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# Type I interferon in rheumatic diseases

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## Abstract

The type I interferon pathway has been implicated in the pathogenesis of a number of rheumatic diseases, including systemic lupus erythematosus, Sjögren syndrome, myositis, systemic sclerosis, and rheumatoid arthritis. In normal immune responses, type I interferons have a critical role in the defence against viruses, yet in many rheumatic diseases, large subgroups of patients demonstrate persistent activation of the type I interferon pathway. Genetic variations in type I interferon-related genes are risk factors for some rheumatic diseases, and can explain some of the heterogeneity in type I interferon responses seen between patients within a given disease. Inappropriate activation of the immune response via Toll-like receptors and other nucleic acid sensors also contributes to the dysregulation of the type I interferon pathway in a number of rheumatic diseases. Theoretically, differences in type I interferon activity between patients might predict response to immune-based therapies, as has been demonstrated for rheumatoid arthritis. A number of type I interferon and type I interferon pathway blocking therapies are currently in clinical trials, the results of which are promising thus far. This Review provides an overview of the many ways in which the type I interferon system affects rheumatic diseases.

Overactivity of the type I interferon pathway has been observed in several rheumatic conditions, including both monogenic diseases (for example, Aicardi–Goutieres syndrome (AGS)[1]) and polygenic diseases (for example, systemic lupus erythematosus (SLE)[2–4]). Human genetic studies of rheumatic diseases have identified numerous disease-risk genes that function within the type I interferon pathway. In many cases, these genetic variations augment the function of type I interferons. Data suggest that heterogeneity in type I interferon pathway activation and genetic make-up contribute to the clinical heterogeneity observed in rheumatic diseases[5]. Given that the type I interferon pathway is deeply entwined with the pathogenesis of multiple rheumatic diseases, a robust effort is underway to determine whether type I interferon activity might be a predictor of treatment response, or

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whether the type I interferon pathway could be targeted by treatment. It is attractive to think that differences in type I interferon-related genes and pathway activation between patients might lead to rational selection of immunomodulatory therapy.

In this Review, we discuss the role of the type I interferon pathway in rheumatic diseases, focusing on the clinical implications. We briefly discuss type I interferon biology, followed by the interferon signature and other measurements of type I interferon in rheumatic diseases. We also examine genetic factors related to the type I interferon pathway, focusing on common gene variants associated with rheumatic disease, as well as the rare monogenic interferonopathies. We review current data regarding type I interferons in SLE, Sjögren syndrome, myositis, systemic sclerosis (SSc), and rheumatoid arthritis (RA). Finally, we consider treatments targeting type I interferons and the type I interferon pathway in rheumatic diseases.

## Type I interferon biology

Interferons are functionally related cytokines that have important roles in infection, cancer, inflammation and autoimmunity. The antiviral properties of interferons were identified more than 50 years ago[6], and the roles of interferons in cell survival, proliferation, differentiation and activation have since been highlighted and are reviewed elsewhere[7]. There are three major types of interferon: type I, type II and type III. Each type signals via a specific cell surface receptor complex. The type I interferons in humans include twelve interferon-α (IFNα) subtypes, IFNβ, IFNω, IFNκ and IFNε (reviewed elsewhere[8]). Each subtype is produced by particular cells in response to specific stimuli. In this Review, we will focus on IFNα and IFNβ, the most extensively studied type I interferons in rheumatic diseases.

### Type I interferon induction

Many cells can produce type I interferons (FIG. 1); plasmacytoid dendritic cells (pDCs) are the predominant producers of IFNα, whereas many cell types (for example, fibroblasts, epithelial cells, dendritic cells, phagocytes and synoviocytes) produce IFNβ. Production of type I interferons depends on the cell type and the environmental context. For example, pDCs constitutively express high levels of interferon regulatory factor 7 (IRF7), which, in part, enables them to produce relatively high amounts of IFNα[9,10], whereas other cell types must be ‘primed’ before high levels of type I interferons can be produced[10]. In a steady state, IFNβ is present at physiological levels, which seems to be important for priming cells for subsequent exposures[11,12]. Of note, over the past 5–10 years there has been strong interest in the microbiome and its effect on inflammation and rheumatic diseases. Interestingly, commensal intestinal flora influence this baseline production of IFNβ[13].

Type I interferon production can be induced fol-lowing the detection of microbial products by patternrecognition receptors (PRRs), such as Toll-like receptors (TLRs) or cytosolic nucleic acid sensors[14,15]; for example, lipopolysaccharide (LPS), a microbial cell wall component, is detected by surface TLR4; endosomal TLRs (TLR3, TLR7, TLR8, and TLR9) are ligated by nucleic acids delivered to the endosome via immune complexes; and nucleic acids in the cytosol are detected by sensors such as retinoic acid inducible gene 1 (RIG-I, also known as DDX58), melanoma differentiation-associated protein 5 (MDA5, also

known as IFIH1) and stimulator of interferon genes protein (STING) (FIG. 1). In normal immune responses, these events occur after the sensing of pathogen-derived material. However, PRRs can also detect nucleic acids from endogenous sources (for example, nucleic acids within nucleic acid-containing antibody complexes, nucleic acids released as a result of defective nucleic acid metabolism[16] or reactivity with endogenous transcripts that contain virus-like nuclear repeat elements (NREs)[17]) and might thereby contribute to the pathogenesis of rheumatic diseases. Interestingly, activation of the inflammasome can negatively regulate type I interferon production via the cyclic GMP-AMP synthase (cGAS)–STING pathway in the context of viral infection[18]. In normal conditions, cytosolic double-stranded DNA (dsDNA) triggers the synthesis of cyclic GMP-AMP (cGAMP) by cGAS, which activates STING, leading to type I interferon production. However, upon canonical and non-canonical inflammasome activation, caspase-1 cleaves cGAS and thereby dampens STING-mediated type I interferon production[18].

Interferon regulatory factors (IRFs) are activated downstream of PRRs, and translocate to the nucleus, where they function as transcription factors[19]. In phagocytes and dendritic cells, stimulation of TLR3 or TLR4 leads to the activation of IRF3 via the adaptor TIR domain-containing adaptor molecule 1 (TICAM1, also known as TRIF)[20]. Activation of cytosolic nucleic acid sensors (MDA5 and RIG-I by RNA or STING by DNA) also upregulate the activation of IRF3 (REF. 21), which upregulates expression of *IFNB1*. The adaptor mitochondrial antiviral-signalling protein (MAVS) interacts with RIG-I and MDA5 to facilitate activation of IRF3 in phagocytic and dendritic cells, and of IRF7 in pDCs. In pDCs, recognition of nucleic acids by TLR7, TLR8 or TLR9 leads to recruitment of the adaptor protein MyD88, which in turn interacts with IL-1 receptor-associated kinase 1 (IRAK1) and IRAK4 (REF. 22) (FIG. 1b). This signalling complex results in the phosphorylation of IRFs, such as IRF5 and/or IRF7. The translocation of IRF5 to the nucleus culminates in the transcription of genes encoding type I interferons, pro-inflammatory cytokines (IL-6 and TNF) and IL-12p40, whereas IRF7 promotes expression of type I interferons[23].

