Article:
Savic, S orcid.org/0000-0001-7910-0554, Caseley, EA orcid.org/0000-0001-7591-143X and McDermott, MF orcid.org/0000-0002-1015-0745 (2020) Moving towards a systems-based classification of innate immune-mediated diseases. Nature Reviews Rheumatology, 16 (4). pp. 222-237. ISSN 1759-4790

https://doi.org/10.1038/s41584-020-0377-5

Moving towards a systems-based classification of innate immune-mediated diseases

Sinisa Savic[1,2,3]*, Emily A. Caseley[1], Michael F. McDermott[1]*

[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM), St James's University Hospital, Leeds, UK

[2] National Institute for Health Research–Leeds Musculoskeletal Biomedical Research Unit (NIHR-LMBRU), Leeds, UK

[3]Department of Clinical Immunology and Allergy, St James's University Hospital, Leeds, UK

*email: S.Savic@leeds.ac.uk; M.McDermott@leeds.ac.uk

Abstract

Autoinflammation as a distinct disease category was first reported in 1999 as a group of monogenic disorders characterized by recurrent episodes of systemic and organ-specific inflammation, known as periodic fever syndromes. Since this original description, the focus has shifted considerably to the inclusion of complex multifactorial conditions with an autoinflammatory basis. Furthermore, the boundaries of what are considered to be autoinflammatory disorders are constantly evolving, and currently encompass elements of immunodeficiency and autoimmunity. Notable developments in the intervening 20 years include substantial progress in understanding how the different inflammasomes are activated, how infection is sensed by the innate immune system, how intracellular signalling systems are consequently activated and integrated with many different cellular functions in the autoinflammatory process. With these developments, the field of autoinflammation is moving from a gene-centric view of innate immune-mediated disease towards a systems-based concept, which describes how various convergent pathways, including pyrin and the actin cytoskeleton, protein misfolding and cellular stress, NF-κB dysregulation and interferon activation, contribute to the autoinflammatory process. The development and adoption of a systems-based concept of systemic autoinflammatory diseases is anticipated to have implications for the development of treatments that target specific components of the innate immune system.

[H1] Introduction

What defines autoinflammation, and which disorders fit under the umbrella of systemic autoinflammatory diseases, are subjects of intense debate that do not have easy answers. In part, this difficulty arises from our ever-increasing appreciation of the complex interplay between the innate and adaptive immune systems, and of the intricate connection of immunity with other cellular processes, such as metabolism, cytoskeletal rearrangements and endoplasmic reticulum (ER) stress, amongst many others[1,2]. Thus, it is not entirely surprising that an 'autoinflammatory signature' might also be identified in other disease entities (that is, other than autoinflammatory diseases) in which the predominant immune dysfunction might manifest either as a primary immunodeficiency, autoimmunity or even allergy.

Various attempts to classify systemic autoinflammatory diseases have met with difficulties. Grouping of these diseases according to genetic causes, clinical features, response to treatment or predominant molecular abnormalities have always encountered some exceptions. For example, familial Mediterranean fever (FMF)[3,4] and pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND)[5] are both caused by gain-of-function mutations in MEFV, yet the clinical manifestations and response to therapy of these two conditions differ considerably. Considering response to therapy, FMF is more like TNF receptor (TNFR)–associated periodic syndrome (TRAPS), as these two conditions both show a more consistent response to IL-1-blocking therapy than does PAAND[6,7].

A classification scheme was proposed in 2006 whereby the majority of inflammatory conditions can be placed along an immunological disease continuum, with monogenic autoinflammatory disorders at one end and monogenic autoimmune disorders at the opposite end[8]; this classification helped to bring the term autoinflammation to a wider audience and into mainstream medical thinking. However, including primary immunodeficiency disorders with autoinflammatory features, for example, within this scheme has proved to be quite challenging. A 2018 consensus proposal for taxonomy and definition of the autoinflammatory diseases refined the definition of these disorders and provided guidelines for naming them, focusing mainly on monogenic autoinflammatory diseases[9]. The expert group that devised the taxonomy stringently adhered to the original the original definition of autoinflammation by excluding several conditions from the taxonomy that had been considered as autoinflammatory diseases, including PLCG2-associated antibody deficiency and immune dysregulation (PLAID) or heme-oxidised IRP2 ubiquitin ligase1 (HOIL-1) deficiency, since some of these conditions

also have autoimmune features (mainly autoantibody production)). This new classification (taxonomy) is mostly limited to monogenic diseases, whereas in this Review we also make reference to complex, multifactorial disorders, such as rheumatoid arthritis (RA), in which a surprising number of patients exhibit an innate-immune myeloid signature as an RA pathotype, defined by synovial histology[10].

The aim of this Review is not to produce a new classification of systemic autoinflammatory diseases or to redefine the term autoinflammation, but to illustrate the complex interplay of the molecular mechanisms and systems that are central to many monogenic and polygenic conditions with autoinflammatory features. Previously adopted gene-centric classifications of disease have often been somewhat restrictive, and a move towards systems-based classification is likely to be beneficial both for improving our understanding of these diseases and for effective therapeutic targeting. Technical advances, such as next-generation sequencing (also known as high-throughput sequencing), with associated bioinformatics, have enabled the recognition of an ever-increasing range of conditions. In this Review, we describe the molecular pathogenesis of some of the monogenic autoinflammatory conditions and attempt to develop a holistic concept of the synergistic contributions of various convergent pathways towards the autoinflammatory process, including pyrin activation and the actin cytoskeleton, protein misfolding, NF-κB dysregulation and interferon activation. We also discuss the search for novel therapies for the broad range of autoinflammatory conditions.

[H1] Pyrin and the actin cytoskeleton

Amongst the numerous mechanisms implicated in monogenic systemic autoinflammatory diseases, the activation of inflammasomes and associated inflammatory signalling pathways are central constituents of the autoinflammatory phenotype (Box 1). A steadily increasing number of inflammasome complexes, built around a range of different proteins including NLRP3, NLRC4, AIM2, NLRP6 and pyrin have been recognised. These large, multimeric protein complexes link the sensing of microbial products and metabolic stress to the production of pro-inflammatory cytokines and associated autoinflammatory pathologies.

[H2] Pyrin-related autoinflammatory diseases.

Pyrin, encoded by MEFV, is an intracellular pattern recognition receptor **[G]** that assembles the pyrin inflammasome complexes in response to pathogenic infections (Figure 1). As mentioned earlier, FMF, the most common monogenic autoinflammatory disease, is caused by gain-of-function mutations in MEFV[11-13], as is PAAND, a condition first described within the past few years . The pathogenesis of PAAND is a result of p.S242R, p.S208T, p.S208C and E244K substitutions in pyrin[5,7,14], which disrupt pyrin phosphorylation at these amino acid residues and prevent binding of the inhibitory 14-3-3 protein. The resultant constitutive activation of the pyrin inflammasome culminates in release of IL-1β and IL-18 and, ultimately, caspase 1-dependent inflammatory cell death, known as pyroptosis[13,15]. By contrast, constitutive activation of the pyrin inflammasome is not seen in FMF, but rather the activation threshold is lowered[16] (as demonstrated by the robust reaction of the pyrin inflammasome to low doses of Clostridium difficile toxin B [17]) , which is likely to contribute to the heightened inflammatory response in patients with FMF.

Although these conditions are both borne of mutations within the same gene, patients with FMF and PAAND differ in their clinical phenotypes, disease severity and response to treatment[7]. Whereas patients with FMF almost universally respond to colchicine and anti-IL-1 therapy, patients with PAAND have a more severe disease and their treatment response to these two medications is less predictable, indicating a more complex pathogenesis, including excessive pyroptosis and a role for other pro-inflammatory cytokines, such as TNF[7]. Mevalonate kinase deficiency (MKD), caused by loss-of-function mutations in MVK[18,19], is another monogenic systemic autoinflammatory disease that has a complex pathogenesis, in part because of loss of pyrin inhibition, and a less predictable response to anti-IL-1 therapy compared with FMF[13]. Mevalonate kinase-mediated production of geranylgeranyl phosphate, which is required for the prenylation of small GTPases, ensures the localisation of the GTPase RhoA at the cell membrane[20]. Here, RhoA can activate the serine-threonine kinases PKN1 and PKN2, which phosphorylate serine residues at positions 208 and 242 of pyrin, mediating binding of the inhibitory protein 14-3-3 and thereby suppressing pyrin function. The prenylation deficiency in MKD results in RhoA inactivity and subsequent constitutive pyrin inflammasome activation[13]. Although most patients with MKD respond to anti-IL-1 therapy, like those with PAAND, some patients with MKD show a better response to anti-TNF or anti-IL-6 therapy[21-23].

[H2] Pyrin-actin interactions

Pyrin inflammasome activation is also dependent on the actin cytoskeleton and microtubular network, via the interaction of pyrin with both actin and the adaptor protein ASC to enable NLRP3 inflammasome assembly[24] (Figure 1). Pyrin–ASC interactions occur at sites of actin polymerisation[25], and microtubule dynamics are vital for ASC recruitment and oligomerisation[15,16]; disturbances of this actin–pyrin network can result in autoinflammation.

Further evidence for the role of actin cytoskeleton in pyrin activation comes from the observation that a massive influx of myeloid cells, primarily neutrophils, is seen during acute inflammatory attacks in FMF[26]. Cell migration is regulated by cytoskeletal reorganisation, which results in net displacement of the cells during their effector functions[27]. These properties explain the efficacy of colchicine, the primary treatment for FMF, the therapeutic activity of which has been attributed to its ability to bind tubulin, causing microtubule disruption and depolymerisation with subsequent inhibition of the cytoskeletal changes required for pyrin inflammasome assembly and neutrophil migration[28]. Similarly, a unifying feature of SAIDs, discussed in the following paragraph, is the presence of actin dysregulation, with subsequent weakening of the cytoskeleton of the cell leading to cellular instability and lysis.

Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, which is caused by mutations in proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP-1)[29,30], is the first condition in which a pyrin–ASC interaction was reported. The PSTPIP-1 protein is involved in cytoskeletal organisation via its regulation of the ratio of podosomes and filopodia in macrophages[31]. Mutated forms of PSTPIP-1 are hyperphosphorylated and consequently bind with a higher affinity to the autoinhibitory B-box domain of pyrin**,** compared with non-mutated forms. [29,30]. The resulting constitutive activation of the pyrin inflammasome leads to increased IL-1β production, which is a key constituent of the autoinflammatory phenotype[32].

Actin cytoskeleton dysregulation has also been implicated in a syndrome of autoinflammatory periodic fevers, immunodeficiency, and thrombocytopenia (PFIT) associated with mutations in WD40 repeat protein 1 (WDR1). WDR1 is a ubiquitously expressed negative regulator of filamentous actin **[G]** (F-actin) and the mutated form of WDR1 promotes actin filament disassembly[33]. In a mouse model of PFIT, autoinflammatory complications were linked to pyrin-dependent IL-18 production[34]. In 2019 , defects in actin polymerization arising from biallelic mutations in ARPC1B were described in another condition with a complex phenotype that includes combined immunodeficiency, bleeding tendencies, and various combinations of autoinflammatory, autoimmune and allergic

complications[35]. The protein encoded by ARPC1B, actin-related protein 2/3 complex subunit 1B (ARPC1B), is a component of the actin-related protein 2 (ARP2)–ARP3 complex, which is essential for branching of F-actin. In patients with ARPC1B mutations, defective actin polymerization has been shown to negatively affect platelet function (impaired platelet spreading), T cell number and function (impaired immune synapse formation and reduced regulatory T cell function) and effective chemotaxis[35]. Although a direct mechanistic link between these immunological abnormalities, inflammasome activation and the autoinflammatory complications, seen in these cases of ARPC1B deficiency, including macrophage activation syndrome, inflammatory bowel disease (IBD), arthritis and leukocytoclastic vasculitis, has not yet been defined, such connections may not be easily established given the multitude of cellular functions that rely on actin cytoskeleton. However, a link between defective autophagy **[G]** and dysregulated inflammasome activation, with autoinflammatory complications, has been clearly demonstrated in Wiskott–Aldrich syndrome, caused by mutations in the Wiskott–Aldrich syndrome protein (WASp); as with the ARPC1B protein, WASp interacts with the ARP2–ARP3 complex, and Wiskott–Aldrich syndrome has a phenotype similar to that seen in patients with ARPC1B deficiency[36].

It is evident from these examples that the pyrin inflammasome has a central role in an evolutionarily important inflammatory response pathway. Pyrin activity is integrated with many different cellular functions, and it is therefore not entirely surprising that many autoinflammatory complications, which occur, to varying degrees, in a seemingly disparate group of disorders, might result from dysregulated pyrin inflammasome activation.

