Autoinflammation and autoimmunity across rheumatic and musculoskeletal diseases

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Abstract | Most rheumatic and musculoskeletal diseases (RMDs) can be placed along a spectrum of disorders, with autoinflammatory diseases (including monogenic systemic autoinflammatory diseases) and autoimmune diseases (such as systemic lupus erythematosus and antiphospholipid syndrome) representing the two ends of this spectrum. However, although most autoinflammatory diseases are characterized by the activation of innate immunity and inflammasomes and classical autoimmunity typically involves adaptive immune responses, there is some overlap in the features of autoimmunity and autoinflammation in RMDs. Indeed, some 'mixed-pattern' diseases such as spondyloarthritis and some forms of rheumatoid arthritis can also be delineated. A better understanding of the pathogenic pathways of autoinflammation and autoimmunity in RMDs, as well as the preferential cytokine patterns observed in these diseases, could help us to design targeted treatment strategies.

When discussing rheumatic and musculoskeletal diseases (RMDs), it is not always clear whether the disease is strictly an autoimmune disease or is an autoinflammatory disease with unchecked inflammation but without autoimmunity[1–4]. Therefore, it is important to revisit the classification used to describe RMDs[1–4].

When considering whether a disease is an autoimmune disease versus an autoinflammatory disease, systemic lupus erythematosus (SLE) and monogenic systemic autoinflammatory diseases (SAIDs) can be considered as prototypes of autoimmune and autoinflammatory diseases, respectively[3,4]. Autoimmune diseases are characterized by the loss of immune tolerance, the recognition of self-antigens and the activation of T cells and B cells, followed by the production of specific autoantibodies and the damage of multiple organs owing to a dysregulated adaptive immune response[1,3,5]. Autoinflammatory diseases are not directed by specific antigens, and they harbour systemic chronic inflammation without a break in immune tolerance or the generation of specific autoantibodies[4,6]. External environmental factors such as infections, temperature changes or mechanical stress can also lead to the development of inflammation and provoke flare in certain genetic backgrounds, expanding the definition of autoinflammation[4,6].

RMDs are distributed along a spectrum based on the involvement of autoimmunity and autoinflammation in them (FIG. 1). Monogenic SAIDs are at the autoinflammatory end of the spectrum, and SLE and antiphospholipid syndrome (APS) are at the autoimmune end. Rare monogenic autoimmune diseases such as autoimmune polyendocrine syndrome 1, immune dysregulation, polyendocrinopathy, enteropathy, X-linked and autoimmune lymphoproliferative syndrome will not be discussed in this Review as they are not classical RMDs[7]. Diseases related to autoimmunity that are discussed here include SLE, rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), systemic sclerosis (SSc), APS, primary Sjögren syndrome (pSS), idiopathic inflammatory myopathies (IIMs), mixed connective tissue disease and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)[3,4,8–10] (FIG. 1). As discussed later, a mechanistic immunological classification of RA has been proposed based on the heterogeneity of disease subtypes[8,9]. In addition to monogenic SAIDs, diseases related to autoinflammation and discussed in this Review include gout, spondyloarthritis (SpA), systemic juvenile idiopathic arthritis (sJIA), oligoarticular juvenile idiopathic arthritis, adult-onset Still disease (AOSD), Behçet disease and Schnitzler syndrome[3,4] (FIG. 1). As described previously, most of these autoimmune and autoinflammatory diseases can also be considered to be 'mixed-pattern' conditions[4]. Indeed, there is no strict divide between autoimmune and autoinflammatory diseases as some RMDs comprise elements of autoimmunity and autoinflammation. In such mixed-pattern RMDs,

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https://doi.org/10.1038/s41584-021-00652-9

Key points

- Rheumatic and musculoskeletal diseases (RMDs) form a continuum between classical autoimmune and autoinflammatory conditions.
- Classical autoinflammatory and autoimmune diseases are associated with the activation of innate immunity and adaptive immune responses, respectively.
- There are some 'mixed-pattern' disorders that carry the features of both autoimmune and autoinflammatory conditions, and one disorder might have autoimmune and autoinflammatory characteristics at different stages of disease development.
- The autoimmune, autoinflammatory or mixed phenotype of RMDs might help us to develop and administer therapies targeted to specific disease phenotypes.

autoantibody-mediated pathology has been observed alongside activation of the innate immune system, including of Toll-like receptors (TLRs) and of the inflammasome. Moreover, immune cells and mediators characteristic of both autoimmunity and autoinflammation can be involved in these diseases[1,3,5,11] (FIG. 1).

Indeed, in terms of immunity, autoimmune and autoinflammatory conditions can have an innate or adaptive immunological background[2,3] (FIG. 2). Innate immunity delivers non-specific cellular and humoral immune responses and confers the first defensive responses against pathogens. Innate immune responses are usually directed against pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). Several molecular systems, including TLRs, NOD-like receptors (NLRs), the caspase recruitment domain (CARD) receptor family, proteins of the complement system, cytoplasmic DNA-sensing molecules and inflammatory multimolecular complexes such as inflammasomes, have evolved to permit diverse recognition and activation and effector function within innate immunity. Immune cells activated during innate immune responses include macrophages, natural killer cells, neutrophils and mast cells (FIG. 2). In addition, other cell types, such as epithelial and endothelial cells, are also induced to express molecules recognizing DAMPs and PAMPs and are classed as 'innate responders'. Epithelial barriers and their dysfunction, partially through alterations in the microbiome, might also play a crucial role in RMDs. The activation of innate immune responses is primarily characteristic of autoinflammation and the development of autoinflammatory diseases (FIG. 1). Within the cytokine superfamilies, the IL-1 family, TNF superfamily members, IL-6 and the type I interferons are particularly implicated in innate immune responses[1,4,12–14].