IFNβ production is also stimulated as a result of sig-nalling through TNF receptors (TNFRs), such as receptor activator of nuclear factor-κB (RANK) and TNFR2. In macrophages and endothelial cells, TNF induces IFNβ production via IRF1, and can also induce an IFNβ autocrine loop that functions in synergy with canonical TNF signals to induce sustained expression of inflammatory genes and delayed expression of signal transducer and activator of transcription 1 (STAT1)-dependent interferon stimulated genes (ISGs)[24] (FIG. 1c). This synergy primes macrophages for increased responses to subsequent challenges[24]. In human endothelial cells, this cascade seems to depend on TNFR2 and results in the promotion of monocyte recruitment[25]. Interaction between RANK and RANK ligand (RANKL) activates pathways that include TNFR associated factor 6 (TRAF6) and c-Fos, which promote expression of IFNβ and can also promote osteoclastogenesis (FIG. 1d). IFNβ promotes the transcription of genes that inhibit c-Fos activity[26] and induce nitric oxide, which inhibits osteoclastogenesis[26].

## Type I interferon signalling

Type I interferons bind to a shared cell surface receptor, the type I interferon receptor (IFNAR). IFNα and IFNβ induce different conformational changes in the cytosolic portion of the receptor, which enables differential signalling by the two cytokines through the same receptor[28]. Upon engagement, IFNAR activates kinases (for example, Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) in canonical type I interferon signalling), prompting phosphorylation, dimerization and nuclear translocation of STAT proteins. The resulting STAT complexes control distinct gene-expression programmes. For example, the interferon-stimulated gene factor 3 (ISGF3) complex (composed of STAT1, STAT2 and IRF9) activates classic antiviral genes. By contrast, STAT1 homodimers induce pro-inflammatory gene expression, and STAT3 homodimers suppress pro-inflammatory gene expression[29].

IFNα signalling activates antigen-presenting cells, and increases the expression of CD86, as well as MHC class I and II molecules on these cells, which provide co-stimulatory signals and augment antigen presentation, respectively[30]. Thus, IFNα can bridge the innate and adaptive immune systems, demonstrating its importance in setting thresholds for self-reactivity and autoimmunity. IFNβ shares many downstream signalling properties with IFNα, but also has anti-inflammatory and antiproliferative properties. ISG expression is complex and seems to be cell and context dependent[31] (reviewed elsewhere[29]). Signalling pathways that are also triggered by interferon receptor engagement (for example, mitogen-activated protein kinase (MAPK), nuclear factor-κB (NF-κB) and protein kinase B (RACα serine/threonine-protein kinase, also known as AKT) pathways) influence the transcription of ISGs and/or translation of ISG mRNA downstream of type I interferon-activated JAK–STAT pathways[32,33]. Physiological activation of the type I interferon pathway is even more complex, as IFNβ can function in synergy with TNF, which is produced at early stages following innate recognition of a pathogen[34]. Co-stimulation with IFNβ and TNF induces a synergy-dependent delayed antiviral response via an as yet uncharacterized pathway that is dependent on TYK2, STAT2 and IRF9, but is independent of STAT1 signalling[34]. Thus, various cytokine signalling pathways functioning through different receptors can affect the outcome of type I interferon signalling.

## Measuring type I interferon in blood

Traditionally, the term ‘interferon signature’ has been used to describe the pattern of increased expression of >100 type I ISGs in studies comparing the expression of genes in peripheral blood cells from patients with SLE and controls[2–4]. In addition to being present in SLE, such a signature has been found in other rheumatic diseases, including Sjögren syndrome, myositis, SSc and RA[35]. An important caveat regarding the interferon signature is that genes that are type I interferon-induced can sometimes also be induced by other factors. For example, type II interferons can induce the expression of some of the same genes as type I interferons, and evidence is accumulating for a circulating type II interferon signature in SLE[36].

Many studies of the interferon signature have examined gene expression in either whole blood or in peripheral blood mononuclear cells (PBMCs)[2,37]. In these approaches, multiple different cell types are mixed together. Different individuals typically have different

proportions of immune cell types; thus, a difference in the amount of a measured transcript reflects a combination of the amount of transcript expressed by each cell type and the proportion of each cell type in the cellular mixture. This limitation can be partially addressed by enumerating the proportion of each immune cell type in the sample before study, although adjusting for these differences in cell numbers with covariates is also challenging and cannot account for every possibility in the data. To address this issue, individual immune cell populations can be sorted before lysing the cells and measuring gene expression[31,38]. Interestingly, such analysis has shown that different immune cell types from the same blood sample express different ISGs[31]. These data suggest a great diversity in the downstream type I interferon responses of different cell types, and highlight the fact that we are still just beginning to understand the varied consequences of chronic type I interferon stimulation in human cellular immunity.

To address the limitations of interferon signature studies, functional assays have also been used to assess type I interferon activity in large cohorts of patients[39] (BOX 1). These functional assays are sensitive and utilize IFNAR and the downstream gene expression cascade to detect even very small amounts of type I interferons. To date, many commercial enzyme-linked immunosorbent assays (ELISAs) and multiplex assays that measure type I interferon protein levels have proven to be insufficiently sensitive or specific in detecting type I interferons in human samples[40]. However, a new method for detecting type I interferons was described by Wilson et al. in 2016 (REF. 41) that uses single-molecule array (Simoa) digital ELISA technology. This method reportedly detects attomolar (femtograms per milliliter) concentrations of IFNα protein in human samples[41]. This methodology is based on counting individual enzyme-labelled immune complexes captured on paramagnetic beads in single-molecule arrays[41,42] and utilizes unique high-affinity anti-IFNα antibodies isolated from patients with autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED)[43]. Additional validation of this technology is anticipated in the future.

## Type I interferons in SLE

### Disease initiation

Type I interferons have been linked with SLE initiation. Some patients being treated with recombinant human IFNα for viral hepatitis and haematologic malignancy develop de novo SLE[44,45]. When IFNα therapy is stopped, the rheumatic symptoms usually improve, supporting a causal role for type I interferons in the initiation of SLE in some patients[45]. Circulating type I interferon activity is frequently high in unaffected relatives of patients with SLE and familial correlations in type I interferon activity have been observed[46,47], suggesting that high levels of type I interferon in the circulation is a heritable risk factor for SLE. This heritability of high levels of type I interferon activity is shared across patients with SLE from all ancestral backgrounds[46] and follows a polygenic inheritance pattern. In longitudinal studies of serum samples from patients before they were diagnosed with SLE, type I interferon activity increases precipitously in the year before disease onset[48], also supporting the importance of type I interferon in disease initiation in SLE.

## Genetic factors

Among the SLE-associated loci identified in case–control genetic studies, there is an over-representation of genes involved in type I interferon signalling, production and response[49]. In general, many of the SLE-associated variants in type I interferon pathway genes are associated with increased activity in the type I interferon pathway in humans (reviewed elsewhere[49]). Variants have also been associated with increased circulating type I interferon activity or increased ISG expression[50,51]. Genes that are overexpressed in peripheral blood cells (creating the interferon signature) are not necessarily the same as the genes that are implicated as genetic risk factors[5].

**Interferon response factors.—**IRFs coordinate type I interferon and ISG expression in a cell-type specific manner (reviewed elsewhere[23]). IRF5 is involved in the production of both pro-inflammatory cytokines and type I interferons in innate immune cells[52], and IRF5 also influences B cell responses downstream of TLR stimuli[53]. Human genetic variants in *IRF5* have been identified as rheumatic disease susceptibility factors in SLE[54,55], Sjögren syndrome[56], SSc[57], RA[58] and juvenile idiopathic arthritis (JIA)[59].