[H1] Protein misfolding and cellular stress

The unfolded protein response (UPR) is an intracellular homeostatic signalling response, related to ER stress that can be induced by the accumulation of misfolded or unfolded proteins in the ER. A variety of mechanisms have evolved in cells in order to maintain intracellular protein homeostasis and prevent the spread of inflammation (Figure 2). Such mechanisms include the degradation of specific pro-inflammatory protein complexes, such as ubiquitinated and oxidated proteins, which can accumulate in the cytoplasm in the case of immunoproteasome defects as, for example, found in chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, usually owing to PSMB8 mutations. Another disorder, described in 2018, arising from dysregulated protein homeostasis is POMP-related autoinflammation and immune dysregulation disease

(PRAID)[37]. POMP encodes proteasome maturation protein, an essential factor in the assembly and folding of various proteasome subunits[38]. The PRAID phenotype has some clinical similarities to CANDLE but is not a direct phenocopy owing to the presence of overlapping autoimmunity and immune deficiency components in individuals with truncating POMP variants but that are not found in CANDLE syndrome[37]. Thus, this syndrome further emphasizes the overlapping incidence of autoimmunity, immunodeficiency and autoinflammation in many autoinflammatory diseases.

Other mechanisms to maintain protein homeostasis include tightly regulated protein translation and autophagy. For instance mutations in TRNT1, encoding mitochondrial CCA tRNA nucleotidyltransferase 1 (TRNT1), cause aberrant tRNA processing and an autosomal recessive autoinflammatory syndrome of congenital sideroblastic anaemia, B-cell immunodeficiency, periodic fevers and developmental delay[39,40]. These mutations disrupt normal autophagy in specific cells, and the subsequent accumulation of unprocessed or misfolded proteins can cause ER stress that activates the UPR signalling network in TRNT1-deficient cells with resulting TNF production, which is partly responsive to TNF inhibition[41].

Oxidative stress has also emerged as an important trigger of intensified inflammatory responses in autoinflammatory conditions. The UPR can be co-opted by Toll-like receptor (TLR) signalling and mitochondrial reactive oxygen species (mROS) generation to induce inflammatory responses, in monogenic conditions such as TNF receptor (TNFR)-associated periodic syndrome (TRAPS) and cystic fibrosis[42,43]. Defective protein homeostasis and ROS-mediated inflammation are also associated with the pathogenesis of several polygenic conditions with autoinflammatory features, such as type 2 diabetes mellitus, Parkinson disease and Alzheimer diseases[44-46].

[H1] Dysregulation of NF-κB activation

Although the term NF-κB originates from the initial discovery of this transcription factor in 1986[47,48], as the main driver of κ-chain expression in B cells, subsequent studies revealed that NF-κB is expressed in almost all cell types, has a role in diverse cellular functions, and regulates the expression of hundreds of thousands of genes[49,50]. One of its critical roles is in mediating a range of immunological functions, particularly inflammatory responses[51]. In this context, NF-κB can be activated by a host of mediators and cellular events including, but

not limited to, cytokines (such as IL-1β and TNF)[52-54], pathogens (via pattern recognition receptors such as TLRs), cell lysis products (for example, damage-associated molecular patterns such as ATP)[55], physiological insults (ER and oxidative stress)[56] and physical stress (UV light and cold temperatures)[57].

The activation of NF-κB via canonical (TNFR or IL-1 receptor), non-canonical (CD40) and atypical (genomic stress) pathways has been mapped out in detail (Figure 3)[58]. It is beyond the scope of this Review to describe these pathways in detail, but it is important to emphasise that a series of ubiquitinating, deubiquitinating and phosphorylation events can converge, at the level of IκB kinases (IKKs), to eventually release NF-κB homodimers or heterodimers from IκB inhibition, leading to translocation of the transcription factor to the nucleus[59].

[H2] Phenotypes that are predominantly immunodeficiency, with some autoinflammation.

One of the first immunological conditions to be associated with dysregulation of the NF-κB pathway and linked with autoinflammatory complications is NF-κB essential modulator (NEMO) deficiency[60]. NEMO is also known as IKKγ and functions as a regulatory component of the IKK complex[61]. The IKK complex contains two kinases, IKKα and IKKβ, which are activated by self-phosphorylation when brought into complex with NEMO, leading to subsequent phosphorylation of IκB. IκB then becomes a target for ubiquitination and proteosomal degradation. NEMO is encoded by IKBKG located on the X chromosome[62]. Mutations resulting in complete loss of NEMO function are typically lethal, in utero, in males. Hypomorphic mutations **[G]**, however, result in a complex phenotype with up to 77% of affected males presenting with anhidrotic ectodermal dysplasia **[G]**, but invariably all have some degree of immunodeficiency[63]. A similar phenotype to NEMO deficiency was described in a male infant who had a heterozygous mutation in IκBα that prevented phosphorylation of the mutant IκBα[64]. In this patient, a substitution at serine 32 of IκBα, one of two serine residues that are targets for IKK phosphorylation and are critical for ubiquitination and degradation of phosphorylated IκBα, resulted in a dominant gain-of-function inhibitor of NF-κB. The non-immunological manifestations in these genetic disorders of NF-κB activation are attributable to the inability of the ectodysplasin A receptor (a TNFR family member that is distributed in ectodermal tissues) to induce NF-κB activation following ligation[65].

In the largest case series of male patients with NEMO mutations reported to date, up to 23% of the patients developed autoinflammatory complications, the most common being non-infectious colitis[64]. Colitis was associated with variants such as L153R, which results in a more profound loss of NEMO function compared to other mutations. This association is in keeping with mouse studies in which specific ablation of NEMO in intestinal epithelial cells resulted in increased cell apoptosis and microbiota-driven chronic inflammation in the colon[66-68]. Interestingly, a combined deficiency of the NF-κB family members p65 (also known as RelA), RelB and proto-oncogene c-Rel resulted in increased intestinal epithelial cell death, but not colitis, and this latter complication (that is, colitis) could be prevented by inhibition of receptor-interacting protein kinase 1 (RIPK1)[67]. These findings suggest that NEMO has a gut-protective function independent of NF-κB, and that RIPK1 could be useful target in treating IBD[67].

However, a 2018 report of human RIPK1 deficiency described four patients from three unrelated families who presented with a combination of primary immunodeficiency and systemic autoinflammatory features, including early-onset IBD and progressive polyarthritis[69]. Functional studies showed a partial reduction in NF-κB activation with a marked decrease in p38 mitogen-activated protein kinase and AP-1 phosphorylation, resulting in reduced production of IL-6, TNF and IL-12. At the same time, IL-1β production was preserved or increased, in studies using various cell sources (whole blood and monocytes) and stimuli such as phytohemagglutinin and lipopolysaccharide. This imbalance seems to result from increased necroptosis and IL-1β release as a result of diminished pro-survival signals that are necessary to sustain the cells during immune activation. During the writing of this Review, two manuscripts were simultaneously published describing a novel autoinflammatory disorder, without features of immunodeficiency, due to heterozygous mutations in RIPK1.[70,71] Two groups independently identified families and sporadic cases of an early (childhood) onset disorder characterized by episodic high fevers, lymphadenopathy, splenomegaly, oral ulceration, and responsiveness to IL-6 blockade. All cases had a heterozygous mutation in RIPK1 resulting in the inability of caspase 8 to cleave the mutated protein and, therefore, terminate the RIPK1-mediated inflammatory response.[70,71]

A dysregulation of immune responses and related clinical picture is also seen in patients with linear ubiquitin chain assembly complex (LUBAC) deficiencies. LUBAC consists of HOIL-1 interacting protein (HOIP; encoded by RNF31) and two accessory proteins: heme-

oxidized IRP2 ubiquitin ligase 1 (HOIL-1; encoded by RBCK1) and SHANK-interacting protein like 1 (SHARPIN; encoded by SIPL1)[72,73]. After receptor engagement, LUBAC attaches linear ubiquitin chains to target proteins, such as NEMO, RIPK1, IL-1 receptor-associated kinases and MyD88, in order to stabilise various receptor signalling complexes associated with TNFR1, TLRs, IL-1 receptor and CD40[74]. Disruption of LUBAC results in a disorganised and disjointed immune response, as evidenced by the inability of stimulated fibroblasts and B cells from patients with LUBAC deficiencies to upregulate NF-κB activity, with exaggerated responsiveness to IL-1 stimulation and excessive production of IL-6 and CCL3 by the patients' fibroblasts and peripheral blood mononuclear cells[74].

[H2] Phenotypes that are predominantly autoinflammatory

A more selective, inflammatory-only phenotype is seen in patients with OTULIN-related autoinflammatory syndrome (ORAS, or otulipenia) [75]. Ubiquitin thioesterase OTULIN, encoded by OTULIN, is a deubiquitinase that acts as a negative regulator of LUBAC. The first four patients identified with ORAS were found to have rare homozygous mutations in OTULIN that led to loss of protein function, with an early onset severe multisystem autoinflammatory disorder affecting the skin, gastrointestinal tract and joints[75]. In a subsequently reported case, a patient with a homozygous c.841G>A variant in OTULIN died at 8.5 months of age, after developing systemic inflammatory illness and pulmonary oedema[76]. As anticipated from what is known about OTULIN function, peripheral blood mononuclear cells and fibroblasts from patients with ORAS had increased degradation of IκBα and increased phosphorylation of IKKα, IKKβ and IκBα in comparison with cells from healthy individuals, in keeping with NF-κB pathway activation that resulted in increasedproduction of a multitude of cytokines[75]. OTULIN deficiency is associated with cell type-specific LUBAC degradation, dysregulated TNF signalling and cell death[76]. Both the IL-1 receptor antagonist, anakinra, and anti-TNF therapy have been shown to be effective in this condition[77] and haematopoietic stem cell transplantation is potentially curative in severe cases[76].

Heterozygote carriers of OTULIN mutations are asymptomatic[75], which suggests that reduced protein expression of OTULIN can be tolerated and might not be critical for maintenance of immune homeostasis. However, this is not the case for A20 (also known as TNF alpha-induced protein 3), another protein with deubiquitinating activity[74]. A20 is encoded by TNFAIP3, a highly conserved gene with poor tolerance to genetic variation, in particular to

loss-of-function mutations[78]. A20 is known as a negative regulator of NF-kB[79]. It has combined ubiquitinating and deubiquitinating (E3 ligase) functions. The OTU/DUB (ovarian tumour protease/deubiquitinase) domain of A20 catalyses hydrolysis of K63-linked polyubiquitin chains, thus destabilising receptor signalling complexes, whilst A20 simultaneously adds K48-linked polyubiquitin chains to target proteins such as RIPK1 and IκBα for proteasomal degradation[80]. Haploinsufficiency of A20 (HA20) due to heterozygous mutations in TNFAIP3, principally resulting in reduced (50%) expression of the protein, has been associated with a broad range of inflammatory conditions[46]. In addition to the initially reported Behcet-like disease, phenotypes resembling autoimmune lymphoproliferative syndrome, systemic lupus erythematosus (SLE), RA, juvenile idiopathic arthritis, adult-onset Still's disease and cases of complex undifferentiated systemic autoimmune or autoinflammatory disorders have all been described in association with HA20[81,82]. The stimulation of cells from patients with HA20 leads to increased NF-κB activation associated with increased production of a plethora of pro-inflammatory cytokines[81], which is clinically relevant since no single treatment strategy is effective for all patients. Furthermore, genome-wide association studies have found associations between low-penetrance variants of TNFAIP3 and a wide range of autoimmune and inflammatory conditions. Altogether, these findings suggest that, unlike other monogenic conditions in this group of NF-κB-associated disorders, the full clinical phenotype of HA20 might be more dependent on additional genetic and environmental factors. Furthermore, making a clinical diagnosis of HA20, or developing set of diagnostic criteria for this condition, would be exceptionally difficult.

Heterozygous mutations in RELA (encoding p65) have, since 2017, been shown to produce an autoinflammatory condition, named RELA haploinsufficiency, that resembles HA20 in many ways[83]. The patient in the first reported case was found to have a heterozygous mutation in RELA that resulted in a premature stop codon and a reduction in RELA mRNA expression by 50% (compared with non-mutated RELA). The clinical phenotype of recurrent mouth ulceration, fevers, vomiting, acute ileitis and elevated markers of inflammation is thought to result from a dysregulated response to TNF. In the context of reduced p65 levels, engagement of the TNF signalling pathway results in enhanced cell apoptosis, hence the development of mucosal ulcers in RELA haploinsufficiency. The systemic inflammatory response was thought to be secondary to effects of the local intestinal microbiome, with the ulcerated mucosa stimulating further TNF release. As with HA20, the second case of RELA

haploinsufficiency presented with entirely different clinical features, which resembled autoimmune lymphoproliferative syndrome rather than Behçet's syndrome[84].

[H2] Mixed immunodeficiency and inflammatory phenotypes.

Lastly, NFKB1 heterozygous mutations have been shown to produce a range of diverse clinical phenotypes in a mutation-specific fashion. NFKB1 in effect encodes two transcription factors with diverse effects. The full-length protein product, p105, inhibits NF-κB signalling by preventing nuclear entry of p65, c-Rel and p50[85]. The short form, p50, which is generated by proteosomal degradation of p105, can heterodimerise with c-Rel or RelA to activate canonical NF-κB signalling or to form homodimers that function as repressors of pro-inflammatory gene expression. In one case series, patients with a heterozygous NFKB1 p.I553M variant predominantly showed antibody deficiency and multiorgan autoimmunity; the p.H67R variant was associated with autoinflammatory complications resembling Behcet's syndrome, and patients with a p.R157X stop-gain variant **[G]** showed increased NLRP3 inflammasome activation and experienced hyperinflammatory responses to surgery[86]. Functional studies demonstrated that the p.R157X mutation resulted in loss of both short and full-length variants, the p.I553M mutation predominantly affected the stability of p105, and the p.H67R mutation caused reduced nuclear entry of p50[86].