Adaptive immunity is teleologically younger than innate immunity and exists only in vertebrates. As it enables an immunological memory to form in response to the first encounter with a pathogen, a prompt immune response can develop after consecutive contacts with the same external stimulus. Adaptive immunity is pathogen-specific and driven by T lymphocytes and B lymphocytes, and long-term defence can develop. Temporal and spatial regulation of such a response, as well as its attenuation, is needed to prevent tissue and organ damage. The sustained activation of adaptive immune responses and immunoregulatory defects can lead to the development of classical autoimmune diseases[1–3,5] (FIG. 1).

During the past decade, multiple efforts have been made to better understand the nature of autoimmunity and autoinflammation[1,4], including those using genome-wide association studies, mRNA sequencing, molecular imaging and the study of tissue-specific antigen and gene expression patterns[1,3,4]. In this Review, we first discuss the key features of diseases that are predominantly autoimmune or predominantly autoinflammatory, before describing the overlap between autoimmunity and autoinflammation in RMDs. We also underscore mechanisms shared by autoimmunity and autoinflammation, such as the involvement of pathogenic pathways that are characteristic of autoinflammation in autoimmune conditions (and vice versa), and we highlight how understanding these shared mechanisms might enable us to enhance the efficacy of therapeutics and realize the potential of personalized medicine in rheumatology.

Major features of autoimmune RMDs

SLE, a prototype of systemic autoimmunity, produces more than 100 autoantibody specificities and manifests in various systemic organs (FIG. 1). SLE is based on robust T cell and B cell activation and the formation of immune complexes, whereas cells and mediators that are characteristic of autoinflammation, such as inflammasome activation and the production of IL-1, do not seem to have a major role in this disease[15]. Nonetheless, innate immunity still has an important role in SLE. Indeed, single-nucleotide polymorphisms associated with SLE include those in the genes encoding TLRs (*TLR7* and *TLR9*), complement receptors (*C3*, *C4* and *C1Q*) and Fc receptors (*FCGR2A* and *FCGR3B*), all of which are components of the innate immune response (TABLE 1). The accumulation of 'cellular debris' in tissues and blood in patients with SLE, including as a result of secondary necrosis and the formation of neutrophil extracellular traps (NETs), leads to a breach in immune tolerance and the formation of immune complexes, which triggers the release of inflammatory mediators and organ damage[15,16]. This cell debris-induced breach in immune tolerance is closely linked to dysfunction in complement receptors and Fc receptors. Indeed, mutations in genes encoding proteins of the complement system and the activation of a type I interferon (that is, IFNα and IFNβ) signature, which is also a feature of an innate immune response, are central features of SLE[14,15,17]. The complement genes responsible for susceptibility to SLE are *C1Q*, *C2* and *C4* (REF.[15]). Partial or complete deficiency in C1, C2 or C4 disrupts early steps of the complement cascade, resulting in inadequate clearance of immune complexes. In addition, the Fc receptors FcγRIIIA and FcγRIIIB have anti-inflammatory activity as they clear immune complexes, and mutations in genes encoding these proteins impair this clearance function. In carriers of single-nucleotide polymorphisms associated with SLE, environmental factors that induce cell death, such as ultraviolet light, are necessary for development of the disease[15,18–20]. In SLE, extracellular DNA triggers an *IFN* gene response associated with the production of IFNα and IFNβ. DNA activates *IFN* genes (for example,

IFNA) via the stimulator of interferon genes (STING)–IRF3 pathway and TLR7 and TLR9 (REFS[15,19]). Eventually, the persistence of an interferon signature contributes to disease progression[15,18,21].

The importance of the type I interferon signature and that of other risk alleles associated with components of the innate immune response has also been described in the predominantly autoimmune diseases SSc, IIMs and pSS. For example, in SSc, the type I interferon signature appears early in disease, before the onset of fibrosis, and correlates with an increase in the expression of B cell-activating factor (*BAFF*) mRNA (the protein product of which promotes B cell activation) and an increase in collagen synthesis[22,23]. In the IIMs polymyositis and dermatomyositis, the expression of type I interferon-regulated genes has also been associated with disease activity[24]. Furthermore, high expression of interferon-induced genes has been observed in the skin of patients with dermatomyositis[25]. In pSS, clinical symptoms, disease activity and B cell activation are also associated with the type I interferon signature[26,27]. Finally, certain subsets of RA presumably show a type I interferon signature that promotes the production of autoantibodies such as anti-citrullinated protein antibody (ACPA), anti-carbamylated protein (anti-CarP) and rheumatoid factor[17,28–30], and RA also carries other autoinflammatory features (see below)[8,31,32].

Features of autoinflammatory RMDs

SAIDs comprise an expanding group of diseases, including monogenic diseases caused by inborn errors (also known as periodic fever syndromes) and adult-onset SAIDs such as AOSD, Schnitzler syndrome and idiopathic recurrent autoimmune pericarditis (IRAP)[33–36].

Monogenic autoinflammatory RMDs. In contrast to autoimmune RMDs, monogenic SAIDs are exclusively autoinflammatory conditions[37] (FIG. 1; TABLE 1). A common feature of these diseases, which include both sporadic and monogenic inherited diseases with an overactive innate immune system, is recurrent febrile episodes in the absence of infectious agents. The best described diseases in this group include familial Mediterranean fever (FMF), periodic fever, aphthosis, pharyngitis and adenitis syndrome, hyper-IgD and periodic fever syndrome (also known as mevalonate kinase deficiency), TNF receptor-associated periodic syndrome (TRAPS), Blau syndrome and cryopyrin-associated periodic syndromes (CAPS). CAPS include three diseases caused by mutations in *NLRP3*, the gene encoding the

