alpha$ , encoded by *COPA*, is a part of coat protein complex I that regulates retrograde transport from the Golgi to the endoplasmic

reticulum (ER). Mutations in *COPA* cause an autosomal dominant syndrome of autoimmunity, inflammatory arthritis, interstitial lung disease and diffuse alveolar hemorrhage.<sup>89</sup> ER stress from disrupted intracellular trafficking skews effector T cells towards a Th17 phenotype. Patients with COPA may also have a type I IFN signature, raising the possibility that it is an interferonopathy.<sup>90</sup> Consistent with this finding, COPA has been found to regulate normal trafficking of STING<sup>91, 92</sup>. 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.<sup>93</sup> Numerous immunosuppressive agents have been trialed in COPA syndrome with variable success.<sup>94</sup> JAKinib treatment was effective in one COPA patient with severe arthritis, although the type I IFN signature was not assessed.<sup>95</sup>

**PLAID/APLAID.**—*Phospholipase C gamma 2 (PLCG2)-associated antibody deficiency and immune dysregulation* (PLAID) further exemplifies the intersection of autoinflammation, autoimmunity/allergy, and immunodeficiency (Figure 2). PLC $\gamma$ 2 hydrolyzes phosphatidylinositol-4,5-bisphosphate into diacylglycerol and inositol trisphosphate, triggering calcium release from the ER to mediate cell activation.<sup>96</sup> In PLAID, heterozygous genomic deletions in the autoinhibitory domain of PLCG2 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.<sup>97</sup> 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 (APLAID) is characterized by recurrent blistering skin lesions, interstitial pneumonitis and bronchiolitis, eye inflammation, enterocolitis, cellulitis and immunodeficiency.<sup>98, 99</sup> Treatment for PLAID includes cold avoidance, antihistamines, and antibiotic prophylaxis and/or IVIG for immunodeficiency.<sup>100</sup> Experience with APLAID is limited, but corticosteroids, hydroxychloroquine, and IL-1 inhibitors have not shown sustained efficacy.<sup>99</sup>

**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-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.<sup>101</sup>

## 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 the autoinflammatory diseases but understanding of pathogenesis remains too limited to draw firm conclusions. These conditions belong to the “autoinflammatory penumbra” (Figure 3).

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.<sup>102</sup> Cholesterol crystals activate the same inflammasome, conferring an autoinflammatory element to atherosclerosis, consistent with the (modest) efficacy of IL-1 $\beta$  blockade in cardiovascular disease.<sup>103–105</sup> Ankylosing spondylitis is strongly associated with the MHC class I allele HLA-B27; this association may reflect the propensity of HLA-B27 to mis-fold and thereby trigger the unfolded protein response rather than its antigen specificity.<sup>106</sup> 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 due their presentation with episodic fever.<sup>107</sup> 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.<sup>108</sup> 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-1 $\beta$  blockade. These features resemble 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.<sup>109–111</sup> Inflammatory bowel disease likely reflects both immune hyper-responsiveness and defects in mucosal barrier function.<sup>112</sup>

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 higher prevalence of ankylosing spondylitis and vasculitis.<sup>113–115</sup> Patients with CDC42 deficiency, ARPC1B deficiency or homozygous mutations in *WDR1* present with recurrent infections but also clinical features of autoinflammation (Table 1). 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 (Figure 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 four-step approach (Figure 4).

### 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 (CRP) and the erythrocyte sedimentation rate (ESR). Many patients have skin involvement, including evanescent or persistent rashes, sometimes with vasculitis. Inflammation typically affects many organ systems, sometimes including lung 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 suggests an interferonopathy. Childhood-onset stroke with livedo suggests DADA2. 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.<sup>116</sup>

### 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, while 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.<sup>117</sup> 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/>.<sup>118, 119</sup>

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 $\gamma$ .<sup>120</sup> 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.<sup>10, 121</sup> 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 non-coding regions such as promoters and enhancers.