Considering the plethora of upstream signalling pathways that converge at the point of NF-κB activation, the many cellular functions governed by this transcription factor and the complex network regulatory factors controlling this process, it is not surprising that a range of immunological conditions with overlapping phenotypes arises from monogenic defects affecting this pathway. In the context of a hierarchy of signalling defects, those that are upstream, for example RIPK1 deficiency, seem to result in more severe and wide-ranging abnormalities, compared with downstream signalling defects. Likewise, conditions in which there is complete or near complete loss of a protein, such as NEMO and LUBAC deficiency syndromes and otulipenia, are associated with more severe disease than conditions arising from partial loss of protein expression. However, considering the varying effects of partial loss of expression on the delicate balance between pro-inflammatory, apoptotic and survival signals, all of which are governed by the NF-κB pathway, the phenotypes associated with partial loss of protein expression, such as HA20, are harder to predict.

[H1] Dysregulated type I interferon signalling

The presence of foreign DNA or self DNA in the cytoplasm of mammalian cells is a danger signal that triggers a potent innate immune response in the host that is characterized by release of type I interferons[87]. A complex biochemical mechanism (biomedical machinery) has therefore evolved to prevent inappropriate activation in response to self-DNA and to prompt the recognition of nucleic acids of microbial origin (Figure 4). A great deal of what we have learned about this protective system comes from the study of rare disorders collectively named interferonopathies. There are currently 26 monogenic conditions that are in some way linked to dysregulated type I interferon signalling and considered to belong to this group of conditions; however, a direct link between high levels of interferon and the pathogenesis of these disorders remains to be established[88]. It is beyond the scope of this Review to discuss all of these conditions in detail; a summary can be found in the table 1 and an in-depth discussion is published in ref. 82. Evidence for the role of type I interferon in these diseases comes from observations that these disorders are linked with monogenic defects leading to altered nucleic acid processing and recognition, or impaired control of expression of interferon-stimulated genes (ISGs). These conditions also have overlapping clinical phenotypes resulting from different genotypes, and accumulating evidence indicates that therapeutic strategies targeting interferon signalling (with inhibitors of Janus kinase 1 (JAK1) and JAK2) are efficacious in some patients[89-91].

Notably, an interferon signature is also frequently found in autoimmune conditions such as SLE[92,93] as well as in a variety of systemic autoimmune rheumatic diseases in which the signature might be present but is usually less prominent compared to the signature in interferonopathies, such as primary Sjögren syndrome[94], systemic sclerosis[95] and also in a subset of patients with RA[95,96]. Distinct interferon signatures have also been reported to stratify inflammatory myopathies [97]; dermatomyositis can present with a strong type I interferon (IFNα and IFNβ) signature, whereas anti-synthetase syndrome and inclusion body myositis are more commonly associated with a type II IFNγ signature.

[H2] SAVI phenotypes with autoinflammation and immunodeficiency

The challenge of delineating the various pathways and biological processes involved in the pathogenesis of these conditions associated with dysregulated type I interferon signalling is illustrated by a condition called STING-associated vasculopathy with onset in infancy

(SAVI)[98,99]. This autoinflammatory disorder is caused by gain-of-function mutations in TMEM173, encoding stimulator of interferon genes protein (STING), which lead to constitutive activation of the protein. STING is typically activated by binding of cyclic GMP-AMP (cGAMP), which is produced by cGAMP synthase (cGAS) after cGAS binds to DNA of microbial or host origin. Consequently, activated STING transmigrates from the ER membrane to the Golgi where it activates the kinases IKK and serine/threonine-protein kinase TBK1 and, eventually, interferon regulatory factor 3 (IRF3), resulting in the expression of ISGs and the production of type I interferons[100]. Patients harbouring pathogenic STING mutations present with a severe inflammatory disorder characterised by interstitial lung disease, peripheral vascular inflammation and severe ulceration and necrosis of the skin. Although most of these clinical manifestations are considered to be attributable to the effects of high levels of interferon activity, a mouse model revealed that animals with the N153S STING mutation develop lung disease independently of type I interferon but requiring the involvement of T cells[101]. A similar observation was made previously in another mouse study.[102] Relevant to these findings, STING signalling is known to modulate adaptive immunity and affect T cell priming[103,104]. This requirement for fully functioning adaptive immunity in order to achieve complete disease penetrance is also suggested by the identification of stromal interaction molecule 1 (STIM1) as a negative regulator of STING[105,106]. STIM1 is involved in T cell activation, proliferation and cytokine production via its role in activation of calcium release-activated calcium channels on T cells, and loss of function or reduced expression of STIM1 can result in combined immune deficiencies of varying severity[107]. STIM1 is usually located at the ER membrane, where it serves as an intracellular calcium sensor to regulate plasma membrane calcium channel activation. However, STIM1 is also able to retain STING within the ER to regulate its activation. Pathogenic mutations associated with SAVI interfere with STING–STIM1 interactions, with subsequent release of STING from the ER and its constitutive activation[105]. Interestingly, patients with STIM1 deficiency also have highly elevated concentrations of type I interferon and ISG expression, but their clinical phenotype is unusual as none of those studied had substantial lung disease and only one had cutaneous manifestations suggestive of SAVI[106]. Moreover, all of the patients had demonstrable deficiencies of T cell activation but remarkably did not get many infections[106]. In the setting of STIM1 deficiency, therefore, high concentrations of type I interferon seem to provide protection against common infections, whilst deficient T cell function might prevent development of the inflammatory complications typical of SAVI. However, this interpretation might oversimplify a complex interplay between the molecular pathways involved in STING

activation and downstream signalling. For example lymphopenia has been described both in patients with SAVI[99,108] and also in a mouse model[102] of the disease. In addition, reports exist of patients with clinical features of immunodeficiency associated with reduced T cell activation and yet who went on to develop inflammatory complications typical of SAVI[109,110].

[H1] Towards a systems-based classification

Classification of autoimmune and autoinflammatory disorders has been moving gradually from a gene-centric view towards more systems-based classifications[111,112] (Figure 5), with the ultimate goal of providing personalized diagnoses and medicine for each patient. In the 2018 taxonomy[9], autoinflammatory disorders are defined as "clinical disorders caused by defect(s) or dysregulation of the innate immune system, characterized by recurrent or continuous inflammation (elevated acute phase reactants-APR) and the lack of a primary pathogenic role for the adaptive immune system (autoreactive T-cells or autoantibody production)." However, when taking into consideration the complex interplay between the innate and adaptive immune systems, a number of conditions do not fit readily into this taxonomy. A number of interferonopathies, for example, have features of autoimmunity and autoinflammation, with overlapping phenotypes from different genotypes[113]. An alternative approach, using a systems approach to examine signalling pathway dysregulation profiles in autoimmunity and autoinflammation[111], found that although all of the diseases studied involved activation of certain common inflammatory processes, disease-specific variation in the relative representations of these inflammatory processes was also identified. For instance, there is increasing evidence, particularly from genome-wide association studies and transcriptomic analyses, that innate immune-mediated inflammation has an essential role in the pathogenesis of some of the more common chronic systemic conditions, such as Crohn's disease[114], type 2 diabetes mellitus[115] and a myeloid pathotype of RA [116] (see Box 2). However, our understanding of how these different disease categories develop and progress remains very incomplete.

One recommendation has been the development of a multidimensional immunological continuum, with diseases being ordered along gradients of measurable variables, to include first-line variables that reflect innate immune involvement, such as levels of the acute-phase reactants (for example, C-reactive protein and serum amyloid A), in addition to first-line

variables of the adaptive immune system, such as levels of serum β_2 microglobulin and total lymphocyte count[112]. Furthermore, individual axes for discrete properties, such as the presence of inflammatory amyloid A amyloidosis, could also be incorporated in such a continuum, to enable the location of each individual patient's disease signature within the resulting multidimensional space and a diagnosis specific to the individual in question (Figures 5 and 6). A real-life example of this might be the classification of RA (a particularly complex, heterogeneous disorder with an innate immune-mediated subtype) in an individual patient based on a series of parameters, including HLA genotype, the presence or absence of shared epitope alleles, seropositivity for anti-citrullinated protein antibodies and/or rheumatoid factor, synovial histology (to determine if the inflammatory cell infiltrate is predominantly myeloid or lymphoid), radiological changes and other investigations relevant to the patient's presentation. The logical progression and conclusion of this approach is that each patient would emerge with a specific diagnosis unique to their condition, and an associated therapeutic regimen adapted to their individual needs – in other words, personalised or individualised medicine.

[H1] Implications for new therapies

Each discovery in the field of autoinflammation increases the possibility of developing better treatments to target specific components of the innate immune system that might be overactive in systemic autoinflammatory diseases [117]. With the recognition of the various signalling defects involved, it is likely that drugs, such as targeted small-molecule therapeutics, will be developed to block the various dysregulated signals that trigger inflammation mediated by innate immune cells. For example, inhibition of mROS production within dopaminergic neurons is already one of the neuroprotective strategies currently being studied for the management of Parkinson disease[118], and improved understanding of these complex systems is also likely to result in the use of specific ROS inhibitors as adjunct therapies in autoinflammation. Furthermore, the recognition that itaconate **[G]** is an important anti-inflammatory metabolite[119] highlights its potential as a metabolic reprogrammer[120] to restore homeostasis in specific cells of the innate immune system, for instance by driving pro-inflammatory M1 macrophages towards an anti-inflammatory M2 phenotype[120,121]. Finally, microbial modulation of the gut microbiome is another promising therapeutic avenue for treating autoinflammation, but these approaches are still in their infancy[122,123].

[H1] Conclusions

Twenty years have elapsed since the term autoinflammation was introduced to encompass some of the distinct clinicopathological features of the hereditary periodic fevers, which are characterised by recurrent episodes of inflammation without high-titre autoantibodies or antigen-specific T cells[124]. During that time, it has become increasingly apparent that dysregulation of innate immune responses lies at the heart of these disorders[125]. More than 30 monogenic diseases are currently listed in the Infevers Database of autoinflammatory disorders, with a vast range of clinicopathological entities falling under the umbrella of autoinflammatory disorders [126]. This diverse group of disorders has already provided many unique insights into the biological mechanisms and treatment of inflammation, and it seems plausible that many other conditions remain to be discovered.

In this Review we have attempted to show how the field of autoinflammation is moving towards a systems-based concept and description of innate immune-mediated disease. With the application of current and emerging technological advances, the complex mechanisms involved in initiation, progression and disease resolution will be further defined, with the potential to enable the prevention, diagnosis and treatment of these conditions in the form of personalised medicine in the near future.

Key points

- The definition of autoinflammatory disease has evolved since its original description, with increasing awareness of the influence of various processes in the pathogenesis, including metabolism, cytoskeletal perturbation and infection
- The scope of what is considered autoinflammation is widening, and now includes not only monogenic periodic fever syndromes, but also polygenic conditions and disorders with autoimmune and immunodeficiency components.
- Gene-centric classifications of disease have often been quite restrictive, and a move towards systems-based classifications would be beneficial in the investigation and management of these disorders.
- Many autoinflammatory disorders arise, either partly or fully, because of 'collateral damage' caused by the innate immune system striving to maintain cellular homeostasis, such as in pyrin-linked cytoskeletal imbalance.
- Appreciation of the complex overlap between the manifold systems related to autoinflammation, autoimmunity and immunodeficiency can enable the exploration of therapeutic interventions that were not previously considered.

Acknowledgements

The authors are supported by the EU Horizon 2020 research and innovation programme (ImmunAID; grant agreement number 779295). We are grateful to T. Scambler, F. Berenbaum and S. Lara-Reyna for critical reading of the manuscript.

Competing Interests

S.S. declares that he has received a travel grant and honoraria from SOBI and Novartis. The other authors declare no competing interests.

Author contributions

The authors contributed equally to all aspects of the article.

Publisher's note

Table 1: Monogenic autoinflammatory syndromes by main biological systems involved.