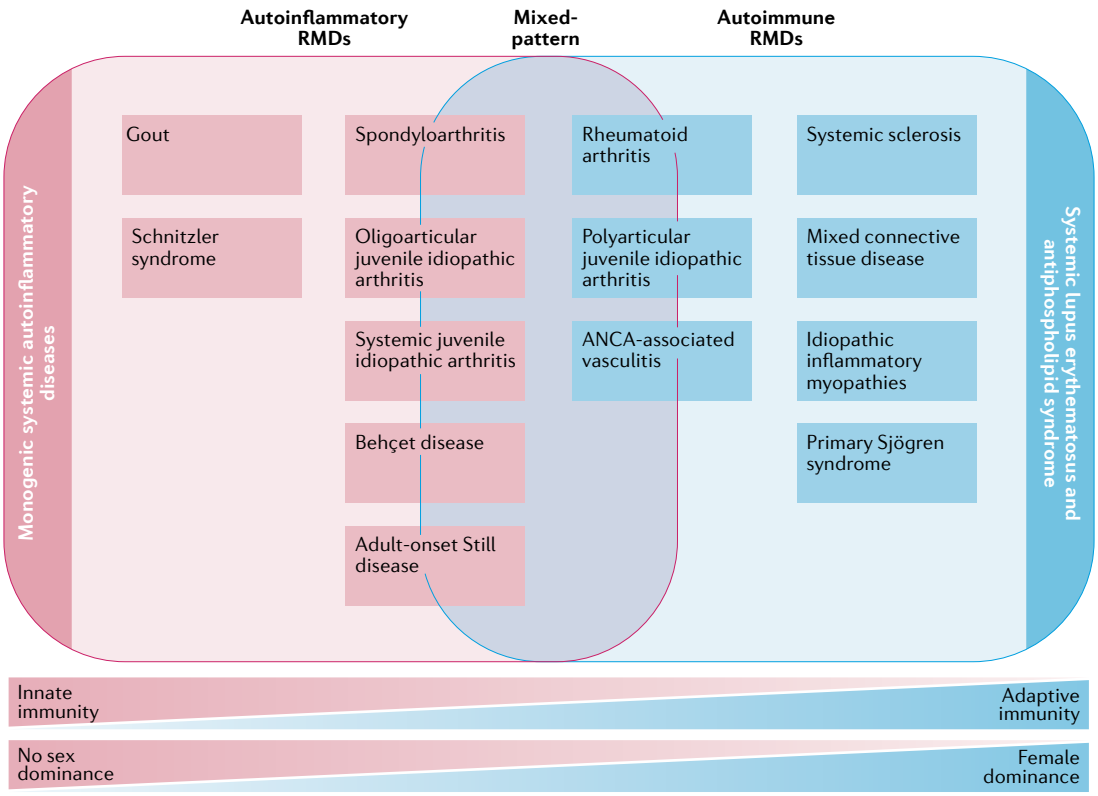

Fig. 1 | **Spectrum of autoinflammatory, mixed-pattern and autoimmune diseases.** Prototypes of a classical autoinflammatory disease are the group of monogenic systemic autoinflammatory diseases known as periodic fever syndromes (pink). Prototypes of classical autoimmune disease are systemic lupus erythematosus and antiphospholipid syndrome (blue). Diseases in the middle of the spectrum might be considered mixed-pattern rheumatic and musculoskeletal diseases (RMDs; mixed colour). Indicated by the spectra at the bottom of the figure, classical autoinflammatory conditions are characterized by a predominance of innate immunity and have no sex dominance. By contrast, classical autoimmune conditions are associated with more prominent adaptive immune responses and female dominance. ANCA, antineutrophil cytoplasmic antibody.