#### **Fourth, consider empiric therapy.**

Many autoinflammatory diseases operate through pathways or mediators for which inhibitors are available. NSAIDs and corticosteroids are anti-inflammatory but have little value as therapeutic diagnostics. The exception of PFAPA, in which abrogation of fever with a single dose of corticosteroids strongly supports the diagnosis.<sup>122</sup> By contrast, response to colchicine supports an autoinflammatory etiology, since 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.<sup>123–125</sup> 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.<sup>126</sup> Another option is empiric canakinumab (anti-IL-1 $\beta$  antibody), although this drug has a considerably longer half-life (26 days).<sup>22</sup> JAKinibs such as tofacitinib, baricitinib, and ruxolitinib can be employed to explore the role of interferon signaling, albeit with caution because of their broad immunosuppressive reach and uncertain safety in bacterial and viral infection.<sup>10, 49</sup> IL-18 blockade can establish the causative contribution of this cytokine, as exemplified by experience in NLRC4-related disease.<sup>31</sup> Careful utilization of targeted immunomodulators provide a diagnostic and therapeutic path forward for the >50% of patients with presumed autoinflammatory disease who defy diagnosis despite genetic testing and expert evaluation.<sup>124, 125</sup>

### **Conclusion: 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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## Abbreviations

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

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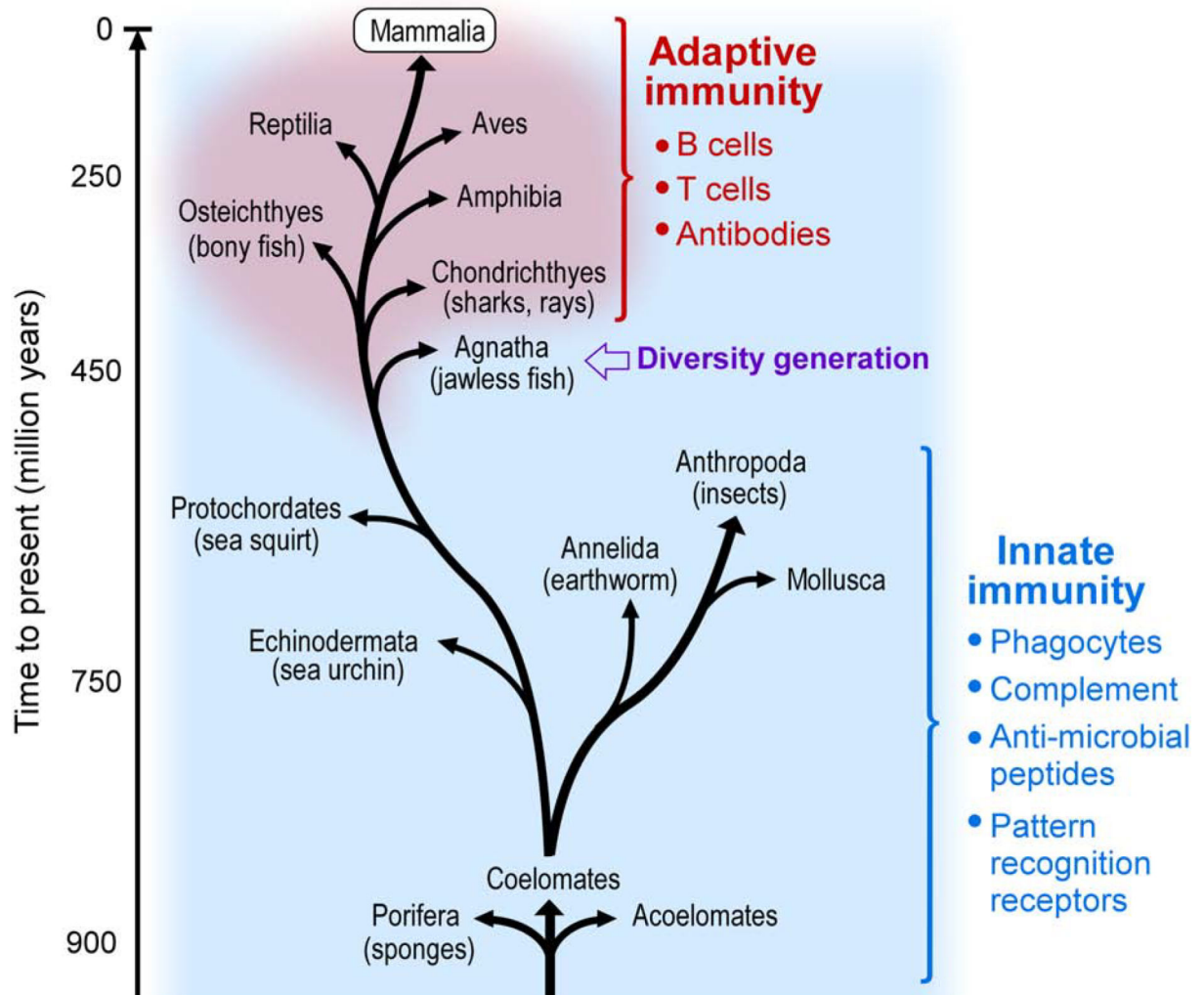
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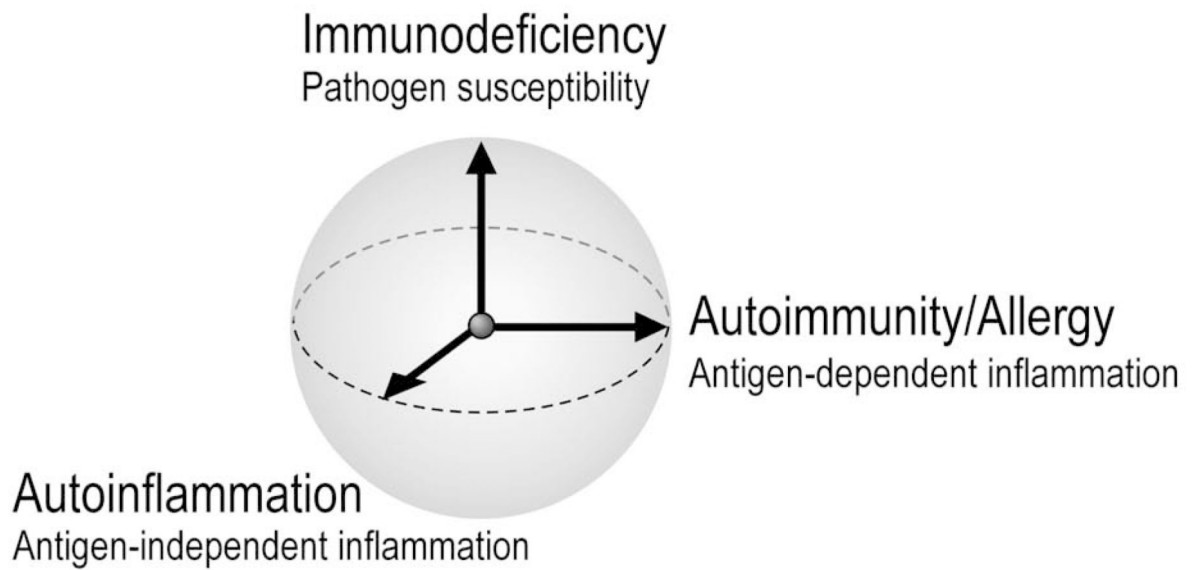
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**Figure 1. Innate and adaptive immunity in evolution.**