Disease	Gene	Protein	Inheritance	Main symptoms/signs	Main therapy
Inflammasomopathies					
FMF	*MEFV*	Pyrin	AR/AD	Peritonitis, joint attacks and joint pain	Colchicine, IL-1 blockade
PAAND	*MEFV*	Pyrin	AD	Neutrophilic dermatosis (Pyoderma gangrenosum) arthralgia, myalgia	IL-1 blockade, TNF blockade
MKD	*MVK*	Mevalonate kinase	AR	Lymphadenopathy, abdominal and joint pain, diarrhoea, skin rashes, and headache	NSAIDs, glucocorticoids, IL-1 blockade, TNF blockade
NLRP3-AID	*NLRP3*	NLRP3	AD[a]	Conjunctivitis, general malaise, headaches, rash, joint pain	IL-1 blockade
NLRP12-AID[c]	*NLRP12*	Monarch-1 protein	AD	Skin rash, lympha-denopathy, aphthous ulcers, abdominal complaints	IL-1 blockade, glucocorticoids
NLRC4-AID	*NLRC4*	NLRC4	AD	Infantile enterocolitis, macrophage activation syndrome	IL-1 blockade, IL-18 blockade[d]
NLRP1-AID[c]	*NLRP1*	NLRP1	AD	Dyskeratosis, arthritis	Acitretin, IL-1 blockade
Actinopathies (actin cytoskeleton dysregulation)					
PAPA syndrome	*PSTPIP1*	CD2 binding protein-1	AD	Juvenile-onset arthritis, painful ulcers and acne	Glucocorticoids, IL-1 blockade, TNF blockade
PFIT	*WDR1*	WD repeat domain 1	AR	Autoinflammatory periodic fevers, immunodeficiency and thrombocytopenia	N/A
ARPC1B deficiency	*ARPC1B*	Actin-related protein 2/3 complex subunit 1B	AR	Combined immunodeficiency, bleeding tendencies and autoinflammatory, autoimmune and allergic complications	N/A
Interferonopathies					
Aicardi-Goutières syndrome	*TREX1* *RNASEH2A* *RNASEH2B* *RNASEH2C* *SAMHD1*	Exonuclease, subunits of RNase H2 endonuclease complex SAM domain and HD domain 1	AD/AR	Encephalopathy, hepatosplenomegaly, skin lesions	Symptomatic treatment, JAK inhibition, reverse transcriptase inhibitors
DNASE2 deficiency[c]	*DNASE2*	Deoxyribonuclease	AR	Neonatal anaemia, deforming arthropathy, GN, liver fibrosis,	
PRAAS, CANDLE[c]	*PSMB3* *PSMB4* *PSMB8* *PSMB9*	Proteasome	AR	Skin eruptions, progressive lipodystrophy,	Oral glucocorticoids, JAK inhibition

	POMP			hepatosplenomegaly, myositis,	
SAVI	*TMEM173*	STING	AD	Vasculopathy, skin lesions (leading to ulcers and necrosis), Raynaud phenomenon	JAK inhibition
Other interferonopathies	*POLA1, ADAR1, IFIH1, RIG-1, SKIV2L, PNTP1, NGLY1, ATM, DCLRE1C, ISG15, UPS18, ACP5, C1q*	Proteins related to RNA sensing, editing and metabolism, DNA synthesis and repair inhibition of ISG transcription, phosphatase activity, alternative complement pathway activity	X-linked recessive, AR or AD	Complex mixture; for details please see ref. 82	JAK inhibition is efficacious in some patients
NF-κB dysregulation					
HA20	*TNFAIP3*	A20	AD[a]	Oral, gastrointestinal and genital ulcers; arthralgia	Colchicine, systemic glucocorticoids, IL-1 blockade, IL-6 blockade, TNF blockade
Biallelic RIPK1 mutations	*RIPK1*	Receptor-interacting serine/threonine kinase 1	N/A	Early-onset inflammatory bowel disease, and progressive polyarthritis	HSCT successful in one patient
HOIL-1 or HOIP deficiency	*HOIL-1, HOIP*	LUBAC components (HOIP, HOIL-1, SHARPIN)	AR	Amylopectinosis, increased susceptibility to viral and bacterial infections	HSCT
(ORAS)	*OTULIN*	Otulin (de-ubiquitinator protease)	AR	Panniculitis, diarrhoea, swollen joints	Anti-TNF
RELA (p65) haploinsufficiency	*RELA/p65*	REL-associated protein	AD	Abdominal pain, mucocutaneous ulceration vomiting, leucocytosis	Anti-TNF
Protein misfolding and ER stress					
TRAPS[c]	*TNFRSF1A*	TNF receptor 1	AD	Skin rash, abdominal pain, myalgia	Glucocorticoids, IL-1 blockade, TNF blockade
Cystic fibrosis	*CFTR*	Cystic fibrosis transmembrane conductance regulator	AR	Recurrent lung infections (mainly *P. aeruginosa* and *B. cepacia*), poor growth, salty-tasting skin	Antibiotics, CFTR chaperones and potentiators, mucolytic agents
PRAAS, CANDLE[c]	*PSMB3 PSMB4 PSMB8 PSMB9 POMP*	Proteasome	AR	Skin eruptions, progressive lipodystrophy, hepatosplenomegaly, myositis	Oral glucocorticoids, JAK inhibition

SIFD[c]	*TRNT1*	TRNA nucleotidyl transferase 1	AR	Delayed psychomotor development, variable neurodegeneration, recurrent fevers	
Others[c]					1
DADA2	*CECR1*	Adenosine deaminase 2	AR	Mottled rash (livedo reticularis), anaemia, joint pain, fatigue	Anti-TNF, HSCT
DIRA	*IL-1RN*	IL-1Ra	AR	Painful joint swelling, pustular rash, hepatosplenamegaly	IL-1 blockade
LACC1-mediated monogenic Still's disease	*LACC1*	NSAIDs	AR	Quotidian fever, characteristic rash	
IL-1RN variation (systemic JIA)	*IL1RN*	IL-1Ra	AR	Homozygous *IL1RN* high expression alleles correlated with lack of response to anakinra therapy	IL-6 blockade, IL-1 blockade, glucocorticoids
DITRA	*IL-36RN*	IL-36Ra	AR	Pustular psoriasis, asthenia	IL-1 blockade, TNF blockade

3 Main clinical features aside from apparent high fever are included in the table. Key references
4 used to construct this table: [127 82 128 129 130 131 83]. AD, autosomal dominant; AID, associated
5 inflammatory disease; AR: autosomal recessive; CANDLE, chronic atypical
6 neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome; DADA2,
7 deficiency of adenosine deaminase 2; DIRA, deficiency of IL-1Ra; DITRA, deficiency of IL-
8 36 receptor antagonist; FCAS2, familial cold autoinflammatory syndrome 2; FMF, familial
9 Mediterranean fever; HSCT, haematopoietic stem cell transplantation; IL-1Ra, IL-1 receptor
10 antagonist; IL-36Ra, IL-36 receptor antagonist; LUBAC, linear ubiquitin chain assembly
11 complex; MKD, mevalonate kinase deficiency; N/A. not applicable; ORAS, otulin-related
12 autoinflammatory syndrome; PAAND, pyrin-associated autoinflammation with neutrophilic
13 dermatosis; PAPA syndrome, pyogenic arthritis, pyoderma gangrenosum, and acne syndrome;
14 SAVI, STING-associated vasculopathy with onset in infancy; TRAPS, TNF receptor-
15 associated periodic fever syndrome.
16 [a]Reports of sporadic cases as well.
17 [b]These diseases are included for informational purposes, but not discussed in the Review.
18 Readers are encouraged to research these pathways in the literature.
19 [c]Anti-IL-18 therapy is currently in clinical trials and not routinely available.

Box 1 | What are inflammasomes?

A fundamental element of the innate immune response is inflammasome activation. Inflammasomes are multimeric complexes consisting of various cytosolic proteins, which assemble in response to a range of pathogenic or physiological stimuli, including damage-associated molecular patterns (endogenous signals released as a result of cell or tissue damage) and pathogen-associated molecular patterns (molecules such as lipopolysaccharide that are largely produced by microbes)[132]. These stimuli are detected by sensors known as pattern recognition receptors, which include nucleotide-binding domain–like receptors (NLRs), absent in melanoma 2–like receptors (ALRs) and pyrin[133]. These pattern recognition receptors combine with other structural components to make up the inflammasome; typically, the other components are the adaptor protein ASC (apoptosis-associated speck-like protein containing a caspase-activation and recruitment domain (CARD)) and the cysteine protease pro-caspase-1. Inflammasome activation leads to the oligomerisation of ASC into large protein complexes known as 'specks', which engage pro-caspase-1 and convert it into caspase-1 via proximity-induced autocatalytic cleavage. The active caspase-1 subunits p10 and p20 then cleave the inactive cytokine precursors pro-IL-1β and pro-IL-18 to produce the mature inflammatory cytokines IL-1β and IL-18[134]. The active inflammasome also results in pyroptosis, a specific form of inflammatory cell death promoted by the pore-forming protein gasdermin D[135,136].

The prototypic inflammasome, NLRP3, consists of the sensor NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3), ASC and pro-caspase-1. The NLRP3 inflammasome is the most widely studied inflammasome, partly owing to the nature of its response to a wide range of different stimuli but also because of its involvement in disease states[137,138]. NLRP3 inhibition has been found to be disrupted in NLRP3-associated autoinflammatory disease (formerly referred to as cryopyrin-associated periodic syndromes (CAPS)); this group of autoinflammatory disorders is caused by gain-of-function mutations in NLRP3 and is one example of the important role that inflammasomes may have in disease, in general. [139]. Various syndromes that are related to dysregulation of the different inflammasomes, including the NLRC4 and pyrin inflammasomes, are described in depth elsewhere in this Review.

Box 2 | Autoinflammation in complex disorders

Although the main focus of this Review is monogenic diseases, evidence is increasing that immune-mediated inflammation has an essential role in the pathogenesis of some chronic systemic conditions such as Crohn's disease[114], type 2 diabetes mellitus[115] and a myeloid

pathotype of rheumatoid arthritis (RA)[116]. Much of the evidence supporting this suggestion has come from genome-wide association studies, and several such studies investigating groups of patients with RA have provided support for the existence of a myeloid subtype of RA. Two studies from Japan that interrogated whole-blood gene expression data as a source of biomarkers to predict drug response in patients with RA found innate immune signatures [140,141]. In a study that categorized patients into remission and non-remission groups, the expression of both neutrophil-specific and natural killer (NK) cell-specific genes was upregulated in patients treated with abatacept in the non-remission group[140]. A multiomics study identified highly upregulated gene transcripts in neutrophils of patients with RA[141], which is consistent with a 2016 study of paediatric patients with SLE, in which a neutrophil signature was associated with disease progression to active nephritis[92].

Further to these studies is the burgeoning concept of osteoarthritis (OA) as an example of a mechanically-driven disease that could be considered as an autoinflammatory disease[142,143]. OA pathogenesis results from mechanical stress activating cells, primarily joint cells such as chondrocytes and osteocytes, via mechanoreceptors[144]. This results in innate immune activation which ultimately results in activation of kinases, such as MAPK, and a subsequent increase in the expression of ROS, pro-inflammatory cytokines and metalloproteinases[145,146]. This immune response is exacerbated by the metalloproteinase-induced release of matrix fragments such as fibronectin into the synovial fluid, causing activation of the innate immune system in the synovium[147]. As such, an autoinflammatory component can be seen in OA, which has in the past been considered primarily a mechanically driven disease[143].

Together, these reports underline the central role of the innate immune system in both the pathogenesis of these complex polygenic conditions and the diversity of systems that can converge to result in an autoinflammatory response.