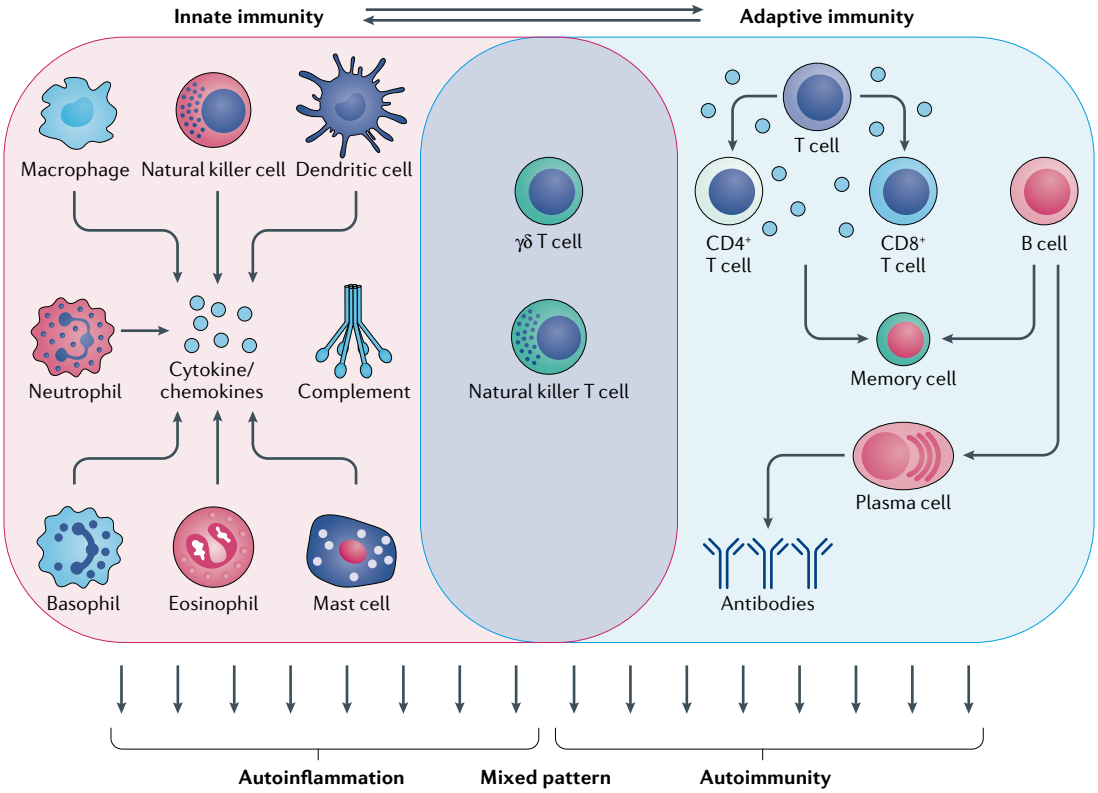

Fig. 2 | **Cellular mediators of autoimmunity and autoinflammation.** Cells of the innate immune system, including macrophages, natural killer cells, dendritic cells, mast cells and different granulocyte subsets, and the complement system promote autoinflammation. Cells of the adaptive immune system, including different T lymphocyte subsets, B cells and plasma cells, as well as T memory cells and B memory cells, are primarily involved in the development of autoimmunity. Natural killer T cells and γδ T cells are at the crossroads of autoinflammation and autoimmunity and promote the development of mixed-pattern immune-mediated inflammatory diseases. Most of the cells involved in the development of autoinflammation and autoimmunity produce cytokines and chemokines (as indicated by the blue circles), whereas plasma cells release antibodies.

NLRP3 protein, namely familial cold autoinflammatory syndrome, Muckle–Wells syndrome and chronic infantile neurologic cutaneous and articular syndrome[38,39]. The clinical features of these monogenic SAIDs have been discussed elsewhere[37–39]. Most of these diseases are caused by inborn errors, although some such as FMF, TRAPS, CAPS, hyper-IgD and periodic fever syndrome, deficiency of adenosine deiminase 2 (ADA2), periodic fever, aphthosis, pharyngitis and adenitis syndrome, and type I interferonopathies can also have adult onset[33,34]. Monogenic SAIDs are mostly associated with mutations in *MEFV*, the gene encoding pyrin, *NLRP3*, or other genes encoding proteins that regulate inflammation, metabolism and body temperature (for example, *NOD2*; also known as *CARD15*)[37,39–41] (TABLE 1). Currently, our understanding of monogenic SAIDs is moving from a gene-centric view towards a systems-based view, and various convergent pathways — such as pyrin and the actin cytoskeleton, protein misfolding and cellular stress, NF-κB dysregulation and interferon activation — have been associated with autoinflammation in SAIDs[42].

Molecular pathways underlying autoinflammation. Activation of the NLRP3 inflammasome and the IL-1β pathway are key events in the pathogenesis of most monogenic SAIDs and polygenic SAIDs (introduced below)[12,43,44]. In the presence of a characteristic genetic mutation, certain external environmental factors (for example, infection, smoking or hormonal factors) can cause uncontrolled activation of the inflammasome, resulting in the development of a cytokine-mediated systemic inflammatory condition[12,43,44]. DAMPs and PAMPs are involved in the initiation of inflammasome activation. Activation of the NLRP3 inflammasome is mediated by the NLR family protein NLRP3 and leads to the activation of caspase 1, which cleaves the cytokine precursors pro-IL-1β and pro-IL-18 to produce the biologically active forms of IL-1β and IL-18, respectively[12,40,41,43]. In response to increased production of IL-1β and IL-18, the endogenous cytokine antagonists IL-1 receptor antagonist (IL-1Ra) and IL-18 binding protein (IL-18bp) restore the balance of these cytokines in the body[12,40,41,43]. Loss of function mutation in genes encoding cytokine antagonists also leads to increased activation of IL-1α and IL-1β (REFS[40,41]).

Activation of NF-κB signalling contributes to the development of certain autoinflammatory diseases, and NOD2, a NLR family protein in addition to NLRP3 that recognizes bacterial dipeptides, is an important regulator of NF-κB signalling. *NOD2* mutation has a role

in the pathogenesis of Blau syndrome and in Crohn's disease[40].

Monogenic SAIDs associated with IL-1β family activation include FMF, familial cold autoinflammatory syndrome, chronic infantile neurologic cutaneous and articular syndrome, hyper-IgD and periodic fever syndrome, Muckle–Wells syndrome and pyogenic arthritis, pyoderma gangrenosum and acne[40,41]. The different gene mutations present in each disease result in activation of the NLRP3 inflammasome and uncontrolled secretion of IL-1β (REFS[40,41]). In addition to IL-1β and IL-18, TNF is also involved in the pathogenesis of some monogenic autoinflammatory disorders[40,41]. Other pathogenetic mechanisms that affect innate immunity and have been implicated in the pathogenesis of SIADs include NF-κB activation, endoplasmic reticulum stress, mutations in genes encoding endogenous cytokine antagonists, dysregulation of actin filament formation (in actinopathies), enhanced expression of *IFN* (in interferonopathies) or a reduction in the enzymatic activity of ADA2 (REFS[33,34]). TRAPS, which is one of the most prevalent monogenic SAIDs, is associated with heterozygous variants in *TNFRSF1A*, the gene encoding TNF receptor 1 (REFS[33,45,46]). Possible pathogenic mechanisms of TRAPS include enhanced NF-κB and NLRP3 activation through increased endoplasmic reticulum stress, defective autophagy or defective receptor shedding leading to TNF-induced cell death and, eventually, autoinflammation[33,45,46].