In SLE, risk variants of *IRF5* are associated with increased circulating type I interferon activity in patients with SLE; this association is dependent upon the presence of anti-RNA-binding protein (RBP) or anti-dsDNA autoantibodies[60,61]. These data suggest that *IRF5* risk variants might be an important factor in the ‘stimulated’ scenario, in which the autoantibody immune complexes provide a constant endogenous stimulus that synergizes with a hyperresponsive TLR system, resulting in chronic over-production of type I interferons. The SLE *IRF5* risk haplotype is associated with the production of autoantibodies in otherwise healthy individuals[62], suggesting a potential feed-forward loop. In such a loop, an *IRF5* risk variant predisposes individuals to the production of autoantibodies, possibly via hyperactivity of the TLR pathway in B cells, and the autoantibodies produced can then form nucleic acid immune complexes that stimulate the overactive TLR system in innate immune cells. Genetic variants in both *IRF7* and *IRF8* have been associated with an increased risk of SLE[55,63,64], and such variants are also associated with altered type I interferon responses in patients with SLE[23,65,66].

**Other interferon-related genes.—**Beyond the IRF family, a number of other genes associated with risk of SLE (for example, *STAT4*, *MAVS*, *IFIH1* (which encodes MDA5) and *PTPN22*) have also been demonstrated to alter type I interferon pathway function[50,51,67–69]. Variants in some of these genes have also been associated with other rheumatic diseases, for example, *STAT4* is associated with Sjögren syndrome[70], SSc[71], RA[72], psoriasis[73] and, possibly, JIA[74]; *IFIH1* is associated with late-onset psoriasis[75]; and *PTPN22* is associated with RA and JIA[76,77]. Overall, type I interferon activity is clearly controlled to some degree by genetic factors and is a polygenic trait.

Interestingly, thus far, robust evidence demonstrating gene–gene interactions between interferon pathway genes (that is, the effect of one gene being modified by one or several interferon pathway genes) is lacking. Studies that have examined type I interferon in patients in the context of these risk variants have demonstrated additive effects without evidence for

either synergy or redundancy to date[50,51,65]. In addition, other factors, such as epigenetic regulation[78], probably influence the effect of these risk variants.

**Tissue expression.—**Most studies in SLE have examined circulating type I interferons, however, the action of type I interferons in the tissue is likely to be important and complex. Genetic polymorphisms in *IFNK* (encoding IFNκ) are implicated in the pathogenesis of cutaneous lupus erythematosus, and disease associated single-nucleotide polymorphisms in *IFNK* differ between male and female patients[79]. Interestingly, type I interferon activity was frequently increased in the circulation of female patients with such *IFNK* variants compared with that in healthy controls[79]. However, IFNκ was not a major contributor to the type I interferon activity observed in the circulation of these patients[46,79]. The *IFNK* variants could instead be influencing type I interferon production by pDCs in the affected skin, and thereby increasing type I interferon activity in the circulation[79]. Keratinocytes from the skin of patients with cutaneous lupus erythematosus produce more IL-6 in vitro than keratinocytes from healthy individuals after exposure to TLR agonists or ultraviolet B (UVB) radiation; this increased IL-6 production seems to be dependent on IFNκ[80]. Such cytokine production might also contribute to the skin inflammation observed in cutaneous lesions in SLE.

## Heterogeneity in SLE

IFNα is the predominant circulating type I interferon in patients with SLE[46]. Serum IFNα activity varies widely between patients with SLE, and in 40–50% of patients, serum IFNα activity is normal[46]. Therefore, type I interferon is probably not an important pathogenic factor for all patients with SLE, contributing to the pathological heterogeneity of this disease. A high degree of functional circulating type I interferon activity is strongly correlated with the presence of anti-RBPs, such as antibodies to 52 kDa SSA/Ro antigen (Ro52, also known as TRIM[21]) and ribonucleoprotein (RNP), in patients with SLE[39]. These autoantibody titres frequently do not change considerably over time, supporting the idea of a stable subset of patients with SLE who have high levels of type I interferon activity. A study comparing gene expression in African American and European American patients with SLE demonstrated that patients from both ancestral backgrounds had a type I interferon signature, but in African Americans this signature was particularly dependent on the presence of anti-RBP autoantibodies[81]. This finding is interesting as these autoantibodies, particularly anti-RNP and anti-Sm antibodies, are more common in African American patients than in European American patients[39], suggesting differences in the molecular pathogenesis of SLE between ancestral backgrounds.

Case–case genome-wide genetic studies, which com-pare patients with high levels of type I interferon activity to those with low levels of type I interferon activity, have implicated additional genes that modulate circulating IFNα activity in patients with SLE[5,47]. These studies identified a number of novel loci associated with risk of SLE and high degree of type I interferon activity that were not identified in case–control studies, including risk loci in *PRKG1*, *PNP*, and *ANKS1A*[5,47]. Further bioinformatic analyses suggested that these loci mediate functional effects in DCs and natural killer (NK) cells[5]. NK cells cooperate with DCs to induce IFNα production in SLE[82]. The *PNP* variant is a loss-of-function mutation in the gene encoding purine nucleoside phosphorylase (PNP), an enzyme involved in purine

metabolism, that leads to cell-cycle abnormality (a block in S phase entry) and type I interferon pathway activation in human lymphocytes[83]. Interestingly, this block in S phase can be rescued in vitro by providing hypoxanthine and adenosine, supporting the notion that relative PNP deficiency is the cause of the S-phase block, and suggesting a potential for personalized therapeutics in patients with SLE who harbour this *PNP* variant[83].

### Clinical implications

In SLE, the peripheral blood type I interferon signature correlates with disease severity[2]. In a cross-sectional study, patients with a prominent peripheral type I interferon signature fulfilled a substantially higher number of SLE clinical diagnostic criteria and, upon retrospective review, more commonly had kidney, central nervous system (CNS) and/or haematologic involvement at some point during the course of their disease[2]. However, in longitudinal studies, the interferon signature in blood is relatively stable and cannot be used to predict SLE disease flares over time[84,85]. The expression of certain chemokines (CXC-chemokine ligand 10 (CXCL10), CC-chemokine 2 (CCL2), and CCL-chemokine ligand 19 (CCL19)) that are induced by interferons and other cytokines also correlate with disease activity and might predict risk of flares over time in SLE[86], suggesting that other factors beyond type I interferon are involved in disease flares. Gene expression studies support this idea, showing that other non-type I interferon-induced gene signatures, such as the plasmablast signature, correlated more strongly with disease activity than the interferon signature[37]. Thus, type I interferons might be more important in disease initiation and in the early phases of disease than in disease flares.

## Type I interferon in Sjögren syndrome

Some of the genes associated with increased type I interferon pathway activation in SLE (such as *IRF5* and *STAT4*) are also associated with risk of Sjögren syndrome[56], and a type I interferon signature has been reported in both the blood and tissues of patients with Sjögren syndrome[87–89]. In Sjögren syndrome, a peripheral blood type I interferon signature strongly correlates with the presence of anti-SSA/Ro antibodies[88], which parallels the association observed between anti-RBP antibodies and the interferon signature in SLE. Thus, despite the many clinical differences that exist between Sjögren syndrome and SLE, parallels can be drawn between these two diseases regarding type I interferon pathway activation with respect to autoantibody associations and background genetics. Although anti-SSA/Ro antibodies are associated with increased type I interferon activity in patients with either SLE or Sjögren syndrome, asymptomatic individuals with high anti-Ro antibody titres do not have high levels of circulating type I interferon activity[90]. This finding suggests that other disease-associated factors must be present in addition to anti-SSA/Ro antibodies to cause a chronic increase of circulating type I interferon[90].