Figures

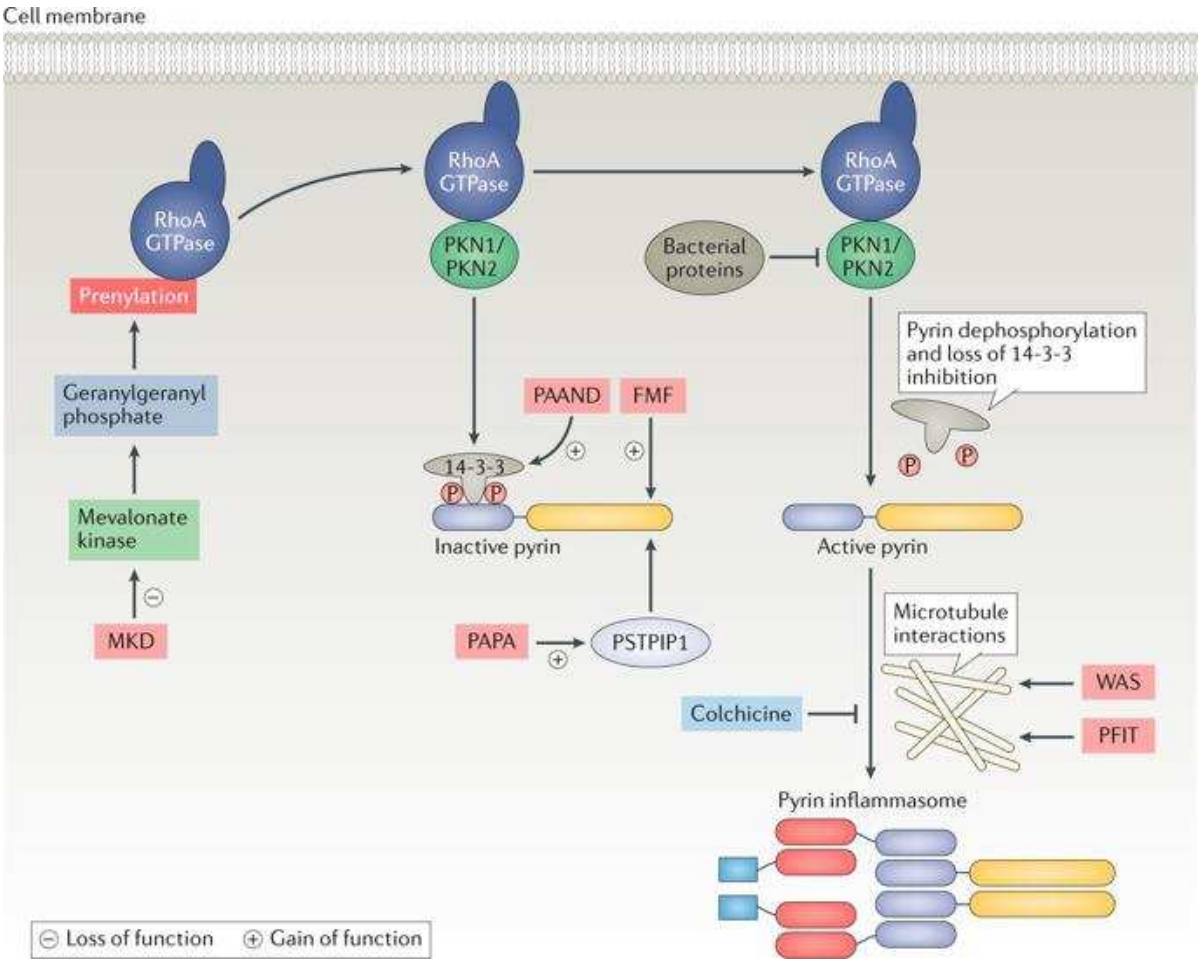

Figure 1 | Pyrin and the cytoskeleton in systemic autoinflammatory diseases. Mevalonate kinase (MVK) mediates the production of geranylgeranyl phosphate, leading to prenylation of RhoA GTPases and their subsequent localisation to the cell membrane. RhoA GTPases activate protein kinase N1 (PKN1) and PKN2, which facilitate binding of the inhibitory protein 14-3-3 to pyrin by phosphorylating it at serine residues 208 and 242 (S208 and S242), resulting in inactive pyrin. Pyrin becomes active when bacterial proteins that inactivate RhoA GTPases, such as Clostridium difficile toxin B (TcdB), reduce PKN1 and PKN2 activity, causing pyrin dephosphorylation and loss of 14-3-3 inhibition. Active pyrin forms the mature pyrin inflammasome via a cytoskeleton-dependent interaction with ASC, consisting of a pyrin domain (PYD) and a caspase activation and recruitment domain (CARD), allowing caspase-1 to be recruited. Dysregulation of this pathway is implicated in the recently defined diseases highlighted.

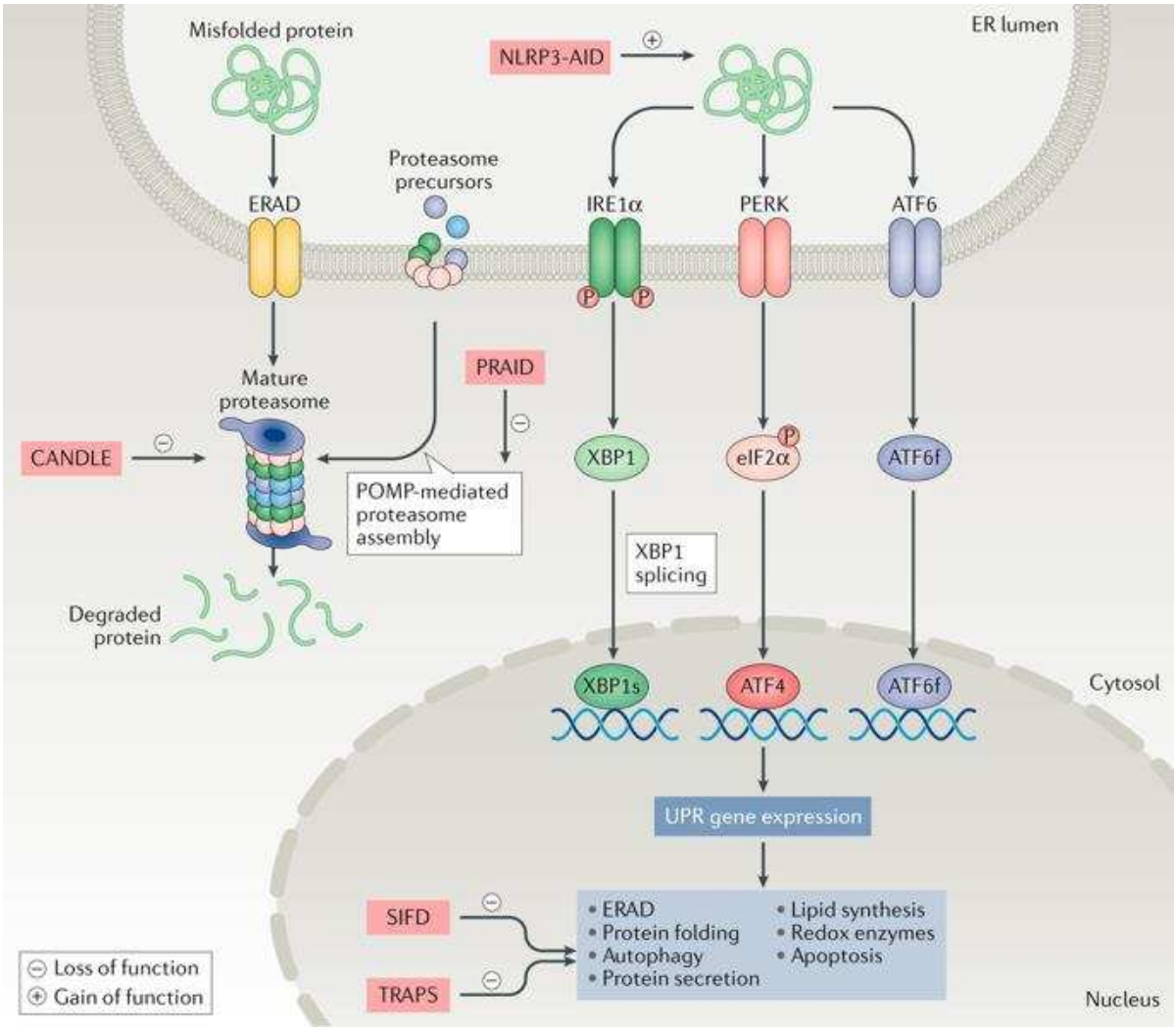

Figure 2 | The unfolded protein response

Under usual conditions, the accumulation of misfolded protein in the ER lumen causes the protein to undergo endoplasmic reticulum-associated degradation (ERAD). This is mediated by proteasome maturation protein (POMP), an ER membrane-associated molecular chaperone required for the assembly of proteasomes. The mature cytosolic proteasome can subsequently degrade the misfolded protein, reducing the cellular burden. If the accumulated protein is not sufficiently cleared to restore normal function of the cell, the unfolded protein response (UPR) is triggered. The UPR is initiated by three transmembrane stress receptors localised to the endoplasmic reticulum (ER); inositol-requiring protein 1α (IRE1α), protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK) and activating transcription factor 6 (ATF6). These sensors activate downstream events through different mechanisms to increase protein folding and reduce misfolded proteins in the ER. IRE1α dimerization and subsequent phosphorylation activates this receptor's RNase activity, allowing it to process the mRNA encoding un-spliced X box-binding protein 1 (XBP1), generating the transcription factor spliced XBP1 (XBP1s).

Activation of PERK causes it to phosphorylate eukaryotic translation initiator factor 2α (eIF2α), which in turn leads to the production of activating transcription factor 4 (ATF4). ATF6 is transported to the Golgi apparatus, where it undergoes proteolysis to release its cytosolic domain fragment (ATF4f) which contains a transcription factor. The three resulting transcription factors control the transcription of genes vital to the UPR; genes regulated by XBP1s are related to ER-associated degradation (ERAD), lipid synthesis and protein folding, ATF4 influences genes underlying redox enzymes, autophagy and apoptosis, whereas ATF6f primarily regulates genes related to ERAD. These transcriptional responses collectively increase protein-folding capacity in the ER. Perturbations of this pathway which are implicated in disease are highlighted, with disease names shown in boxes outlined in red.

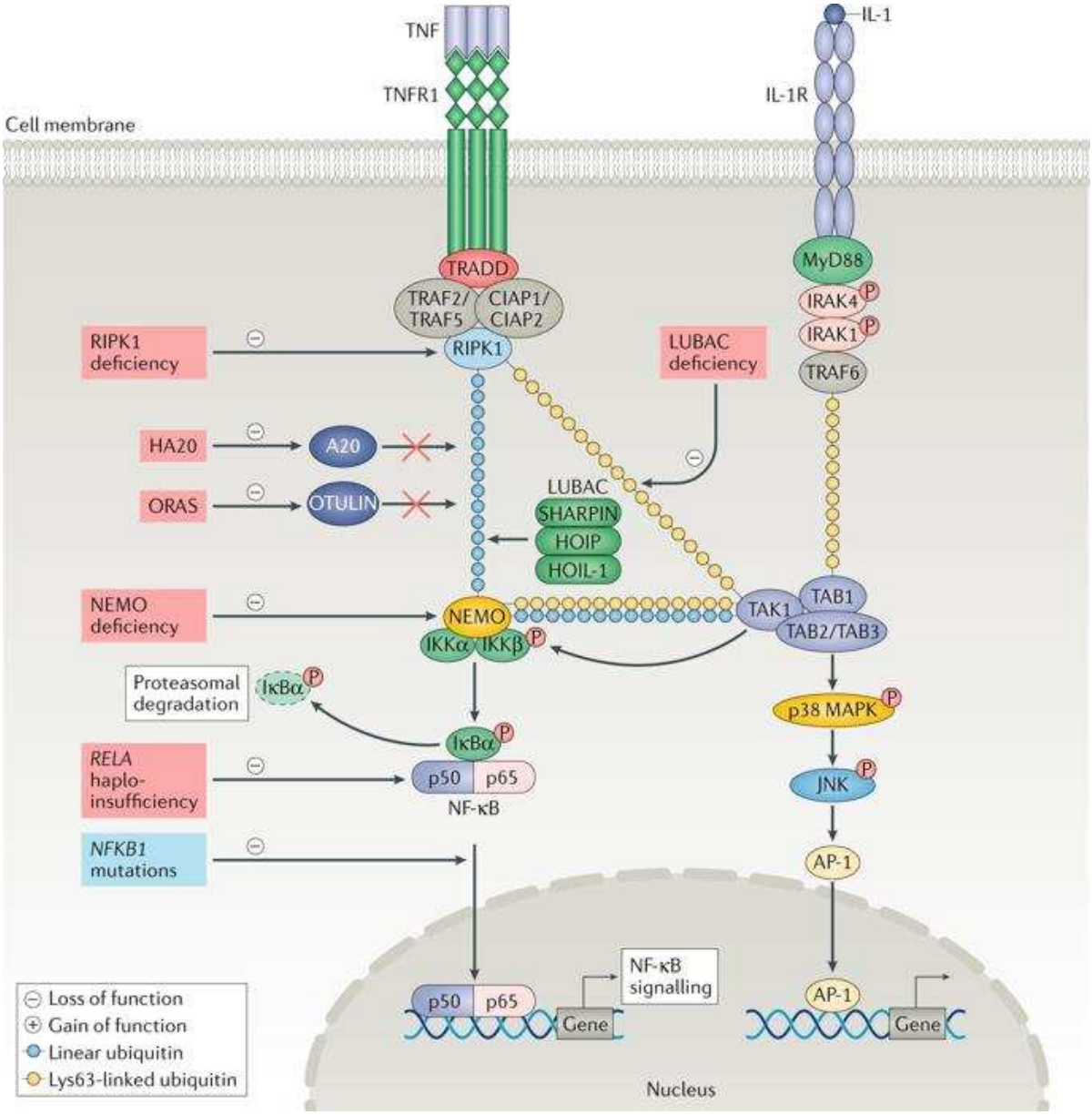

Figure 3 | Defects in NF-κB pathway-related genes

TNF binds to TNF receptor 1 (TNFR1) and initiates the formation of complex 1, consisting of TNFR1-associated death domain (TRADD), TNFR-associated factor 2/5 (TRAF2/5), cellular inhibitor of apoptosis protein 1 or 2 (CIAP1/2) and receptor-interacting serine/threonine-protein kinase 1 (RIPK1). Lys-63-linked and linear ubiquitination of RIPK1 by the the linear ubiquitin chain assembly complex (LUBAC) (comprised of HOIP, HOIL, and SHARPIN) and CIAP1/2, respectively, activate the transforming growth factor β (TGFβ)-activated kinase 1 (TAK1) complex (consisting of TGFβ-activated kinase 1 and mitogen-activated protein kinase (MAPK)-binding protein 2 and 3 (TAB2 and 3) and TAK1) and the IκB kinase (IKK) complex (NEMO and IKKα/β). The TAK1 complex phosphorylates p38 mitogen-activated protein kinase (MAPK), Jun N-terminal kinase (JNK), and the IκB kinase (IKK) complex, causing the translocation of NF-kB transcription factors (p50/p60) and AP1 into the nucleus and subsequent gene transcription. A20 and Otulin cleave ubiquitin chains from RIPK1 and the IKK complex, inhibiting NF-κB signalling. Perturbations of the pathway which are implicated in disease are highlighted; disease names are shown in boxes outlined in red, whereas NFKB1 mutations, which represent a series of mutations related to clinical phenotypes, is outlined in blue.