Polygenic autoinflammatory RMDs. Among polygenic autoinflammatory conditions we will discuss sJIA and gout, two well-known prototypes. sJIA is a typical autoinflammatory disease associated with fever, rash, hepatosplenomegaly and lymphadenopathy, especially in the early, acute phase[47]. Genetic and epigenetic changes are associated with this disease but, although mutations have been described in several genes, unlike in periodic fever syndromes, none of these mutations alone results in sJIA[47]. Gene mutations characteristic of monogenic diseases (for example, mutations in *NLRP3*, *NOD2* and *MEFV*) are not observed in sJIA[47]. sJIA has, rather, been associated with genes encoding pro-inflammatory cytokines (such as *IL1*, *IL1R*, *IL6*, *IL10* and *IL20*) and other mediators of inflammation (such as *IL8* and *MIF*; *MIF* encodes macrophage migration inhibitory factor)[47] (TABLE 1). The proteins encoded by these genes are involved in the innate immune response and, ultimately, create an inflammatory microenvironment; the activation of effector T cells only occurs as a consequence of autoinflammation[3,47]. In the more advanced stage of sJIA, activation of the adaptive immune system and joint tissue destruction can be observed, suggesting that sJIA is associated with the activation of innate and (to a lesser extent) adaptive immunity at different stages of the disease[48,49]. Nonetheless, B cell-mediated autoimmunity is absent in sJIA. Important questions are how and when spurious inflammation in sJIA switches to chronic inflammation[1,49], and whether this switch can be prevented or delayed by early intervention with anti-IL-1 or anti-IL-6 strategies[50].

Autoinflammation is also essential in the development of gout and the central event of gouty inflammation is the activation of white blood cells by monosodium urate (MSU) crystals[12,51,52]. Cell membrane damage by activated leukocytes and their mediators results in the activation of pattern recognition receptors, inducing a response against cellular debris to try to minimize the damage. MSU crystals act as DAMPs and are phagocytosed through TLR2 and TLR4 to form a phagolysosome. Phagolysosome formation is followed by activation of the NLRP3 inflammasome, which leads to the activation of caspase 1 and to the release of IL-1β and IL-18 (REFS[12,51,52]). The production and release of the pro-inflammatory cytokines IL-1, IL-6 and TNF from cells of the innate immune system, independent of inflammasome activation, initiate an inflammatory cascade in which additional mediators of inflammation, such as matrix metalloproteinases, prostaglandins, leukotrienes and reactive oxygen species, also play a role[12,51].

Although monogenic SAIDs, sJIA and gout are the prototypes of autoinflammatory RMDs, AOSD, Behçet disease, IRAP, synovitis, acne, pustulosis, hyperostosis, osteitis syndrome and Schnitzler syndrome can also be classified as adult-onset SAIDs[33–35,38] (FIG. 1). AOSD is an acquired fever syndrome characterized by well-defined clinical (intermittent fever, typical rash and arthritis) and laboratory (hyperferritinaemia, leucocytosis, neutrophilia and abnormal transaminase levels) features. AOSD has been associated with an increased production of cytokines, including of IL-1, IL-6, IL-18 and TNF[53]. Activation of the NLRP3 inflammasome and pathological IL-1 signalling have also been observed in patients with AOSD[53]. Mutations in *MEFV* and *TNFRSF1A* (the gene encoding TNF receptor 1) have been described in patients with AOSD, linking AOSD to monogenic SAIDs[54] (TABLE 1). Behçet disease is a systemic vasculitis affecting the small vessels, and most commonly manifests as mucosal and genital ulcers and uveitis.

Table 1 | **Genes associated with common autoimmune and autoinflammatory disorders**

Classification	Disease	Associated genes
Autoimmune diseases	Systemic lupus erythematosus	*TLR7*, *TLR9*, *C3*, *C4*, *C1Q*, *FCGR2A*, *FCGR3B*, *IFNA*
	Systemic sclerosis	*IFN* signature genes
	Idiopathic inflammatory myopathy	*IFN* signature genes
Autoinflammatory diseases	Monogenic systemic autoinflammatory diseases	*NLRP3*, *NOD2*, *MEFV*, *TNFRSF1A*, *MVK*, *TNFAIP3*, *ADA2*, *TREX1*, *UBA1*
	Systemic juvenile idiopathic arthritis[a]	*IL1*, *IL1R*, *IL6*, *IL10*, *IL20*, *IL8*, *MIF*
	Adult-onset Still disease[a]	*MEFV*, *TNFRSF1A*, *NLRP3*
	Behçet disease[a]	*MEFV*, *TNFRSF1A*, *NLRP3*, *HLAB51*
Mixed-pattern diseases[a]	Ankylosing spondylitis	*HLAB27*, *ERAP1* (also known as *ARTS1*)
	Rheumatoid arthritis	*HLADRB1*, *PTPN22*, *NLRP3*, *MEFV*, *NOD2*

This table is not comprehensive and shows only the most common diseases and their genetic associations. [a]Diseases that can also be mixed-pattern diseases.

In addition to other cytokines, the NLRP3–IL-1 system is important in the development of Behçet disease, meaning that this is a predominantly autoinflammatory condition that can also have mixed-pattern features (see below)[55–57]. Again, mutations in *MEFV* and *TNFRSF1A* are more common in this disease compared with other autoinflammatory conditions[4]. Schnitzler syndrome is also an acquired fever syndrome and is characterized by chronic urticaria associated with monoclonal gammopathy, recurrent fever, bone pain and arthralgia. It is considered to be a neutrophil dermatosis with notable involvement of neutrophils, cells that are involved in innate immunity[58]. Hereditary factors are unlikely to play a role in the pathogenesis of this disease based on its late onset in patients[33,36,59,60].

Mixed-pattern RMDs

Diseases with features of both autoinflammatory and autoimmune RMDs include SpA and some forms of RA. These disorders have also been termed mixed-pattern RMDs[4] (FIG. 1).