In Sjögren syndrome, a type I interferon signature might help identify clinically meaningful subgroups of patients. A peripheral blood monocyte type I interferon signature identified a subgroup of patients with Sjögren syndrome who had high levels of clinical disease activity, autoantibodies and the expression of B-cell activating factor (BAFF, also known as TNFSF13)-encoding mRNA in their monocytes[91]. *OAS1*, one of the ISGs, is a Sjögren

syndrome risk locus, and disease-associated variants of *OAS1* result in alternate splicing of the gene transcript, leading in multiple alternative transcripts that result in a lack of translational response to type I interferon stimulation[92]. The 620W polymorphism in *PTPN22* is also associated with Sjögren syndrome and with a low expression of ISGs, implying the presence of distinct genetic backgrounds among subsets of patients with Sjögren syndrome that can be defined by type I interferon activity[93]. Interestingly, investigators found that the pattern of expression of RNA-sensing receptors (TLR7, RIG-I and MDA5) in monocytes and pDCs from patients with Sjögren syndrome differed substantially between those who did and did not have a peripheral type I interferon signature[94]. This type of differentiation might help identify subsets of patients who will benefit from therapies targeting these pathways.

In contrast to the type I interferon signature that predominates in the blood in patients with Sjögren syndrome, a type II interferon signature predominates in minor salivary gland (MSG) biopsy samples from such patients[95]. Concomitant low expression of IFNα-encoding mRNA and high expression of IFNγ-encoding mRNA in MSG tissue is strongly associated with lymphomagenesis, suggesting that the ratio between these two mRNA species in MSG biopsy samples can serve as a biomarker for in situ Sjögren syndrome-related lymphoma[95].

## Type I interferon in myositis

In patients with either dermatomyositis or polymyositis, type I interferon levels are increased in the circulation and a type I interferon signature is detectable in muscle tissue[35,96,97]. Muscle tissue from patients with juvenile dermatomyositis has increased numbers of infiltrating pDCs and increased expression of the ISG *MX1*[98] compared with tissue from healthy controls. Multiple studies have shown an association between type I interferon in the circulation and disease activity in myositis[96,99,100]. These studies provide stronger evidence for an association between type I interferon activity and longitudinal disease activity than has been observed in SLE.

Although the genetic basis of inflammatory disease is currently less well described in myositis compared with SLE, a number of polymorphisms in several genes associated with increased type I interferon activity in patients with SLE (for example, *OPN* rs28357094G and *TNFA*-308A alleles) have been associated with high levels of type I interferon activity in patients with dermatomyositis[101]. Furthermore, type I interferon levels are higher in patients with dermatomyositis who have a family history of SLE compared with in those without a family history of SLE[102], which supports the idea of a shared genetic basis for type I interferon pathway activation in various rheumatic diseases. The presence of anti-RBP antibodies in patients with myositis, such as anti-SSA/Ro and anti-Sm antibodies, is associated with high levels of circulating type I interferon activity[103], paralleling that seen in other rheumatic diseases. Interestingly, the use of TNF inhibitors in patients with myositis[104] or Sjögren syndrome[105] results in increased type I interferon activity, which, in myositis, is associated with lack of improvement or worsening of disease[104].

Circulating IFNα is an important contributor to the total functional type I interferon activity observed in dermatomyositis[96]; however, some studies support the idea that IFNβ also

contributes to the interferon signature seen in PBMCs from patients with dermatomyositis[106]. TLR3 stimulation of cultured myoblasts induces the production of IFNβ when combined with IFNγ stimulation, and upregulates the expression of HLA class I molecules[107]. In muscle biopsy samples from patients with polymyositis or dermatomyositis, immature muscle precursor cells that overexpress HLA class I are a source of IFNβ[107]. Thus, IFNβ from immature muscle precursor cells might contribute to the type I interferon signature seen in muscle tissue in myositis. A 2015 study of muscle tissue from patients with dermatomyositis demonstrated that TLR3 and RIG-I are preferentially expressed in the perifascicular fibres, indicating that these type I interferon pathway components might be involved in the formation of perifascicular atrophy, a hallmark feature of dermatomyositis[108]. In the same study, the investigators found that expression of TLRs and RIG-I was upregulated in the muscle tissue of patients with dermatomyositis compared with controls (which included patients with polymyositis, facioscapulohumeral muscular dystrophy, and patients without neuromuscular disease) and that TLR4 and TLR9 were expressed mainly in inflammatory infiltrates[108]. The researchers concluded that endogenous production of type I interferon in dermatomyositis is generated by pDCs, mainly through the TLR9 pathway. However, the TLR4 pathway can also contribute to type I interferon induction[20] (FIG. 1a), and as TLR4 was also expressed in the inflammatory infiltrates, it is conceivable that TLR4 might also contribute to the endogenous type I interferon found in the muscle of patients. Additionally, non-immune cells that produce IFNβ (such as endothelial cells, FIG. 1c) might also contribute to type I interferon production in myositis.

## Type I interferon in SSc

A number of studies have documented increased type I interferon-induced gene expression in patients with SSc, in both circulating blood cells and in affected lung tissue[109–112]. Interestingly, patients with SSc who have antiSSB/Ro antibodies are more likely to have high levels of type I interferon than patients without these antibodies, resembling associations seen in myositis, Sjögren syndrome and SLE[113]. Other autoantibodies have also been associated with high circulating type I interferon expression in SSc, including anti-U1 RNP and antitopoisomerase autoantibodies[109]. This finding suggests that a similar process of immune complex-mediated type I interferon generation might contribute to the increased circulating type I interferon levels observed in many rheumatic diseases.

A number of variants in type I interferon pathway genes (for example, *IRF5* (REF. 57), *IRF7* (REF. 114), *IRF8* (REF. 115), *TREX1* (REF. 116), *IRAK1* (REF. 114), and *STAT4* (REF. 71)) are associated with SSc. pDCs are also implicated in SSc pathogenesis. In SSc, in addition to the role of pDCs in type I interferon production, there is a striking and disease-specific over-production of CXC-chemokine ligand 4 (CXCL4, also known as platelet factor 4) by pDCs, which corresponds with severe skin disease and lung fibrosis[117]. CXCL4, a potent antiangiogenic chemokine that also has profibrotic properties and stimulates the proliferation of regulatory T cells that have impaired function[118–120], is suspected to have a major role in the vasculopathy of SSc and to influence fibrosis by downregulating *FLI1* in endothelial cells and fibroblasts[117]. It is speculated that CXCL4 does not act in isolation[117]; hence other factors, such as alterations in the type I interferon pathway, could function together with CXCL4 to contribute to SSc pathogenesis. Intramuscular administration of

recombinant IFNα showed some initial promise in improving or stabilizing skin scores in a pilot study of patients with diffuse cutaneous SSc[121]. However, in keeping with IFNα having a pathogenic role in SSc, a randomized, double-blind, placebo-controlled trial showed that recombinant IFNα therapy in SSc is ineffective and might in fact be harmful, as those who received the IFNα treatment showed less improvement in skin scores and greater deterioration of lung function than the placebo group[122].

## Type I interferon in RA

A type I interferon signature is detectable in the peripheral blood of patients with RA, and can be present in the preclinical phase of the disease[123]. The relative level of expression of ISGs in the circulation in RA is lower than that observed in SLE and other autoimmune connective tissue diseases[35,124]. However, some of the genes associated with increased type I interferon pathway activation in SLE are also associated with the risk of RA, such as *IRF5* (REF. 58), *IRAK1* (REF. 125), *STAT4* (REF. 72) and *PTPN22* (REF. 77). The finding that particular polymorphisms are associated with the risk of developing a number of rheumatic diseases supports the idea that there is a shared pathway in these diseases[126].