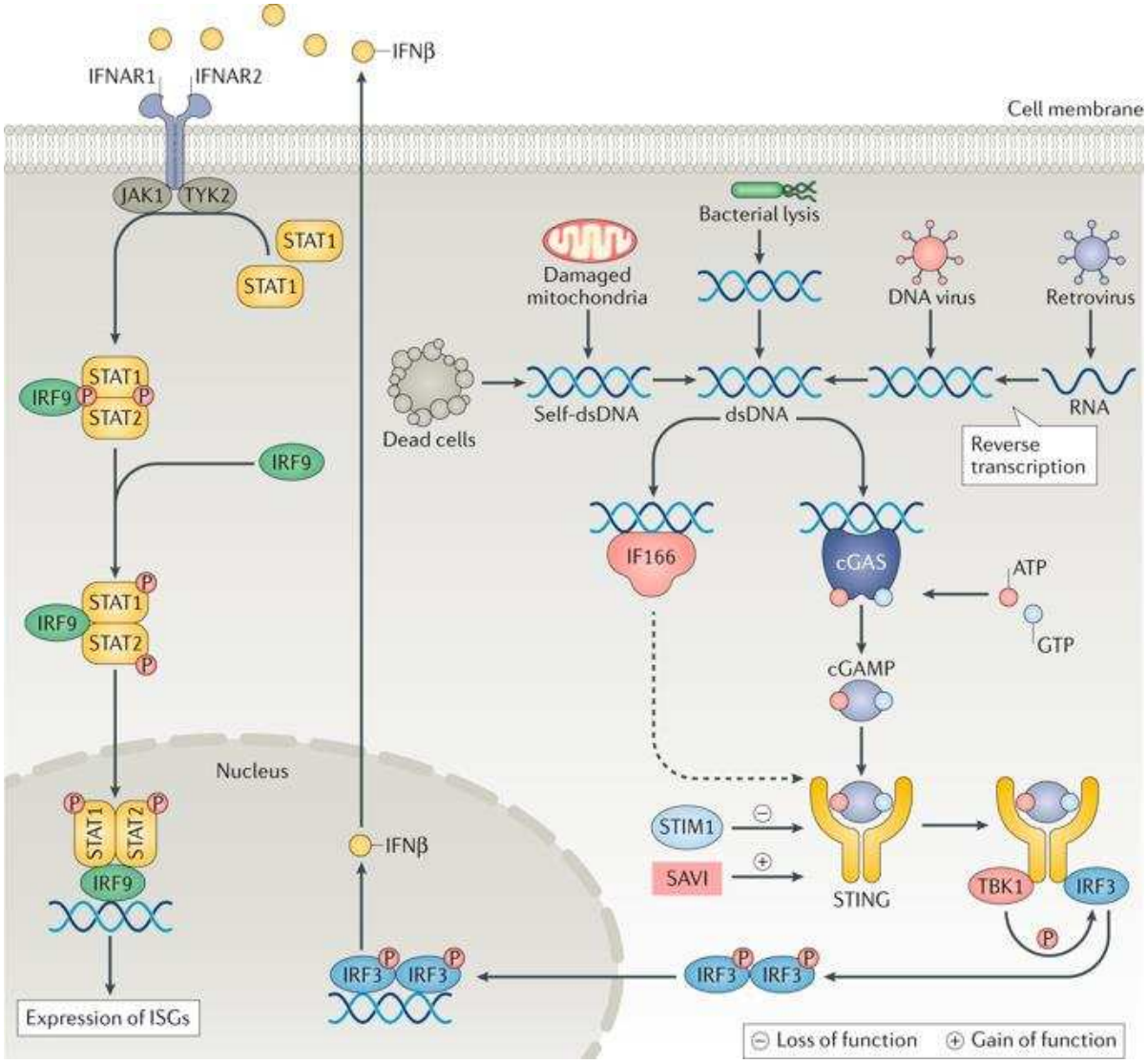

Figure 4 | The interferon pathway. Double stranded DNA (dsDNA) acts as a pathogen-associated molecular pattern when introduced via infection, or a danger-associated molecular pattern when the source is from self-dsDNA, such as dead cells or damaged mitochondria. Cyclic GMP-AMP (cGAS) is activated by dsDNA binding and synthesises cyclic GMP-AMP (cGAMP) from adenosine triphosphate (ATP) and guanosine triphosphate (GTP). cGAMP binds and activates the adaptor protein STING on the ER surface; STING subsequently activates TANK-binding kinase 1 (TBK1), which phosphorylates STING, allowing STING to recruit IFN regulatory factor 3 (IRF3) which is phosphorylated by TBK1. Dimerised IRF3 translocates to the nucleus and stimulates type 1 interferon (IFN-1) expression. IFN binds to IFN receptors, consisting of a dimer of interferon α/β receptor subunit 1 and 2 (IFNAR1 and IFNAR2), which activates the Janus-family tyrosine kinases JAK1 and TYK2, leading to phosphorylation of the signal transducers and activators of transcription (STAT) proteins STAT1 and STAT2. Phosphorylated STATs bind Interferon Regulatory Factor-9 (IRF9) to

form the Interferon-stimulated transcription factor-3 complex, which migrates to the nucleus and initiates interferon-stimulated gene expression. White boxes denote parts of the pathway implicated in disease.

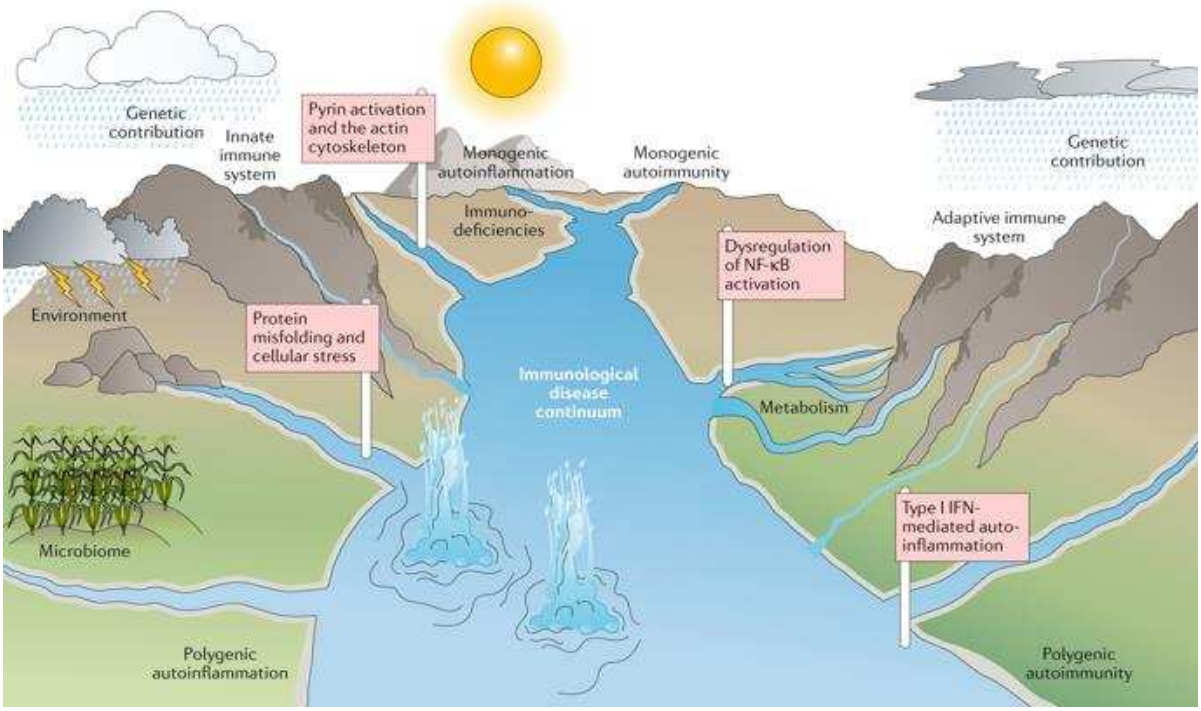

Figure 5 | The autoinflammatory disease landscape. The course of the immunological disease continuum river is shaped by the adjacent landscape, which is inherently dynamic and subject to multiple driving forces, such as environment, microbiome (diet-related), genetic predisposition, and stochastic factors, amongst many others. The flagged elements relate to important discoveries since 2016, and, for that reason, some other major system perturbations in autoinflammatory disease, such as inflammasomes and nucleic acid dysregulation, have not been highlighted. Varying levels of contributory input from the tributaries may lead to different degrees of autoinflammation, autoimmunity and immunodeficiency in the final disease phenotype.

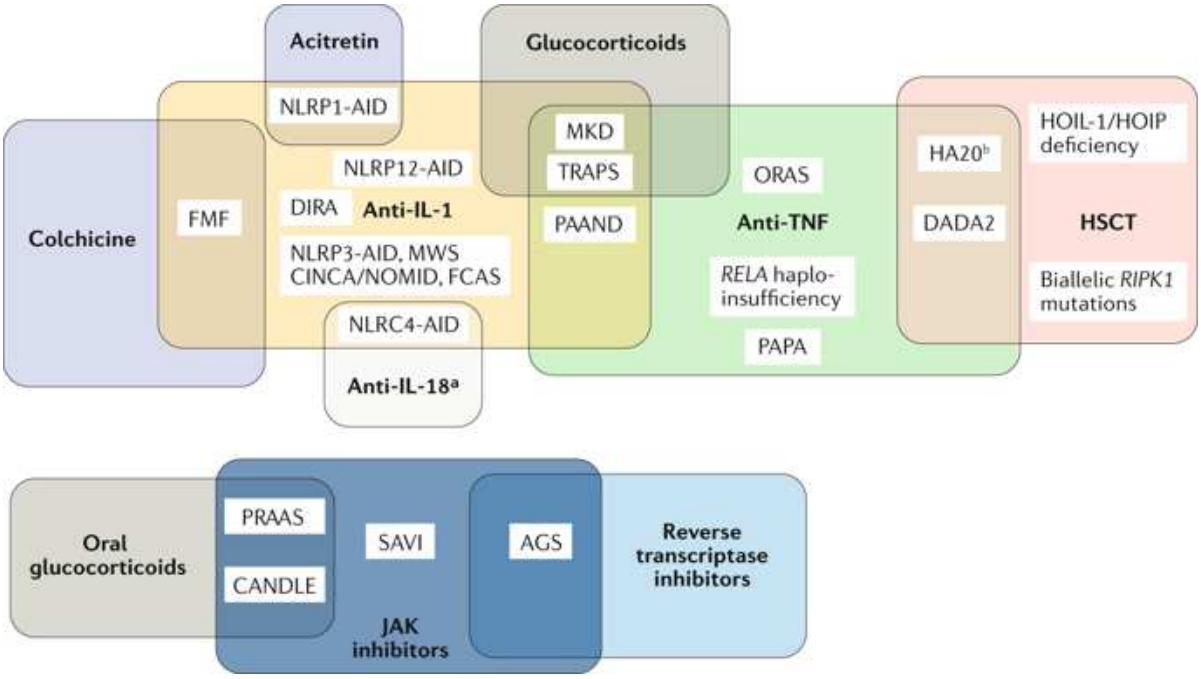

Figure 6 | The overlapping therapeutic options in autoinflammatory disease. The diseases described in this Review and found in Table 1 can be classified by the predominant therapies used in their treatment. Therapies are shown in white boxes.

[a]Anti-IL-18 therapy is in clinical trials and is not routinely available. [b]Other anti-cytokine therapies (anti-IL-1 and anti-IL-6) can also have therapeutic benefit in selected cases.

References

1 Pathak, S., McDermott, M. F. & Savic, S. Autoinflammatory diseases: update on classification diagnosis and management. J. Clin. Pathol. **70**, 1-8 (2017).

2 Beck, D. & Aksentijevich, I. J. F. Biochemistry of autoinflammatory diseases: catalyzing monogenic disease. Front. Immunol. **10**, 101 (2019).

3 International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell **90**, 797-807 (1997).

4 French FMF Consortium. A candidate gene for familial Mediterranean fever. Nat. Genet. **17**, 25 (1997).

5 Masters, S. L. et al. Familial autoinflammation with neutrophilic dermatosis reveals a regulatory mechanism of pyrin activation. Sci. Transl. Med. **8**, 332-345 (2016).

6 De Benedetti, F. et al. Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. N. Engl. J. Med. **378**, 1908-1919 (2018).

7 Moghaddas, F. et al. A novel pyrin-associated autoinflammation with neutrophilic dermatosis mutation further defines 14-3-3 binding of pyrin and distinction to familial Mediterranean fever. Ann. Rheum. Dis. **76**, 2085-2094 (2017).