As well as ankylosing spondylitis (AS) and psoriatic arthritis (PsA), forms of SpA include enteropathic arthritis (also known as inflammatory bowel disease-associated arthritis), reactive arthritis and undifferentiated SpA[61,62]. In contrast to classical autoimmune diseases, SpA is associated with HLA-B but not with HLA-DR, which is characteristic of polygenic autoimmune diseases[61,63–65]. Moreover, unlike other autoimmune diseases, there is no female dominance in SpA. Furthermore, SpA has been associated with autoantibodies; some patients with AS and PsA have autoantibodies to mutated citrullinated vimentin, CarP, sclerostin, heat shock proteins or β_2-microglobulin[61,63–65]. CD74 is the invariable γ-chain of MHC class II, and anti-CD74 antibodies are considered to be specific for SpA in European but not Asian cohorts[65]. Among cytokines, in addition to TNF, IL-17 and IL-23 seem to have a predominant role in mixed-pattern RMDs[61,66]. Associations of SpA with mutations in *ERAP1* (also known as *ARTS1*, encoding endoplasmic reticulum aminopeptidase 1) and with MHC class I suggest that T cells interact with cytokine pathways, including the IL-23–IL-17 axis but not the IL-1 pathway, in patients with this disease[56,57,67] (TABLE 1). In terms of autoinflammation, NLRP3 and caspase 1 are upregulated in AS, suggesting that autoinflammation is involved in the pathogenesis of this disease[68]. In short, features of both autoimmunity (such as autoantibodies) and autoinflammation (such as gender balance and natural immune responses to microbial pathogens) have been identified in SpA[61].

RA generally has autoimmune features in the early phase of the disease but has a macrophage and fibroblast-dominated pathogenesis in the chronic phase. Thus, RA is an example of a condition in which the phase of the disease relates to its autoimmune or autoinflammatory nature[4,10,30,69]. Five patients with seropositive RA had HLA-DRB1*01 and/or HLA-DRB1*04 shared epitopes as well as mutations in *NLRP3*, *MEFV* or *NOD2* (REF.[9]) (TABLE 1). These patients showed features of autoinflammation and responded to colchicine[9]. Based on the findings of this study, the authors proposed an immunology-based reclassification of RA that includes classical seropositive autoimmune RA, autoinflammatory seronegative forms of RA and mixed forms of RA that are seronegative[8,9]. This proposed reclassification reflects the commonly accepted idea that RA is a syndrome based on different pathophysiologic events rather than a single disease.

Juvenile idiopathic arthritis can also be a mixed-pattern disease with both autoinflammatory and autoimmune features. For example, pJIA shares many of the features of adult RA described above[47,70]. Also, although sJIA is largely considered to be a SAID dominated by innate immunity-driven inflammation, in later stages it can progress towards an adaptive immunity-dependent arthritis[47–49].

Among diseases primarily considered to be autoinflammatory, AOSD and Behçet disease have also been associated with adaptive immunity and T cell responses and thus can also be considered mixed-pattern conditions[4,56,57]. AOSD can be systemic with predominantly autoinflammatory features or have a chronic articular pattern resembling classical RA, which could have relevance for therapy. For example, different phenotypes of AOSD respond to different biologics[4,71]. Moreover, genetic analysis has confirmed that sJIA and AOSD might form a continuum of a single disease. Specifically, sJIA and AOSD can share common genes, and the differentiation between these two diseases is mainly based on the age of onset[35]. Behçet disease, a primarily autoinflammatory condition, is also associated with the MHC class I molecule HLA-B51, notable T cell responses and the production of IL-23 and IL-17 (REFS[56,57]), highlighting that it also has features of autoimmune conditions.

Finally, among monogenic SAIDs, haploinsufficiency of A20 — which is caused by mutations in *TNFAIP3*, the gene encoding the NF-κB regulatory protein A20 (REFS[33,72]) — is a good example of a condition with autoimmune and autoinflammatory features that result from the same pathogenetic pathways. This disease carries characteristics of RA, gout, Behçet disease, AOSD, SLE, periodic fever, aphthosis, pharyngitis and adenitis syndrome, as well as skin, ocular and gastrointestinal symptoms. Therefore, diagnosis and differential diagnosis of haploinsufficiency of A20 is difficult[72].

In conclusion, mixed-pattern RMDs carry both classical autoimmune and autoinflammatory features and are often associated with non-rheumatic conditions[1,3,4,8].

Innate immunity in autoimmune RMDs

Having discussed the main features of autoimmune, autoinflammatory and mixed-pattern RMDs, it is important to consider the innate immune mechanisms that most commonly occur in both autoinflammatory and autoimmune diseases.

We have already discussed activation of the NLRP inflammasome and the consequent production of IL-1β and IL-18 in autoinflammation[12,44]. However, these features have also been demonstrated in autoimmune and mixed-pattern conditions. NLRP3 activation and the consequent production of cytokines, as well as relevant genetic polymorphisms (for example, in *NLRP3* and

NOD2), have been associated with RA[30,73–76], SpA[77,78], pJIA and oligoarticular juvenile idiopathic arthritis[70]. NLRP3 is also activated, with inflammasome activation leading to tissue injury, in autoimmune RMDs such as RA[79,80], SLE[76,81,82], SSc[83,84], pSS[85] and IIMs[86]. TLR-dependent pathways and abnormal TLR signalling are also characteristic for SLE, RA and other autoimmune RMDs[82].

Type I interferon is upregulated in genetically based interferonopathies, which are not always linked to autoimmunity. STING is a DNA sensor, and a mutation in the gene encoding this protein can lead to the induction of genes involved in IFNα and INFβ-mediated responses and thus, indirectly, the synthesis of numerous pro-inflammatory cytokines[14,40,87]. Rare examples of these interferonopathies also include STING-associated vasculopathy with onset in infancy as well as Aicardi–Goutiéres syndrome[14,40,87]. As discussed above, type I interferon signatures play a key role in autoimmune diseases such as SLE and can also be involved in RA and SSc[87].