The presence of pDCs and the expression of ISGs, IFNα and IFNβ have been documented in the synovium of patients with RA[127–130]. IFNα positively correlates with TLR3 and TLR7 in the lining and sub-lining of RA synovium. IFNα increases the expression of TLR3 and TLR7 and downstream production of IL-6 and TNF. Additionally, IFNα markedly potentiates TLR4-mediated production of IL-1β and IL-18 in synovial cells from patients with RA[130]. By contrast, IFNβ has an anti-inflammatory effect in inflammatory arthritis. In PMBCs, IFNβ can inhibit the production of IL-1β and TNF and can also increase the production of IL-1 receptor antagonist (IL1Ra) in a dosedependent manner[131]. IFNβ also dose-dependently increases IL1Ra secretion by synovial fibroblasts and enhances the secretion of IL1Ra induced by IL1β in synovial fibroblasts and chondrocytes[132]. Treatment with IFNβ is effective in alleviating arthritis in the collagen-induced arthritis mouse model of RA[133,134]. However, in a multicentre, randomized, double-blind,placebo-controlled phase II study, treatment with subcutaneous recombinant IFNβ resulted in no improvement in patients with active RA[135].

In RA, type I interferon is potentially a predictive biomarker of response to biologic therapies. For example, the presence of a pretreatment type I interferon signature reportedly predicts response to the B cell-depleting therapy rituximab[136]. In another study, the ratio of pretreatment IFNβ activity to IFNα activity (IFNβ:IFNα activity ratio) could predict the response to anti-TNF therapy in RA[137]. A larger study from 2016 supported this idea, finding that the pretreatment serum IFNβ:IFNα activity ratio was strongly predictive of non-response to TNF inhibitors in both discovery and independent replication cohorts[138]. Although the reasons for the differences in the relative proportions of IFNα versus IFNβ in the circulation are unknown, other studies support the idea that these two type I interferons exist in different proportions in different rheumatic diseases[139], with IFNα predominating in the circulation in SLE[46,96], and IFNβ being relatively more abundant in RA[138,139]. Reason for the discrepancy between the finding that IFNβ was anti-inflammatory in early functional studies[131–134,140] and the failure of the clinical trial of recombinant IFNβ treatment[135], as

well as the relatively increased IFNβ levels observed in the circulation of patients with RA who are unlikely to respond to anti-TNF therapy[138], is unclear. Given the complexity of type I interferon signalling regulation (reviewed elsewhere[29]), the effects of IFNβ are probably influenced by the amount, duration and location (for example, the circulation or tissue) of IFNβ expression, and the environmental context.

## Monogenic interferonopathies

The gene variants mentioned thus far moderately effect activation of the type I interferon pathway and/or susceptibility to complex polygenic rheumatic diseases, and it is likely that combinations of these genetic variations are probably required to predispose to disease. However, a number of monogenic diseases are characterized by interferon pathway activation. Interestingly, these diseases are considered to lie on an autoimmune–autoinflammation spectrum that depends on the driver of dysregulated type I interferon production[141]. On the basis of this spectrum, Kim et al.[141] have proposed grouping these conditions into ‘autoinflammatory’ interferonopathies (those caused by a problem in the innate immune sensing system), and ‘autoimmune’ interferonopathies (those caused by immune complex stimulation of endosomal TLRs in B cells and pDCs). Dysregulation can occur from both processes in a given patient; however, the initial ‘driver’ of the interferonopathy is typically at one end of this spectrum. Monogenic forms of SLE (such as those caused by loss-of-function mutations in the genes encoding complement protein C1q, deoxyribonuclease 1 or deoxyribonuclease-γ) are considered to be autoimmune monogenic interferonopathies. Important examples among the autoinflammatory monogenic interferonopathies include AGS, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), and STING-associated vasculopathy with onset in infancy (SAVI).

### AGS and related monogenic diseases

AGS is caused by gain-of-function mutations in *TREX1* or *IFIH1*. The *TREX1* gene encodes the major mammalian 3′−5′ DNA exonuclease that degrades endogenous DNA in the cytoplasm[142]. In addition to AGS[143,144], mutations in *TREX1* have also been reported in SLE[143,145], familial chilblain lupus[144] and retinal vasculopathy with cerebral leukodystrophy (RVCL) (reviewed elsewhere[146]). AGS and RVCL are characterized clinically by CNS inflammation and high levels of type I interferon in the circulation and cerebrospinal fluid. Mutations in the gene encoding nucleic acid sensor RIG-I, *DDX58*, cause an atypical Singleton–Merten syndrome, which manifests with variable clinical presentations of glaucoma, aortic calcification and skeletal abnormalities, such as acro-osteolysis without dental anomalies[147]. Although there are no classical signs of apparent inflammation in patients with Singleton–Merten syndrome, the clinical manifestations are suspected to relate to chronic inflammation, at least in part conferred by constitutive activation of RIG-I resulting in increased type I interferon activity and ISG expression.

### CANDLE

CANDLE is caused by mutations in protein subunits of the proteosome–immunoproteasome system. Disease can be the result of any of several recessive mutations in different protein

subunits of the system, located either in one single subunit (monogenic, homozygous or compound heterozygous inheritance) or in two different subunits (digenic and compound heterozygous inheritance)[148,149]. Defects in the catalytic activity of the proteasome–immunoproteasome system result in a sustained production of type I interferon[148,149] that is independent of STING and MAVS[141].

### SAVI

SAVI is caused by gain-of-function mutations in *STING* and is characterized by cutaneous vasculopathy and pulmonary inflammation[150]. In vitro studies indicate that these *STING* variants stimulate *IFNB1* expression and other gene targets of STING[150]. Data from STING N153S knock-in mice demonstrates that at least some of the phenotype of SAVI occurs independently of IRF3, suggesting that the phenotype is not solely ISGrelated[151]. However, patients with SAVI have a strong type I interferon signature in their PMBCs, and JAK inhibitors reduce the constitutive upregulation of phosphorylated STAT1 in the lymphocytes of these patients in vitro, indicating that JAK inhibition could be a promising therapy for SAVI[150].

## Type I interferon pathway therapies

Insights gleaned from studies of the type I interferon pathway, including those identifying disease risk loci and functional studies of molecules involved in the type I interferon pathway, might help explain the heterogeneity in the molecular pathogenesis of rheumatic diseases. Such insights might explain some of the heterogeneity in treatment responses observed in these diseases, and type I interferon pathway studies could also reveal new targets. These insights should inform the development of new therapies and the design of clinical trials. Multiple antiIFNα, anti-IFNAR and anti-TLR strategies are currently in clinical development for the treatment of rheumatic diseases (TABLE 1).

### Anti-IFNα therapies

Anti-IFNα monoclonal antibodies (such as sifalimumab and rontalizumab) can inhibit the expression of the type I interferon signature in patients with SLE[152–154], and phase II studies examining clinical responses to these antibodies in patients with SLE have had mixed results[155–157]. Rontalizumab did not meet the primary endpoint in one phase II trial, but did demonstrate some efficacy in a subset of patients with SLE and a low type I interferon signature metric (a set of 3 ISGs (*HERC5*, *EPSTI* and *CMPK2*) were used as a surrogate for the type I interferon signature)[157]. Treatment with sifalimumab did result in clinical improvement in various clinical end points in patients with SLE in another phase II study, and the effect was strongest in those patients with a high type I interferon signature score (based on a set of four ISGs: *IFI27*, *IFI44*, *IFI44L* and *RSAD2*)[156]. Although these phase II trial findings seem somewhat contradictory, it is interesting that in both trials the pretreatment type I interferon status of the patients affected the treatment response to anti-IFNα antibodies. It is possible that differences in the strength of interferon blockade between the two therapeutics or the dosing level could explain these differences in clinical efficacy.