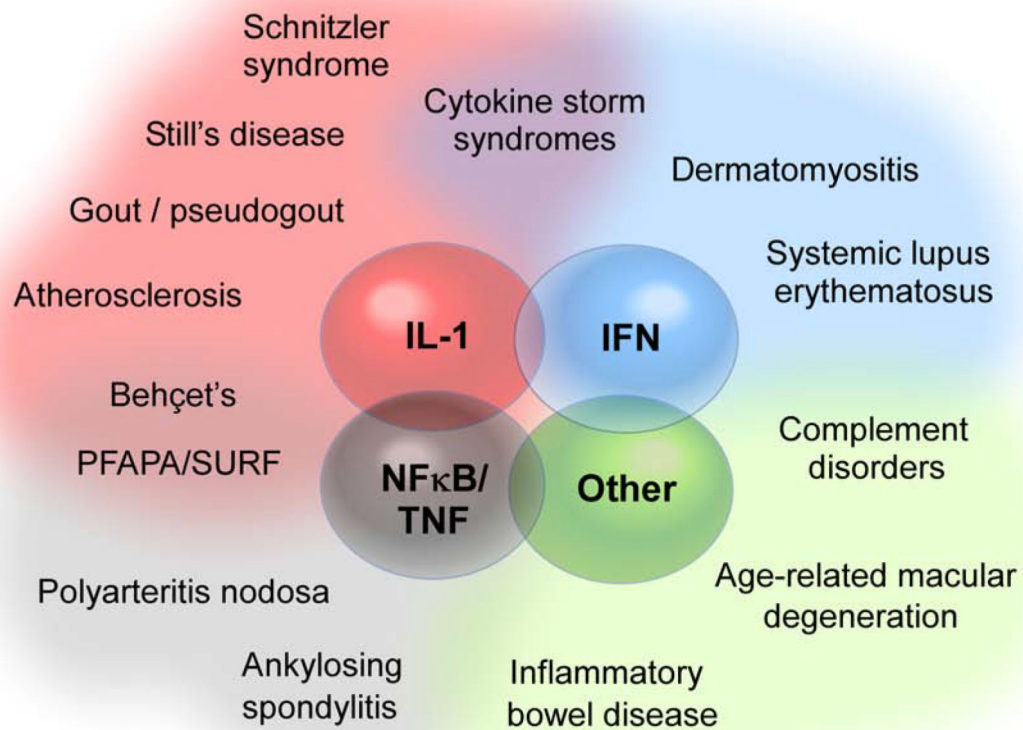
Simplified evolutionary tree of animal phyla depicting the development of adaptive immunity at the stage of jawless fishes. Adapted from Porcelli SA, "Innate immunity" in Kelley and Firestein's Textbook of Rheumatology, Eds: Firestein GS, Budd R, Gabriel SE, McInnes IB, O'Dell JR, 10th ed. 2017 with permission.



**Figure 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*.





**Figure 3. The autoinflammatory penumbra.**

Major families of autoinflammatory disorders include the inflammasome/IL-1 diseases, the interferonopathies, the NFκB/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. PFAPA, Periodic Fevers with Aphthous stomatitis, Pharyngitis and Adenopathy; SURF, Syndrome of Undifferentiated Recurrent Fever.

1	Suspect autoinflammation	<ul style="list-style-type: none"> <li>• Fever, rash, or unexplained multisystem inflammation</li> <li>• Early age of onset</li> <li>• Consanguinity or family history</li> </ul>
2	Pattern recognition	<ul style="list-style-type: none"> <li>• Pattern / duration of fever</li> <li>• Ethnicity</li> <li>• Inheritance pattern</li> <li>• Suggestive features: rash, vasculitis, conjunctivitis, CNS calcifications, stroke, lung disease, colitis</li> <li>• Expert consultation</li> </ul>
3	Testing	<ul style="list-style-type: none"> <li>• Directed gene sequencing</li> <li>• NGS panels for AID / PID</li> <li>• Cytokines, other (CXCL9, ADA2)</li> <li>• Whole exome / genome sequencing</li> <li>• Interferon signature genes</li> <li>• Functional studies</li> </ul>
4	Treatment (Targeted / Empiric)	<ul style="list-style-type: none"> <li>• NSAIDs (low diagnostic value)</li> <li>• Corticosteroids (limited diagnostic value)</li> <li>• Colchicine</li> <li>• IL-1 blockade</li> <li>• TNF inhibition</li> <li>• IFN inhibition (JAKinibs)</li> </ul>

**Figure 4. Clinical approach to patients with suspected autoinflammation.**  
Please see text for discussion of each step.