NETs are web-like structures of decondensed chromatin, histones and antimicrobial peptides that are involved in the defence against pathogens[58,88–90] and, primarily, have a role in autoinflammatory conditions such as gout[91,92] or Schnitzler syndrome[58]. In gout, the formation of NETs might also be a counter-regulatory mechanism aimed at resolving inflammation[91,92]. Specifically, NETs can stop gout episodes by inducing neutrophil death, encapsulating MSU crystals and inactivating cytokines[91,92]. However, neutrophil activation and NET formation contribute to autoimmune-mediated inflammation in SLE[90,93], RA[90,92] and AAV[90,92].

Prolonged innate immunity-based inflammation can induce adaptive immune responses, as described above for sJIA[48]. However, this phenomenon can also be observed in other RMDs. In monogenic SAIDs and other autoinflammatory diseases, an acute 'hyper-inflammatory state' leading to the resolution of inflammation within days and a prolonged 'autonomous inflammatory state' have been proposed to occur[49,94]. In the latter state, prolonged IL-1β and IL-18 production, in part in synergy with IL-6 and IL-23 activation, can promote T cell differentiation, the induction of T helper 17 cells (T_H17 cells) and the production of IL-17 (REFS[49,95]). Moreover, IL-18 can induce adaptive T_H1 cells and B cells[49]. Thus, innate immunity is involved in some autoimmune RMDs. Finally, a sustained innate immune response can induce trained immunity in autoimmune RMDs, which can contribute to the activation of adaptive immune pathways[49,96].

Comorbidities associated with RMDs

Comorbidities are associated with many RMDs and determine their outcome. The most relevant comorbidities are cardiopulmonary disease (including cardiovascular disease, IRAP and interstitial lung disease (ILD)), osteoporotic fractures, neuropsychiatric manifestations, diabetes mellitus and malignancies[97,98].

The inflammatory condition accelerated atherosclerosis and the consequent cardiovascular disease can carry both autoimmune and autoinflammatory features[99–101]. The autoantibodies ACPA[102,103] and anti-carP[104] might be involved in the development of atherosclerosis in RA. Citrullinated proteins have been detected in the atherosclerotic plaque, suggesting a possible target for ACPA in RA[103]. With respect to autoinflammation, in one large study *NLRP3* gene polymorphisms were not associated with cardiovascular disease in RA[105], whereas in another cohort the presence of the *NLRP3*^{Q705K} minor allele doubled the risk of stroke (also known as transient ischaemic attack) but did not increase the risk of myocardial infarction in RA[106]. In patients without rheumatic disease, NLRP3 and caspase 1 transcripts are abundantly expressed in atherosclerotic plaques[107]. Polymorphisms in CARD-containing protein 8 were not associated with any type of cardiovascular event in RA[106]. With respect to pro-inflammatory cytokines, inflammatory atherosclerosis associated with RMDs has been characterized by the increased production of TNF and IL-6 (REFS[99,100]). In addition, both IL-1 and IL-18 are abundantly produced in the atherosclerotic plaques[107,108], and IL-18 is a predictor of mortality in patients with cardiovascular disease[109]. In patients with SLE, IL-18 production has also been associated with kidney damage and cardiovascular disease[82].

The comorbidity IRAP should also be considered when monitoring and treating RMDs. Recurrent pericarditis can occur in viral infections but can also be associated with various autoimmune RMDs (for example, SLE, SSc, IIMs, pSS and RA) and autoinflammatory RMDs (for example, FMF, TRAPS and Behçet disease)[110,111]. IRAP can carry some autoimmune features as it has been linked to the production of anti-heart and anti-intercalated disk autoantibodies, as well as to autoreactive T cells[110]. However, IRAP has also been associated with notable NLRP3 activation, and cases resistant to NSAIDs, corticosteroids and/or colchicine might respond well to the inhibition of IL-1 (REFS[110,111]). Based on these observations, IRAP can also be considered an autoinflammatory disease[110–112].

ILD is mostly associated with autoimmune conditions such as SSc or IIMs, and the presence of specific autoantibodies, such as anti-Scl70, anti-PLββ-7 and anti-PL-12, correlates with an increased risk of developing ILD in these diseases[113,114]. By contrast, there is limited information on the possible involvement of autoinflammation in ILD. One study investigated the role of NLRP3 inflammasomes in patients with idiopathic pulmonary fibrosis and in patients with RA and usual interstitial pneumonia. IL-1β and IL-18 levels were elevated in bronchoalveolar lavage fluid and bronchoalveolar lavage fluid macrophage cultures from patients with RA and usual interstitial pneumonia compared with healthy individuals[115]. However, the role of autoinflammation in ILD has not been confirmed.

A great number of autoimmune (for example, SLE), autoinflammatory (for example, TRAPS and FMF) and mixed-pattern (for example, Behçet disease) diseases also have neuropsychiatric comorbidities. Based on the nature of these manifestations, these comorbidities might not have the same pathogenesis; however, neuroinflammation could be a common link between these disorders[4,57,116,117].

Finally, most RMDs have been associated with generalized bone loss leading to osteoporosis and fragility fractures[68,97,118]. Proinflammatory cytokines, such as TNF, IL-1, IL-6 and IL-17 (REF.[118]), as well as various DAMPs, including purine metabolites and fatty acids, have been implicated in inflammatory bone disorder[68]. Cytokines and DAMPs both stimulate NLRP3 and NLRC4 inflammasomes, and NLRP3-deficient mice are protected from bone loss[68]. Thus, autoinflammation is implicated in osteoporosis that occurs secondary to RMDs.

Treating RMDs across the spectrum

The pathogenesis of autoimmunity and autoinflammation, especially the cytokine networks characteristic of these conditions, might enable effective targeting strategies[43,66,119].