Results from phase I and II studies investigating the induction of humoral polyclonal anti-IFNα responses by immunization with IFNα kinoid (a conjugate of an inactive form of human IFNα and a carrier protein, keyhole limpet haemocyanin) in patients with SLE have also shown some promise in improving control of the disease[158]. Furthermore, in a phase Ib trial, sifalimumab reduced the expression of a type I interferon signature observed in the blood of patients with dermatomyositis or polymyositis[159].

## Anti-IFNAR therapies

Anifrolumab is an antibody that binds to the IFNAR and blocks signals from both IFNα and IFNβ[160]. In a phase II study of patients with moderate to severe SLE[161], anifrolumab treatment resulted in greater rates of improvement across a broad range of composite and organ-specific disease activity measures; a greater proportion of patients achieving and maintaining low disease activity or corticosteroid tapering as well as a trend toward a reduction in flare rate compared with placebo. Greater efficacy was seen in all end points in patients with a high baseline type I interferon signature compared with those with a low baseline interferon gene signature, suggesting that the former group represents a subpopulation of patients who are likely to benefit from anifrolumab treatment. However, the sample size of the low baseline type I interferon signature group was small, limiting interpretations of the data from this group; thus, further studies are warranted to determine efficacy in this subpopulation.

In early phase studies in patients with SSc, anifrolumab inhibited a type I interferon signature (as measured by a composite score from five ISGs: *RSAD2*, *IFI44*, *IFI44L*, *IFI27* and *IFI6*), and this inhibition correlated with decreases in T cell-related transcripts and increases in collagen degradation-related transcripts in the skin[162]. Thus far there have not been overly concerning safety signals with regard to viral infection or malignancy risk with these anti-IFNα and anti-IFNAR therapies, although herpes zoster reactivation has occurred in some patients[161]. In lupus-prone mice, type I interferon-induced synapse loss and behavioural phenotypes are prevented by blocking signalling at IFNAR[163], suggesting that anifrolumab might be helpful in treating neuropsychiatric lupus and should be considered for future clinical trials.

## Hydroxychloroquine and TLR inhibition

Treatment with hydroxychloroquine impairs the ability of pDCs from patients with SLE to produce IFNα and TNF in response to stimulation with TLR9 and TLR7 agonists in vitro[164]. Unless contraindicated, hydroxychloroquine is advocated for use in all patients with SLE owing to its efficacy in reducing the number and intensity of flares, and in reducing damage accrual[165,166]. In the treatment of RA, hydroxychloroquine has also been used in combination with other drugs (for example, the widely use combination of methotrexate plus sulfasalazine and hydroxychloroquine, known as the ‘triple therapy’ regimen); however, hydroxychloroquine has limited efficacy in treating disease activity on its own. In a 2017 systematic review and meta-analysis of studies evaluating the effects of hydroxychloroquine on cardiovascular outcomes in patients with RA, hydroxychloroquine seemed to decrease insulin resistance and incidence of cardiovascular disease; however, the data were too few for meta-analysis[167]. Hydroxychloroquine is currently being tested in phase II trials for

endothelial dysfunction in RA[168], antiphospholipid antibody syndrome[169], neonatal SLE[170], incomplete SLE[171] and in the prevention of clinically apparent RA in seropositive individuals[172].

Several additional TLR-targeting strategies are in early development in SLE[173], and a humanized anti-TLR4 monoclonal antibody is currently being tested in phase II of trials for the treatment of RA[174]. TLR4 inhibition could be interesting in RA if TLR4 activation contributes to the IFNβ levels observed in this disease, which is associated with non-response to anti-TNF therapies.

## Kinase inhibition

The development of small molecule kinase inhibitors that target proteins in the type I interferon pathway has been a major area of drug development, and a number of clinical trials of these inhibitors in various rheumatic diseases are currently underway (TABLE 2).

Tofacitinib, a JAK1 and JAK3 inhibitor, was approved by the FDA in 2012 for the treatment of patients with RA who have had an inadequate response or intolerance to methotrexate. Tofacitinib is now being tested in phase III trials for use in other rheumatic diseases (such as JIA[175–177] and psoriatic arthritis[178–180]), and is being investigated in earlier phases studies for use in SLE[181–183] and dermatomyositis[184]. Baricitinib, a JAK1 and JAK2 inhibitor, is being evaluated in stage III trials for the treatment of RA[185–190], in addition to being used as part of a compassionate use protocol for the treatment of autoinflammatory syndromes marked by high type I interferon (for example, SAVI, AGS and CANDLE)[191]. JAK inhibitors that also inhibit TYK2 are in phase II trials for the treatment of RA[192–197], psoriatic arthritis[198,199] and membranous lupus nephritis[200]. Finally, an IRAK4 inhibitor is currently in phase II trials for the treatment of RA[201]. Kinase inhibitors are also being tested in additional chronic autoimmune or autoinflammatory diseases not covered in this Review (TABLE 2).

## Clinical implications

Differences in type I interferon levels explain some of the heterogeneity in the clinical phenotypes and treatment responses across various rheumatic diseases. Thus, it would be reasonable to divide patients with a given disease (for example, Sjögren syndrome, SLE or RA) into subsets by their type I interferon pathway activity in clinical trials. Such a strategy has already been tested in trials of therapies targeting type I interferons in SLE[156,157], but this same strategy might also yield informative results in the treatment of other rheumatic diseases with either therapies that target the type I interferon pathway or other drugs.

Stratifying patients by type I interferon pathway activity might reveal important differences in particular subgroups of patients that would otherwise be missed and might also enable the prediction of a patient's treatment response to particular therapies, such as that observed with anti-TNF therapy[138]. Monitoring type I interferons during treatment might also be desirable in some patients. For example, caspase inhibitors are an attractive therapy for use in autoinflammatory disorders that result in increased inflammasome activation, such as NLRC4-related macrophage activation syndrome (NLRC4-MAS, also known as syndrome of enterocolitis and autoinflammation associated with mutation in NLRC4 (SCAN4)).

However, blocking caspase-1 activity also pathologically increases type I interferon production in some patients (particularly those who have relatively high levels of type I interferon activity at baseline)[18]. Regular assessment of type I interferon pathway activation could enable better monitoring for possible unwanted consequences in this scenario.

Interestingly, many rheumatic diseases are more frequent in females than in males. In a 2017 transcriptome analysis of human skin samples, the genes that were overexpressed in female healthy skin (compared with male healthy skin) were frequently genes that are associated with autoimmune diseases such as SLE, SSc and Sjögren syndrome[202]. The presence of sex hormones, such as oestradiol or testosterone, did not affect the expression of these genes in cultured keratinocytes. Some of these overexpressed genes were regulated by the transcription cofactor vestigial-like protein 3 (VGLL3), the expression of which also has a strong female bias. ISGs (*LY6E*, *OAS1*, *MX1* and *IFI44*) were among the genes that were targeted by VGLL3. In monocytes, maximal induction of the ISGs identified required the expression of VGLL3, suggesting that VGLL3 might promote inflammation by supporting type I interferon responses[202]. Thus, as we move towards precision medicine, we will need to carefully consider whether it is best to also subset patients with sex-discordant rheumatic diseases by sex in clinical trials.