8 McGonagle, D. & McDermott, M. F. A proposed classification of the immunological diseases. PLoS Med. **3**, e297 (2006).
9 Ben-Chetrit, E. et al. Consensus proposal for taxonomy and definition of the autoinflammatory diseases (AIDs): a Delphi study. Ann. Rheum. Dis. **77**, 1558-1565 (2018).
10 McGonagle, D., Watad, A. & Savic, S. J. Novel immunological based classification of rheumatoid arthritis with therapeutic implications. Autoimm. Rev. **11**, 1115-1123 (2018).
11 Ozen, S. & Bilginer, Y. A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin. Nat. Rev. Rheumatol. **10**, 135-147 (2014).
12 Xu, H. et al. Innate immune sensing of bacterial modifications of Rho GTPases by the Pyrin inflammasome. Nature **513**, 237 (2014).
13 Park, Y. H. et al. Pyrin inflammasome activation and RhoA signaling in the autoinflammatory diseases FMF and HIDS. Nat. Immunol. **17**, 914-921 (2016).
14 Hong, Y. et al. Autoinflammation due to homozygous S208 MEFV mutation. Ann Rheum Dis. **78**, 571-573 (2019).
15 Gao, W., et al. Site-specific phosphorylation and microtubule dynamics control Pyrin inflammasome activation. Proc. Natl. Acad. Sci. USA **113**, 4857-4866 (2016).
16 Van Gorp, H. et al. Familial Mediterranean fever mutations lift the obligatory requirement for microtubules in pyrin inflammasome activation. Proc. Natl. Acad. Sci. USA **113**, 14384-14389 (2016).
17 Jamilloux, Y. et al. Familial Mediterranean fever mutations are hypermorphic mutations that specifically decrease the activation threshold of the pyrin inflammasome. Rheumatology **57**, 100-111 (2017).
18 Drenth, J. P. et al. Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group. Nat. Genet. **22**, 178-181 (1999).
19 Houten, S. M. et al. Mutations in MVK, encoding mevalonate kinase, cause hyperimmunoglobulinaemia D and periodic fever syndrome. Nat. Genet. **22**, 175-177 (1999).
20 Seabra, M. Membrane association and targeting of prenylated Ras-like GTPases. Cell Signal. **10**, 167-172 (1998).
21 Ozen, S. et al. International retrospective chart review of treatment patterns in severe familial Mediterranean fever, tumor necrosis factor receptor–associated periodic syndrome, and mevalonate kinase deficiency/hyperimmunoglobulinemia D syndrome. Arthritis Care & Res. **69**, 578-586 (2017).
22 ter Haar, N. M. et al. The phenotype and genotype of mevalonate kinase deficiency: a series of 114 cases from the Eurofever registry. Arthritis Rheum. **68**, 2795-2805 (2016).
23 Lachmann, H. J. Periodic fever syndromes. Best Pract. Res. Clin. Rheumatol. **31**, 596-609 (2017).
24 Waite, A. L. et al. Pyrin modulates the intracellular distribution of PSTPIP1. PLoS One **4**, 6147 (2009).
25 Waite, A. L. et al. Pyrin and ASC co-localize to cellular sites that are rich in polymerizing actin. Exp. Biol. & Med. **234**, 40-52 (2009).
26 Manukyan, G. et al. Activated phenotype of circulating neutrophils in familial Mediterranean fever. Immunobiology **218**, 892-898 (2013).
27 Vicente-Manzanares, M. & Sanchez-Madrid, F. Role of the cytoskeleton during leukocyte responses. Nat. Rev. Immunol. **4**, 110-122 (2004).
28 Alghamdi, M. Familial Mediterranean fever, review of the literature. Clin. Rheumatol. **36**, 1707-1713 (2017).

29 Wise, C. A. et al. Mutations in CD2BP1 disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder. Human Mol. Genet. **11**, 961-969 (2002).
30 Yeon, H. B., et al. Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome maps to chromosome 15q. Am. J. Hum. Genet. **66**, 1443-1448 (2000).
31 Starnes, T. W. et al. The F-BAR protein PSTPIP1 controls extracellular matrix degradation and filopodia formation in macrophages. Blood. **123**, 2703-2714 (2014).
32 Shoham, N. G. et al. Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. Proc. Natl. Acad. Sci. USA **100**, 13501-13506 (2003).
33 Pfajfer, L. et al. Mutations affecting the actin regulator WD repeat–containing protein 1 lead to aberrant lymphoid immunity. J. Allergy Clin. Immunol. **142**, 1589-1604. (2018).
34 Kim, M. L. et al. Aberrant actin depolymerization triggers the pyrin inflammasome and autoinflammatory disease that is dependent on IL-18, not IL-1β. J. Exp. Med. **212**, 927-938 (2015).
35 Volpi, S. et al. A combined immunodeficiency with severe infections, inflammation, and allergy caused by ARPC1B deficiency. J. Allergy Clin. Immunol. **143**, 2296-2299 (2019).
36 Lee, P. P. et al. Wiskott-Aldrich syndrome protein regulates autophagy and inflammasome activity in innate immune cells. Nat. Commun. **8**, 1576 (2017).
37 Poli, M. C. et al. Heterozygous truncating variants in POMP escape nonsense-mediated decay and cause a unique immune dysregulatory syndrome. Am. J. Hum. Genet. **102**, 1126-1142 (2018).
38 Fricke, B. et al. The proteasome maturation protein POMP facilitates major steps of 20S proteasome formation at the endoplasmic reticulum. EMBO Reports **8**, 1170-1175 (2007).
39 Chakraborty, P. K. et al. Mutations in TRNT1 cause congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay (SIFD). Blood **124**, 2867-2871 (2014).
40 Wiseman, D. H. et al. A novel syndrome of congenital sideroblastic anemia, B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD). Blood **122**, 112-123 (2013).
41 Giannelou, A. et al. Aberrant tRNA processing causes an autoinflammatory syndrome responsive to TNF inhibitors. Ann. Rheum. Dis. **77**, 612-619 (2018).
42 Dickie, L. J. et al. Involvement of X-box binding protein 1 and reactive oxygen species pathways in the pathogenesis of tumour necrosis factor receptor-associated periodic syndrome. Ann. Rheum. Dis. **71**, 2035-2043 (2012).
43 Scambler, T. et al. ENaC-mediated sodium influx exacerbates NLRP3-dependent inflammation in cystic fibrosis. eLife **8**, e49248 (2019).
44 Agyemang, A. F., et al. Protein misfolding and dysregulated protein homeostasis in autoinflammatory diseases and beyond. Sem. Immunopathol. 335-347 (2015).
45 Cherubini, M. & Wade-Martins, R. Convergent pathways in Parkinson's disease. Cell Tissue Res. **373**, 79-90 (2018).
46 Lenart, N., Brough, D. & Denes, A. Inflammasomes link vascular disease with neuroinflammation and brain disorders. J. Cereb. Blood Flow Metab. **36**, 1668-1685 (2016).
47 Sen, R. & Baltimore, D. J. Multiple nuclear factors interact with the immunoglobulin enhancer sequences. Cell **46**, 705-716 (1986).

48 Sen, R. & Baltimore, D. J. C. Inducibility of κ immunoglobulin enhancer-binding protein NF-κB by a posttranslational mechanism. Cell **47**, 921-928 (1986).
49 Mussbacher, M. et al. Cell type-specific roles of NF-κB linking inflammation and thrombosis. Front. Immunol. **10** (2019).
50 Tak, P. P. & Firestein, G. S. NF-κB: a key role in inflammatory diseases. J. Clin. Invest. **107**, 7-11 (2001).
51 Lawrence, T. The nuclear factor NF-κB pathway in inflammation. Cold Spring Harb. Perspect. Biol. **1**, a001651 (2009).
52 Croston, G. E., Cao, Z. & Goeddel, D. V. NF-κB activation by interleukin-1 (IL-1) requires an IL-1 receptor-associated protein kinase activity. J. Biol. Chem. **270**, 16514-16517 (1995).
53 Rea, I. M. et al. Age and age-related diseases: role of inflammation triggers and cytokines. Front. Immunol. **9**, 586 (2018).
54 Beg, A. A. & Baldwin, A. S., Activation of multiple NF-κB/Rel DNA-binding complexes by tumor necrosis factor. Oncogene **9**, 1487-1492 (1994).
55 Newton, K. & Dixit, V. M. Signaling in innate immunity and inflammation. Cold Spring Harb. Perspect. Biol. **4** (2012).
56 Kabe, Y., et al. Redox regulation of NF-κB activation: distinct redox regulation between the cytoplasm and the nucleus. Antioxid. Redox. Signal. **7**, 395-403 (2005).
57 Devary, Y., et al. NF-κB activation by ultraviolet light not dependent on a nuclear signal. Science **261**, 1442-1445 (1993).
58 Jarosz-Griffiths, H. H. et al. TNF receptor signalling in autoinflammatory diseases. Internat. Immunol. **31**, 639-648 (2019).
59 Hayden, M. S. & Ghosh, S. Regulation of NF-κB by TNF family cytokines. Semin. Immunol. **26**, 253-266 (2014).
60 Zonana, J. et al. A novel X-linked disorder of immune deficiency and hypohidrotic ectodermal dysplasia is allelic to incontinentia pigmenti and due to mutations in IKK-gamma (NEMO). Am. J. Hum. Genet. **67**, 1555-1562 (2000).
61 Israel, A. The IKK complex, a central regulator of NF-κB activation. Cold Spring Harb. Perspect. Biol. **2**, 1-14 (2010).
62 Jin, D. Y. & Jeang, K. T. Isolation of full-length cDNA and chromosomal localization of human NF-κB modulator NEMO to Xq28. J. Biomed. Sci. **6**, 115-120 (1999).
63 Kere, J. et al. X-linked anhidrotic (hypohidrotic) ectodermal dysplasia is caused by mutation in a novel transmembrane protein. Nat. Gen. **13**, 409-416 (1996).
64 Courtois, G. et al. A hypermorphic IκBα mutation is associated with autosomal dominant anhidrotic ectodermal dysplasia and T cell immunodeficiency. J Clin. Invest. **112**, 1108-1115 (2003).
65 Orange, J. S. & Geha, R. S. Finding NEMO: genetic disorders of NF-κB activation. J. Clin. Invest. **112**, 983-985 (2003).
66 Nenci, A. et al. Epithelial NEMO links innate immunity to chronic intestinal inflammation. Nature **446**, 557-561 (2007).
67 Vlantis, K. et al. NEMO prevents RIP kinase 1-mediated epithelial cell death and chronic intestinal inflammation by NF-κB-dependent and -independent functions. Immunity **44**, 553-567 (2016).
68 Zaph, C. et al. Epithelial-cell-intrinsic IKK-β expression regulates intestinal immune homeostasis. Nature **446**, 552-556 (2007).
69 Cuchet-Lourenco, D. et al. Biallelic RIPK1 mutations in humans cause severe immunodeficiency, arthritis, and intestinal inflammation. Science **361**, 810-813 (2018).
70 Tao, P. et al. A dominant autoinflammatory disease caused by non-cleavable variants of RIPK1. Nature **577**, 109-114 (2020).

71 Lalaoui, N. et al. Mutations that prevent caspase cleavage of RIPK1 cause autoinflammatory disease. Nature **577**, 103-108 (2020).
72 Boisson, B. et al. Immunodeficiency, autoinflammation and amylopectinosis in humans with inherited HOIL-1 and LUBAC deficiency. Nat. Immunol. **13**, 1178-1186 (2012).
73 Ikeda, F. et al. SHARPIN forms a linear ubiquitin ligase complex regulating NF-kappaB activity and apoptosis. Nature. **471**, 637-641 (2011).
74 Aksentijevich, I. & Zhou, Q. NF-κB Pathway in autoinflammatory diseases: dysregulation of protein modifications by ubiquitin defines a new category of autoinflammatory diseases. Front. Immunol. **8**, 399 (2017).
75 Zhou, Q. et al. Biallelic hypomorphic mutations in a linear deubiquitinase define otulipenia, an early-onset autoinflammatory disease. Proc. Natl Acad. Sci. USA **113**, 10127-10132 (2016).
76 Damgaard, R. B. et al. OTULIN deficiency in ORAS causes cell type-specific LUBAC degradation, dysregulated TNF signalling and cell death. EMBO Mol. Med. **11** (2019).
77 Aksentijevich, I. & McDermott, M. F. Lessons from characterization and treatment of the autoinflammatory syndromes. Curr. Opin. Rheumatol. **29**, 187-194 (2017).
78 Zhou, Q. et al. Loss-of-function mutations in TNFAIP3 leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease. Nat. Gen. **48**, 67-73 (2016).
79 Shembade, N. & Harhaj, E. W. Regulation of NF-κB signaling by the A20 deubiquitinase. Cell Mol. Immunol. **9**, 123-130 (2012).
80 Wu, Y. et al. Ubiquitination regulation of inflammatory responses through NF-κB pathway. Am. J. Transl. Res. **10**, 881-891 (2018).
81 Aeschlimann, F. A. et al. A20 haploinsufficiency (HA20): clinical phenotypes and disease course of patients with a newly recognised NF-κB-mediated autoinflammatory disease. Ann. Rheum. Dis. **77**, 728-735 (2018).
82 Lawless, D. et al. A case of adult-onset Still's disease caused by a novel splicing mutation in TNFAIP3 successfully treated with tocilizumab. Front. Immunol. **9**, 1527 (2018).
83 Badran, Y. R. et al. Human RELA haploinsufficiency results in autosomal-dominant chronic mucocutaneous ulceration. J. Exp. Med. **214**, 1937-1947 (2017).
84 Faruqi, A.J. et al. RELA/p65 haploinsufficiency as a novel cause of primary immune disorder. J. Immunol. **198**, 59.17 (2017).
85 Liu, T., et al. NF-κB signaling in inflammation. Signal. Transduct. Target. Ther. **2**, 17023 (2017).
86 Kaustio, M. et al. Damaging heterozygous mutations in NFKB1 lead to diverse immunologic phenotypes. J. Allergy Clin. Immunol. **140**, 782-796 (2017).
87 Alnemri, E. S. Sensing cytoplasmic danger signals by the inflammasome. J. Clin. Immunol. **30**, 512-519 (2010).
88 Uggenti, C., Lepelley, A. & Crow, Y. J. Self-awareness: nucleic acid–driven inflammation and the type I interferonopathokies. Ann. Rev. Immunol. **37,** 247-267 (2019).
89 Sanchez, G. A. M. et al. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. J. Clin. Invest. **128**, 3041 (2018).
90 Briand, C. et al. Efficacy of JAK1/2 inhibition in the treatment of chilblain lupus due to TREX1 deficiency. Ann. Rheum. Dis. **78**, 431-433 (2019).
91 McLellan, K. E. et al. JAK 1/2 blockade in MDA5 gain-of-function. J. Clin. Immunol. **38**, 844-846 (2018).
92 Banchereau, R. et al. Personalized immunomonitoring uncovers molecular networks that stratify lupus patients. Cell. **165**, 1548-1550 (2016).