Treating autoinflammatory diseases. Autoinflammation often responds well to recombinant IL-1RA (anakinra), anti-IL-1β antibody (canakinumab) or recombinant IL-1R fusion protein (rilonacept)[119–121]. Canakinumab has been registered for the treatment of CAPS, TRAPS, FMF, AOSD, sJIA and refractory gouty flares[122,123]. In addition, rilonacept[124,125] and anakinra[126] are also effective in treating monogenic SAIDs. Among the less common monogenic SAIDs, recombinant IL-18bp can be administered in NLRC4 inflammasome-associated diseases caused by the overproduction of IL-18 (REF.[41]). In autoinflammatory diseases associated with NF-κB activation, such as TRAPS, IL-1 inhibitors are the first-choice treatment; however, TRAPS also responds well to TNF inhibitor therapy as the TNF receptor activates the NF-κB pathway[41]. With respect to gout, IL-1 inhibitors are effective in treating refractory flares, with most data available for canakinumab[12,127], although rilonacept[128] and anakinra[129,130] are also effective in treating gouty flares. For patients with sJIA, canakinumab[131,132], the anti-IL-6 receptor antibody tocilizumab[133] and anakinra[134] are registered for treatment, and rilonacept[135] is also effective in treating this disease. Canakinumab[136] and anakinra[126,137] are effective in, and registered for, treating patients with AOSD. Rilonacept can be administered off-label to patients with AOSD[137], and TNF and IL-6 inhibitors are also effective in treating patients with AOSD[32,138]. IL-1 inhibitors, such as canakinumab and anakinra, also showed efficacy in treating patients with Behçet disease[139]. All IL-1 inhibitors are also effective in patients with Schnitzler syndrome[36,140].

Treating autoimmune diseases. In autoimmune diseases, T cells, B cells and their cytokines play a notable role in disease pathogenesis, and the B cell inhibitor rituximab can be used off-label for treating most autoimmune diseases, including SLE[141], SSc[142], dermatomyositis[143] and pSS[144]. Belimumab, an anti-BAFF antibody, has been approved for the treatment of SLE[145], and the CTLA4–Ig fusion protein abatacept can also be administered to inhibit T cells in selected cases of SLE[146], SSc[147] and pSS[148]. It is also possible that cytokines that activate T_H17 cells (such as IL-17 and IL-23) and are used to treat RMDs with a mixed innate (neutrophil activation) and adaptive (T cell activation) background (such as AS and PsA) might also effectively treat classical autoimmune diseases. By contrast, cytokine inhibitors such as those that block IL-1 and TNF, which are effective in autoinflammatory diseases and in diseases such as RA with both autoinflammatory and autoimmune features, show limited efficacy in these autoimmune diseases. However, the IL-6 inhibitor tocilizumab gave promising results in SSc[149] and might be tried in the treatment of other autoimmune diseases[150,151].

TNF appears to be an excellent target in many inflammatory diseases, such as RA, AS, PsA and pJIA[66]. However, it might not be the optimal target in classical autoimmune disorders, such as SLE, SSc, AAV or pSS[66].

Treating mixed-pattern diseases. JAK inhibitors have been approved for treating RMDs with a mixed innate and adaptive immune activation, such as RA and SpA, and preliminary data suggest that they show promise for the treatment of patients with SLE, IIM, pSS, type I interferonopathies, sJIA, AOSD, Behçet disease and monogenic SAIDs[152]. Mixed-pattern diseases could also be treated with a combination of therapeutic strategies. For example, haploinsufficiency of A20, AOSD, Behçet disease or sJIA can be treated with TNF, IL-1 or IL-6 inhibitors based on the dominance of autoinflammatory versus autoimmune features in the patient[66,71,72].

Finally, trials to inhibit common molecular mechanisms of autoinflammation and autoimmunity, such as inflammasomes or NETs, have been carried out[89]. Several inflammasome inhibitors that target components of the NLRP3 cascade are under investigation for the treatment of autoinflammatory conditions[12,44,153]. Among currently used anti-rheumatic drugs, antimalarials and JAK inhibitors also inhibit NETs[89]. Some inhibitors of the protein arginine deiminase enzyme involved in protein citrullination might also block NET formation[89].

Conclusions

Autoimmune and autoinflammatory RMDs can be considered to be a spectrum of disorders. Monogenic SAIDs, and SLE and APS, are likely to represent the two ends of this spectrum of RMDs. Autoinflammatory diseases such as gout, sJIA, Behçet disease, AOSD or Schnitzler syndrome are characterized by the activation of innate immunity, whereas classical autoimmune diseases such as SSc, IIM, pSS, mixed connective tissue disease or seropositive RA are associated with adaptive immune responses and the production of autoantibodies. In addition to the fact that both autoinflammatory and autoimmune diseases can carry some features of the other disease type, there are mixed-pattern diseases that include SpA, AAV, pJIA, oligoarticular juvenile idiopathic arthritis and some forms of RA. The involvement of characteristic pathogenic proteins or pathways, such as of PAMPs, DAMPs, pattern recognition receptors, complement or inflammasome activation in autoinflammation, or of type I interferon signatures and the production of autoantibodies in autoimmunity, along with preferential cytokine patterns, might help inform the design of directed treatment strategies.

Published online 2 August 2021

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Acknowledgements
This work was supported by the European Union Social Fund TAMOP-4.2.4.A/2-11/1-2012-0001 'National Excellence Program' and the European Union GINOP-2.3.2-15-2016-00015 and GINOP-2.3.2-15-2016-00050 grants (to Z.S.). It was also supported by the Hungarian National Scientific Research Fund (NKFIH-OTKA Grant No. K131844 to S.B.) and the Faculty of Medicine of the University of Debrecen (1G3DBKD0TUDF 247 to S.B.).

Author contributions
All authors contributed to all aspects of the article.

Competing interests
The authors declare no competing interests.

Peer review information
Nature Reviews Rheumatology thanks A. Doria, S. Savic and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.