## Conclusions

The type I interferon pathway is central in both immunity and tolerance, and alterations in this pathway underlie the pathogenesis of different rheumatic conditions. Rheumatic diseases such as SLE, SSc, myositis and RA are heterogeneous and some of the differences observed between patients with rheumatic diseases could be explained by variations in the expression of interferon-related genes or activation of the type I interferon pathway. Hence, certain genetic factors and/or pathogenic pathways might explain particular disease phenotypes, and these underlying factors and/or pathways will not be shared between all patients who have the same rheumatic disease. We suspect variation in the type I interferon pathway is a major factor in the currently unexplained heritability of rheumatic disease.

Studies that compare patient subgroups based on their type I interferon signature or type I interferon activity have furthered our understanding of the molecular mechanisms underpinning the heterogeneity of these diseases and treatment responses. Additional molecular phenotyping should help to further advance our understanding of the pathogenesis of disease subtypes, and help to guide therapy. For example, medications that have seemingly failed in clinical trials of a complex rheumatic disease might still be helpful for treating a subgroup of patients with this disease. Thus, the study of individual samples from clinical trials is important, and insights gleaned from such studies should inform the next steps in an iterative fashion, including the subgrouping of patients by molecular phenotype in subsequent trials.

Functional studies of causal allelic variants should advance our ability to translate genetic associations into clinical applications. A delicate balance exists between the autoimmune and/or autoinflammatory effects and the antipathogen and anticancer effects of type I interferon. Increasing our understanding of the regulation of this pathway in humans will

have important therapeutic and safety implications. By understanding the genetic regulation and molecular underpinnings of type I interferon in rheumatic diseases, we might be able to intervene therapeutically in a more personalized fashion, on the basis of the molecular dysregulation present in a given individual.

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Competing interests

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**Box 1 |**

## Functional assays of type I interferon activity

The most well-known functional assays for measuring type I interferon activity are the luciferase[203] and WISH cell[124] reporter assays. Both reporter assays rely on a cell line bearing the receptor for type I interferon

**Luciferase reporter assay**

The luciferase assay uses a cell line that is transfected with a plasmid carrying the luciferase gene under the control of a type I interferon inducible promoter. The cell line is exposed to samples containing type I interferon, and type I interferon activity is determined by measuring the luciferase expression[203]

**Wish cell reporter assay**

The WISH cell assay uses the WISH epithelial cell line to measure the ability of patient sera to promote type I interferon-induced gene expression. WISH cells are exquisitely sensitive to type I interferon, but do not produce type I interferons and lack other pattern recognition receptors such as TLRs[204,205]. Expression of the interferon stimulated genes (ISGs) *MX1*, *IFIT1* and *EIF2AK2* is measured using quantitative PCR (qPCR). The relative expression of each of these three genes is standardized to that generated with healthy donor sera and summed to generate a score reflecting the ability of sera to cause interferon-induced gene expression, which is referred to as type I interferon activity. The type I interferon activity is reflective of the amount of type I interferon protein present in the sample to ligate the type I interferon receptor. Additional aliquots from the same patients can be tested following pre-incubation with anti-IFNα or anti-IFNβ antibodies to determine how much of the total type I interferon activity is due to IFNβ activity, and how much is due to IFNα activity. IFNγ, TNF, IL-6, and IFNλ do not induce substantial expression of these three transcripts in the WISH cells (REF. 124 and unpublished data).

**Key points**

- Type I interferon has a pathogenic role in many rheumatic conditions, including systemic lupus erythematosus, Sjögren syndrome, myositis and systemic sclerosis.
- Many genetic risk factors for rheumatic diseases lie within the type I interferon pathway as gain-of-function polymorphisms, and both polygenic and monogenic influences have been described.
- Stratifying patients by type I interferon activity levels will inform us about both disease pathogenesis and treatment response in rheumatic diseases.
- A number of therapeutics that target type I interferons, the type I interferon receptor, or the type I interferon pathway are currently in various stages of development.

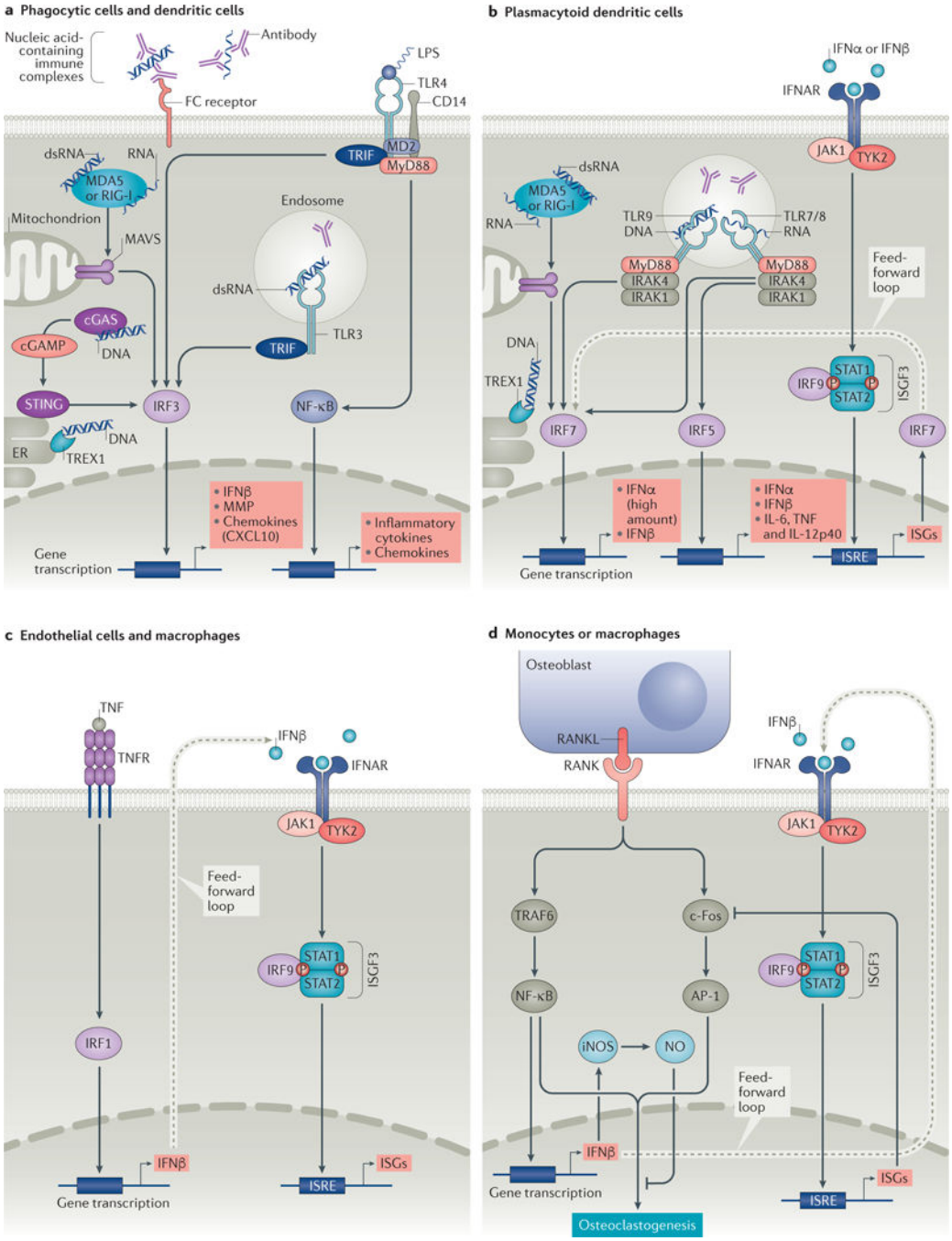


**Fig. 1 |. Major pathways of induction of type I interferon production in different cell lineages.**

**a** | In phagocytes and dendritic cells, stimulation of surface Toll-likereceptor 4 (TLR4) by lipopolysaccharide (LPS) or endosomal TLR3 by double-stranded RNA (dsRNA) results in activation of interferon regulatory factor 3 (IRF3) via a TIR domain-containing adaptor molecule 1 (TICAM-1, also known as TRIF)-dependent pathway, and nuclear factor-κB (NF-κB) via myeloid differentiation primary response protein (MyD88). Activation of cytosolic nucleic acid sensors (melanoma differentiation-associated protein 5 (MDA5) or retinoic acid inducible gene 1(RIG-I) by RNA, or stimulator of interferon genes protein