93 Baechler, E. C. et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc. Natl. Acad. Sci. USA **100**, 2610-2615 (2003).
94 Hjelmervik, T. O. R. et al. Gene expression profiling of minor salivary glands clearly distinguishes primary Sjögren's syndrome patients from healthy control subjects. Arthritis Rheum. **52**, 1534-1544 (2005).
95 Higgs, B. W. et al. Patients with systemic lupus erythematosus, myositis, rheumatoid arthritis and scleroderma share activation of a common type I interferon pathway. Ann. Rheum. Dis. **70**, 2029-2036 (2011).
96 van der Pouw Kraan, T. C. et al. Rheumatoid arthritis subtypes identified by genomic profiling of peripheral blood cells: assignment of a type I interferon signature in a subpopulation of patients. Ann. Rheum. Dis. **66**, 1008-1014 (2007).
97 Rigolet, M. et al. Distinct interferon signatures stratify inflammatory and dysimmune myopathies. Rheum. Musculoskelet. Dis. **5**, e000811 (2019).
98 Li, T. & Chen, Z. J. The cGAS-cGAMP-STING pathway connects DNA damage to inflammation, senescence, and cancer. J. Exp. Med. **215**, 1287-1299 (2018).
99 Liu, Y. et al. Activated STING in a vascular and pulmonary syndrome. N. Engl. J. Med. **371**, 507-518 (2014).
100 Ablasser, A. & Chen, Z. J. cGAS in action: expanding roles in immunity and inflammation. Science **363**, eaat8657 (2019).
101 Luksch, H. et al. STING-associated lung disease in mice relies on T cells but not type I interferon. J. Allergy Clin. Immunol. **144**, 254-266.e8 (2019).
102 Warner, J. D. et al. STING-associated vasculopathy develops independently of IRF3 in mice. J. Exp. Med. **214**, 3279-3292 (2017).
103 Sivick, K. E. et al. Magnitude of therapeutic STING activation determines $CD8^+$ T cell-mediated anti-tumor immunity. Cell Reports **25**, 3074-3085 (2018).
104 Cerboni, S. et al. Intrinsic antiproliferative activity of the innate sensor STING in T lymphocytes. J. Exp. Med. **214**, 1769-1785 (2017).
105 Srikanth, S. et al. The Ca^{2+} sensor STIM1 regulates the type I interferon response by retaining the signaling adaptor STING at the endoplasmic reticulum. Nat. Immunol. **20**, 152 (2019).
106 Rice, L. et al. A report of novel STIM1 deficiency and 6 year follow up of two previous cases associated with mild immunological phenotype. J Clin. Immunol. **3**, 249-256 (2018).
107 Feske, S., Picard, C. & Fischer, A. Immunodeficiency due to mutations in ORAI1 and STIM1. Clin. Immunol. **135**, 169-182 (2010).
108 Jeremiah, N. et al. Inherited STING-activating mutation underlies a familial inflammatory syndrome with lupus-like manifestations. J. Clin. Invest. **124**, 5516-5520 (2014).
109 Konno, H. et al. Pro-inflammation associated with a gain-of-function mutation (R284S) in the innate immune sensor STING. Cell Rep. **23**, 1112-1123 (2018).
110 Saldanha, R. G. et al. A mutation outside the dimerization domain causing atypical STING-associated vasculopathy with onset in infancy. Front. Immunol. **9**, 1535 (2018).
111 Arakelyan, A. et al. Autoimmunity and autoinflammation: A systems view on signaling pathway dysregulation profiles. PLoS One **12**, 1-21 (2017).
112 Grateau, G. et al. How should we approach classification of autoinflammatory diseases? Nat. Rev. Rheumatol. **9**, 624-629 (2013).
113 Savic, S. & McDermott, M. F. Clinical genetics in 2014: New monogenic diseases span the immunological disease continuum. Nat. Rev. Rheumatol. **11**, 67-68 (2015).

114 Savic, S., Dickie, L. J., Wittmann, M. & McDermott, M. F. Autoinflammatory syndromes and cellular responses to stress: pathophysiology, diagnosis and new treatment perspectives. Best Pract. Res. Clin. Rheumatol. **26**, 505-533 (2012).
115 Donath, M. Y. & Shoelson, S. E. Type 2 diabetes as an inflammatory disease. Nat. Rev. Immunol. **11**, 98-107 (2011).
116 Dennis, G., Jr. et al. Synovial phenotypes in rheumatoid arthritis correlate with response to biologic therapeutics. Arthritis Res. Ther. **16**, R90 (2014).
117 Liston, A. & Masters, S. L. Homeostasis-altering molecular processes as mechanisms of inflammasome activation. Nat. Rev. Immunol. **17**, 208 (2017).
118 Yan, M. H., Wang, X. & Zhu, X. Mitochondrial defects and oxidative stress in Alzheimer disease and Parkinson disease. Free Radic. Biol. Med. **62**, 90-101 (2013).
119 Mills, E. L. et al. Itaconate is an anti-inflammatory metabolite that activates Nrf2 via alkylation of KEAP1. Nature **556**, 113-117 (2018).
120 O'Neill, L. & Artyomov, M. N. Itaconate: the poster child of metabolic reprogramming in macrophage function. Nat. Rev. Immunol. **19**, 273–281 (2019).
121 Lara-Reyna, S. et al. Metabolic reprogramming of cystic fibrosis macrophages via the IRE1a arm of the unfolded protein response results in exacerbated inflammation. Front. Immunol. **10**, 1789 (2019).
122 Lukens, J. R. et al. Dietary modulation of the microbiome affects autoinflammatory disease. Nature **516**, 246 (2014).
123 Fishman, J. & Thomson, A. Clinical implications of basic science discoveries: immune homeostasis and the microbiome—dietary and therapeutic modulation and implications for transplantation. Am. J. Transplant. **15**, 1755-1758 (2015).
124 McDermott, M. F. et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell **97**, 133-144 (1999).
125 McDermott, M. F. & Aksentijevich, I. The autoinflammatory syndromes. Curr. Opin. Allergy Clin. Immunol. **2**, 511-516 (2002).
126 Sarrauste de Menthière, C. et al. INFEVERS: the registry for FMF and hereditary inflammatory disorders mutations. Nucleic acids research **31**, 282-285 (2003).
127 Rigante, D., Vitale, A., Lucherini, O. M. & Cantarini, L. The hereditary autoinflammatory disorders uncovered. Autoimmun. Rev. **13**, 892-900 (2014).
128 Berteau, F. et al. Autosomic dominant familial Behçet disease and haploinsufficiency A20: a review of the literature. Autoimmun. Rev. **17**, 809-815 (2018).
129 Cowen, E. W. & Goldbach-Mansky, R. DIRA, DITRA, and new insights into pathways of skin inflammation: what's in a name? Arch. Dermatol. **148**, 381-384 (2012).
130 Liu, Y. et al. Activated STING in a vascular and pulmonary syndrome. N. Engl. J. Med. **371**, 507-518 (2014).
131 Rossi-Semerano, L. et al. First clinical description of an infant with interleukin-36-receptor antagonist deficiency successfully treated with anakinra. Pediatrics **132**, 1043-1047 (2013).
132 Tang, D. et al. PAMPs and DAMPs: signal 0s that spur autophagy and immunity. Immunol. Rev. **249**, 158-175 (2012).
133 Takeuchi, O. & Akira, S. J. C. Pattern recognition receptors and inflammation. Cell **140**, 805-820 (2010).
134 Martinon, F. et al. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-β. Mol. Cell **10**, 417-426 (2002).
135 Lamkanfi, M., & Dixit, V. M. Inflammasomes and their roles in health and disease. Annu. Rev. Cell Dev. Biol. **28**, 137-161 (2012).
136 Strowig, T. et al. Inflammasomes in health and disease. Nature **481**, 278 (2012).

137 Vanaja, S. K. et al. Mechanisms of inflammasome activation: recent advances and novel insights. Trends Cell Biol. **25**, 308-315 (2015).
138 Sutterwala, F. S. et al. Mechanism of NLRP3 inflammasome activation. Ann. N. Y. Acad. Sci. **1319**, 82-95 (2014).
139 Mangan, M. S. et al. Targeting the NLRP3 inflammasome in inflammatory diseases. Nat. Rev. Drug. Discov. **17**, 588-606 (2018).
140 Nakamura, S. et al. Identification of baseline gene expression signatures predicting therapeutic responses to three biologic agents in rheumatoid arthritis: a retrospective observational study. Arthritis Res. Ther. **18**, 159 (2016).
141 Tasaki, S. et al. Multi-omics monitoring of drug response in rheumatoid arthritis in pursuit of molecular remission. Nat. Commun. **9**, 2755 (2018).
142 Konttinen, Y. et al. Osteoarthritis as an autoinflammatory disease caused by chondrocyte-mediated inflammatory responses. Arthritis Rheum. **64**, 613-616 (2012).
143 Berenbaum, F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage **21**, 16-21 (2013).
144 Gilbert, S. J. & Blain, E. J. Chapter 4 - Cartilage mechanobiology: how chondrocytes respond to mechanical load. In Mechanobiology in Health and Disease (Verbruggen, S) 99-126 (Elsevier, 2018).
145 Kalaitzoglou, E. et al. Innate immune responses and osteoarthritis. Curr. Rheumatol. Rep. **19**, 45 (2017).
146 Nefla, M., et al. The danger from within: alarmins in arthritis. Nat. Rev. Rheumatol. **12**, 669-683 (2016).
147 Geyer, M. & Schönfeld, C. Novel insights into the pathogenesis of osteoarthritis. Curr. Rheumatol. Rev. **14**, 98-107 (2018).

Glossary

Pattern recognition receptor: Proteins that recognise conserved molecular structures either found in pathogens, such as bacteria and viruses (pathogen-associated molecular patterns; PAMPs), or released by damaged cells (damage-associated molecular patterns; DAMPs).

Filamentous actin: Actin is the most abundant protein in eukaryotic cells; can be present as either a linear polymeric form, filamentous (F-actin).

Autophagy: A highly regulated process of ‘self-eating’ whereby cell organelles and their contents can be repurposed for other uses

Hypomorphic mutation: A type of mutation that causes a partial loss of gene function, or in which the wild-type gene product is expressed at a reduced level.

Anhidrotic ectodermal dysplasia: A form of ectodermal dysplasia characterized by abnormal development of ectodermal tissues including the skin, hair, teeth, and sweat glands, resulting in an inability to sweat (anhidrosis).

Stop-gain variant: A mutation resulting in a premature termination codon (that is, a stop was gained), which signals the end of translation and results in a shortened protein product.

Itaconate: A derivate of the tricarboxylic acid cycle, this endogenous metabolite has a key role in the regulation of macrophage function; it has been shown to decrease production of pro-inflammatory mediators in lipopolysaccharide-treated macrophages and to ameliorate sepsis and psoriasis in animal models, revealing a novel biological action beyond its regular roles in antimicrobial defences.

Blurb for of Table Contents

The concept of autoinflammation has evolved to include multifactorial conditions and disorders with autoimmune and immunodeficiency components. An appreciation of the contributions of various molecular mechanisms and systems could improve our understanding and treatment of the systemic autoinflammatory diseases.

Subject terms

Health sciences/Rheumatology [URI /692/4023]

Health sciences/Pathogenesis/Immunopathogenesis / [URI /692/420/2780]

Health sciences/Pathogenesis/Clinical genetics/Disease genetics [URI /692/420/2489/144]

Health sciences/Diseases/Immunological disorders / [URI /692/699/249]