**Table 1.**  
**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.

	Mechanism	Disease	Gene	Inheritance	Clinical presentation	Targeted therapy
Inflammasomopathies and other IL-1 family conditions		FMF	<i>MEFV</i>	AR or AD	fever, pain, (abdominal, chest, joint), rash	IL-1, colch.
		PAAND	<i>MEFV</i>	AD	fever, myalgia, myositis, rash, abscesses	IL-1, colch.
	Pyrin activation	MKD	<i>MVK</i>	AR	fever, pain (abdominal, extremity), vomiting, rash	IL-1
		PAPA	<i>PSTPIP1</i>	AD	pyoderma gangrenosum, arthritis	IL-1, TNF
		H <sub>z</sub> /H <sub>c</sub> <sup>127</sup>	<i>PSTPIP1</i>	AD	rash, FTT, hepatosplenomegaly, neutropenia	IL-1, TNF
		PFIT <sup>128</sup>	<i>WDR1</i>	AR	fever, infection, oral inflammation, perianal ulceration	IL-18
	Cryopyrin activation	FCAS	<i>NLRP3</i>	AD	cold urticaria, extremity pain, conjunctivitis, fever	IL-1
		MWS	<i>NLRP3</i>	AD	urticarial rash, extremity pain, hearing loss, conjunctivitis, fever	IL-1
		NOMID	<i>NLRP3</i>	AD	CNS inflammation, urticaria, knee arthropathy, fever	IL-1
		Majeed's <sup>129</sup>	<i>LPIN2</i>	AR	osteomyelitis, fevers, rash, dyserythropoietic anemia	IL-1
	NLRC4 activation	AIFEC	<i>NLRC4</i>	AD	enterocolitis, rash, arthritis, fever	IL-1, IL-18
		FCAS/NOMID	<i>NLRC4</i>	AD	cold urticaria, extremity pain, fever, CNS disease	IL-1
	NLRP12 activation	FCAS	<i>NLRP12</i>	AD	cold urticaria, extremity pain, fever	TNF, IL-1
	NLRP1 activation	NAIAD <sup>130</sup>	<i>NLRP1</i>	AD	Ocular, laryngeal, skin dyskeratosis, fever, arthritis	IL-1, TNF
	Receptor antagonist deficiency	DIRA	<i>IL1RN</i>	AR	pustular rash, osteomyelitis, periostitis, fever,	IL-1
DITRA		<i>IL36RN</i>	AR	pustular psoriasis, fever, malaise	TNF, IL-17/12/23?	
Type I Interferonopathies	Nucleic acid processing and degradation	Aicardi-Goutières syndrome	<i>TREX1, ADAR1, RNASEH2A/B/C, SAMHD1, IFIH1</i>	AR (AD: IFIH1)	fever, neurologic decline, encephalopathy, cerebral calcification, chilblains, autoantibodies	JAK, RTI?
		monogenic SLE complements	<i>DNASE1/2/IL3,</i>	AR (AD: DNASE1)	autoantibodies, cytopenias, glomerulonephritis, skin	JAK?