(STING) by DNA (via cyclic GMP-AMP synthase (cGAS)) also prompt activation of IRF3. IRF3 translocates to the nucleus and induces transcription of IFNβ. **b** | In plasmacytoid dendritic cells (pDCs), activation of endosomal TLR7 or TLR8 by RNA results in activation of IRF7 and/or IRF5. Activation of endosomal TLR9 by DNA or of cytosolic sensors MDA5 or RIG-I by RNA results in activation of IRF7. IRF7 translocates to the nucleus, where it induces transcription of type I interferons. Translocation of IRF5 to the nucleus culminates in transcription of type I interferons and pro-inflammatory cytokines. In pDCs, binding of type I interferon to the type I interferon receptor (IFNAR) results in activation of the canonical Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway that results in transcription of type I interferon stimulated genes (ISGs). ISGs include IRF7, which provides a feed-forward mechanism for production of more type I interferon. **c** | In macrophages and endothelial cells, TNF induces IFNβ via IRF1 and can induce an IFNβ autocrine loop that acts in synergy with canonical TNF signals to induce sustained expression of inflammatory genes and delayed expression of STAT1-dependent ISGs that prime cells for enhanced responses to subsequent challenge. **d** | Receptor activator of nuclear factor-κB (RANK)–RANK ligand (RANKL) interaction activates TNF receptor-associated factor 6 (TRAF6) and c-Fos pathways. TRAF6 activation results in induction of NFκB. c-Fos, together with activator protein 1 (AP-1) leads to a cascade that promotes osteoclastogenesis. NF-κB and c-Fos stimulate production of IFNβ. IFNβ promotes transcription of genes that inhibit c-Fos activity and results in the induction of nitric oxide (NO), which inhibits osteoclastogenesis. cGAMP, cyclic GMP-AMP; CXCL10, CXC-chemokine 10; ER, endoplasmic reticulum; iNOS, inducible nitric oxide synthase; IRAK, interleukin-1 receptor-associated kinase; ISGF3, interferon-stimulated gene factor 3; ISRE, interferon-sensitive response element; MAVS, mitochondrial antiviral-signalling protein; MD2, myeloid differentiation 2; MMP, matrix metalloproteinase; TNFR, TNF receptor; TYK2, tyrosine kinase 2; TREX1, three-prime repair exonuclease 1.

**Table 1 |**

**Biologic therapies in development for rheumatic diseases that target the type I interferon pathway**

| Treatment name | Type | Targeted rheumatic disease(s) | Phase of testing |
|---|---|---|---|
| ***Anti-IFNα therapies*** | | | |
| Rontalizumab | Humanized anti-IFNα IgG1 mAb | Systemic lupus erythematosus | II |
| Sifalimumab | Humanized anti-IFNα IgG1 mAb | Systemic lupus erythematosus | II |
| | | Psoriasis | II |
| | | Dermatomyositis and polymyositis | I |
| AGS-009 | Humanized anti-IFNα IgG4 mAb | Systemic lupus erythematosus | I |
| IFNα Kinoid | IFNα vaccine | Systemic lupus erythematosus | II |
| | | Dermatomyositis | II |
| ***Anti-IFNAR therapy*** | | | |
| Anifrolumab | Fully human anti-IFNAR mAb | Systemic lupus erythematosus | II/III |
| | | Systemic sclerosis | I |
| ***TLR inhibition*** | | | |
| NI-0101 | Humanized anti-TLR4 mAb | Rheumatoid arthritis | II |

IFNAR, type I interferon receptor; mAb, monoclonal antibody; TLR, Toll-like receptor;

**Table 2 |**

**Kinase inhibitor therapies that target the type I interferon pathway and are in clinical development for rheumatic diseases**

| Treatment name | Type | Targeted rheumatic disease(s) | Phase of testing |
|---|---|---|---|
| Tofacitinib | JAK inhibitor (JAK1, JAK3) | Rheumatoid arthritis | IV (FDA approved) |
| | | • Juvenile idiopathic arthritis<br>• Psoriatic arthritis<br>• Psoriasis<br>• Ulcerative colitis | III |
| | | • Systemic sclerosis<br>• Alopecia areata<br>• Ankylosing spondylitis<br>• Crohn's disease | II |
| | | Systemic lupus erythematosus | I/II |
| | | Dermatomyositis | I |
| Baricitinib | JAK inhibitor (JAK1, JAK2) | • Autoinflammatory syndromes (SAVI, AGS, CANDLE)<br>• Juvenile dermatomyositis | III (Compassionate use protocol) |
| | | Rheumatoid arthritis | III |
| | | • Giant cell arteritis<br>• Psoriasis | II |
| Solcitinib (GSK2586184) | JAK inhibitor (JAK1) | Rheumatoid arthritis | II/III |
| | | • Systemic lupus erythematosus<br>• Psoriasis | II |
| Decernotinib (VX-509) | JAK inhibitor (JAK3) | Rheumatoid arthritis | II/III |
| Ruxolitinib (INCB018424) | JAK inhibitor (JAK1, JAK2) | Secondary haemophagocytic syndrome (macrophage activation syndrome) | II |
| | | • Rheumatoid arthritis<br>• Psoriasis | I |
| PF-06651600 | JAK inhibitor (JAK3) | • Rheumatoid arthritis<br>• Alopecia areata<br>• Ulcerative colitis | II |
| Lestaurtinib | JAK inhibitor (JAK2) | Psoriasis | II |
| INCB018424 (topical) | JAK inhibitor (JAK1, JAK2) | • Psoriasis<br>• Vitiligo<br>• Alopecia areata | II |
| Filgotinib (GLPG0634) | JAK and TYK inhibitor (JAK1, JAK2, TYK2) | • Rheumatoid arthritis<br>• Systemic lupus erythematosus (membranous lupus nephritis)<br>• Non-infectious uveitis<br>• Crohn's disease | II |
| PF-06700841 | JAK and TYK inhibitor (JAK1, TYK2) | • Alopecia areata<br>• Psoriasis<br>• Crohn's disease | II |

| Treatment name | Type | Targeted rheumatic disease(s) | Phase of testing |
|---|---|---|---|
| | | • Ulcerative colitis | |
| PF-06263276 (topical) | JAK and TYK inhibitor (JAK1, JAK2, JAK3, TYK2) | Psoriasis | I |
| PF-06650833 | IRAK inhibitor (IRAK4) | Rheumatoid arthritis | II |

AGS, Aicardi– Goutieres syndrome; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; IRAK, interleukin-1 receptor-associated kinase; JAK, Janus kinase; SAVI, STING-associated vasculopathy with onset in infancy; TYK, tyrosine kinase.