	Mechanism	Disease	Gene	Inheritance	Clinical presentation	Targeted therapy
					cytopenias, glomerulonephritis, skin rash, oral ulcers, arthritis	
	Nucleic acid sensing	SMS	<i>IFIH1, DDX58a</i>	AD	calcification of aorta / cardiac valves, osteopenia, acro-osteolysis, dental anomalies	JAK?
		SAVI	<i>TMEM137</i>	AD	Chilblain's rash, small vessel vasculitis, arthritis, ILD	JAK
	Proteasome	CANDLE / PRAAS, PRAID <sup>131</sup>	<i>PSMB4, PSMA3, PSMB8, POMP, PSMG2, PSMB9, PSMB10</i>	Digenic, AR (AD: POMP)	fever, joint contractures, annular plaques, eyelid swelling, hepatosplenomegaly, lipodystrophy, FTT, developmental delay, anemia	JAK
	IFN signaling	AGS-like	<i>USP18, ISG15, STAT2</i>	AR	skin ulcerations, seizures, hydrocephalus, cerebral calcifications, respiratory failure	JAK
	other	SPENCD <sup>132</sup>	<i>ACP5</i>	AR	skeletal dysplasia, short stature, cerebral calcification, cytopenias, autoantibodies	?
NF-KB and/or aberrant TNF activity		HA20	<i>TNFAIP3</i>	AD	oral, gastrointestinal and genital ulcerations, fever, arthritis, recurrent infection	TNF, IL-1, JAK?
	dysregulation of NFKB signaling	RELA haploinsuf. <sup>133</sup>	<i>RELA</i>	AD	oral and gastrointestinal ulcerations, cytopenias, lymphoproliferative disease	TNF
		ORAS	<i>OTULIN</i>	AR	fever, panniculitis, diarrhea, arthritis, FTT	TNF
	LUBAC deficiency <sup>134,135</sup>	<i>HOIL1, HOIP</i>	AR	fever, recurrent infection, FTT, hepatosplenomegaly, amylopectin-like deposits in muscles	TNF?	
	Blau	<i>NOD2</i>	AD	granulomatous dermatitis, uveitis, polyarticular arthritis	TNF	
	Dysregulation of TNF	TRAPS	<i>TNFRSF1A</i>	AD	episodic fever, abdominal pain, headache, conjunctivitis, painful centrifugal rash	IL-1, TNF
DADA2		<i>ADA2</i>	AR	systemic vasculitis, fever, rash, stroke, cytopenias, hypogammaglobulinemia	TNF, HSCT	
CRIA <sup>136,137</sup>		<i>RIPK1</i>	AD	fever, lymphadenopathy, hepatosplenomegaly	IL-6?	
Other mechanisms	Golgi-ER Transport	COPA	<i>COPA</i>	AD	arthritis, ILD, diffuse alveolar hemorrhage, autoantibodies	IL-17? JAK?

Mechanism	Disease	Gene	Inheritance	Clinical presentation	Targeted therapy
Intracellular calcium signaling	PLAID	<i>PLCG2</i>	AD	cold urticaria, atopy, granulomatous dermatitis, hypogammaglobulinemia, infection, autoantibodies	?
	APLAID	<i>PLCG2</i>	AD	blistering skin lesions, ILD, bronchiolitis, eye inflammation, enterocolitis, immunodeficiency	?
tRNA biogenesis	SIFD <sup>138</sup>	<i>TRNT1</i>	AR	fever, developmental delay, seizures, microcytic anemia hypogammaglobulinemia	TNF
Lipid metabolism? ER stress?	LACC1 deficiency <sup>139,140</sup>	<i>LACCI/FAMIN</i>	AR	fever, systemic JIA, oligoarticular/polyarticular JIA	?
Cytokine dysregulation	VEO-IBD <sup>141,142</sup>	<i>IL-10, IL10RA, IL10RB</i>	AR	Early-onset colitis, FTT	HSCT, IL-1?
Actin Assembly	ARPC1B deficiency <sup>143,144</sup>	<i>ARPC1B</i>	AR	platelet abnormalities, bleeding, recurrent infection, small vessel vasculitis, eczema, arthritis	?
Actin polymerization	CDC42 deficiency <sup>145,146</sup>	<i>CDC42</i>	AR	Neurodevelopmental defects, facial dysmorphism cytopenias, recurrent infection, fever, rash	IL-1

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