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Type I IFNs in Autoimmunity

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Abstract

Dysregulated type I interferon responses play crucial roles in the development of multiple forms of autoimmunity. Many patients with lupus, systemic sclerosis, Sjogren's syndrome, and dermatomyositis demonstrate enhanced type I IFN signaling. Type I IFN excess is associated with disease severity, autoantibodies, and could potentially predict response to newer therapies targeting type I IFN pathways. Herein, we provide an overview of the signaling pathway and immune functions of type I IFNs in health and disease. We also review the systemic autoimmune diseases classically associated with type I IFN upregulation and current therapeutic strategies targeting the type I IFN system.

Keywords

Type I IFN; IFN signature; Autoimmunity; systemic lupus erythematosus; Sjogren's syndrome; systemic sclerosis; dermatomyositis

1. Introduction

The type I interferon (IFN-I) system is crucial for antiviral and antitumoral responses. However, dysregulated IFN-I responses contribute to the development of autoimmunity. Increased IFN-I signaling or high circulating IFN levels is a feature of various systemic autoimmune diseases. However, the clinical manifestations and mechanisms of injury vary widely among these disorders. In this review, we provide an overview of the biology, signaling pathways, and immune functions of IFN-I, as well as their roles in triggering and perpetuating systemic autoimmunity. We also review the main systemic autoimmune diseases associated with dysregulated IFN-I responses and current therapeutic strategies targeting the IFN-I system.

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2. The biology of IFN-I

IFN-I are a family of functionally and structurally related cytokines that bind the IFN-I receptor (IFNAR). In humans, the IFN-I family consists of IFN-α (comprised of 13 different subtypes), IFN-β, IFN-ε, IFN-κ, and IFN-ω (Gibbert et al., 2013, Li S. F. et al., 2018). Production of the specific subtypes of IFN-I depends on the cell type and the microenvironment (Ali et al., 2019). For example, plasmacytoid dendritic cells (pDC) are the most potent producers of IFN-α in response to viruses and other endosomal TLR triggers, whereas IFN-β is more ubiquitously expressed. Although most IFN-I are primarily produced following stimulation by pathogens or other damage signals, keratinocytes have been shown to constitutively produce IFN-κ (LaFleur et al., 2001, Siegal et al., 1999, Zhang et al., 2016). IFN-ω is structurally similar to IFN-α and is produced in response to viral infections. IFN-ε is primarily expressed in the glandular endometrial epithelium and is regulated by estrogens and progesterone during the menstrual cycle (Fung et al., 2013).

In normal immunity, IFNs are produced when exogenous or pathogen-derived particles are recognized by pattern recognition receptors (PRR), including the cytosolic nucleic acid sensors and Toll-like receptors (TLR) (Kawai and Akira, 2006). After PRR activation, interferon regulatory factors (IRF) translocate to the nucleus, enhancing the expression of genes encoding IFN-I. Activation of TLR-7 by single-stranded RNA or TLR-9 by unmethylated CpG-rich DNA in the endosomal compartments of pDCs leads to MyD88-dependent phosphorylation of IRF5 and/or IRF7. In the nucleus, IRF5 induces the transcription of pro-inflammatory cytokines such as IL-6 and TNF, whereas IRF7 stimulates the expression of IFN-I (Jensen and Niewold, 2015). In phagocytes and other immune cells, IRF3 is preferentially activated upon stimulation of TLR3 by double-stranded RNA and TLR4 by bacterial lipopolysaccharide. The cytosolic nucleic acid sensors cGAS-STING (DNA sensor) and RIG-I or MDA5 (RNA sensors) also activate IRF3 *via* the common signaling adaptor protein MAVS (Wu and Hur, 2015, Yu and Liu, 2021). PRRs can also recognize endogenous nucleic acids derived from defective nucleic acid metabolism, expression from endogenous virus-like genomic repeat elements, or autoantibody-containing immune complexes (Mavragani et al., 2016, Sisirak et al., 2016).

All IFN-I bind and activate IFNAR, a heterodimeric receptor constituted by IFNAR1 and IFNAR2. These subunits are constitutively associated with members of the Janus kinase (JAK) family by non-covalent interactions (Platanias, 2005). Through the canonical IFN-I signaling pathway, binding of IFN-I to IFNAR results in autophosphorylation and activation of TyK2 and JAK1, followed by recruitment, phosphorylation and dimerization of the signal transducers and activators of transcription (STAT) proteins. Once phosphorylated, STATs form dimers, translocate to the nucleus, and bind specific DNA domains to modulate the expression of IFN-stimulated genes (ISG).

IFN-I signaling is tightly regulated. The nature of the response is determined by a delicate balance between enhancing and suppressive mechanisms that allow an effective antimicrobial response while avoiding deleterious effects to host tissues (Ivashkiv and Donlin, 2014). Certain stimuli such as pro-inflammatory cytokines, viruses, and tumor cells can impair the IFN-I response *via* internalization from the cell membrane, downregulation

of expression and enhanced degradation of IFNAR, and by increasing the expression of negative regulators, including the suppressor of cytokine signaling (SOC) and the ubiquitin carboxy-terminal hydrolase 18 (USP18) proteins (Liu et al., 2009, Mayer-Barber and Yan, 2017, Sarasin-Filipowicz et al., 2009). In contrast, induction of the ISGs STAT1 and IRF9 by IL-6, type I and type II IFNs, and positive regulation of JAK1 by spleen tyrosine kinase (SYK) and protein tyrosine kinase 2 (PYK2) amplify IFN-I responses (Gough et al., 2010, Hu et al., 2002, Tassiulas et al., 2004).

3. Factors influencing IFN-I interferon pathways in autoimmunity

3.1 Genetic associations

Polymorphisms in genes involved in IFN-I-mediated pathways are overrepresented in patients with several forms of autoimmunity, which generally follow a pattern of complex polygenic diseases. Family members of patients with SLE and other autoimmune diseases have an increased risk of developing these disorders (Alarcón-Segovia et al., 2005, Kuo et al., 2015, Sinicato et al., 2019). Previous studies have identified a relative risk of over 300 for the development of SLE in identical twins (Kuo et al., 2015), and an overall heritability estimate of 44–66% (Kuo et al., 2015, Lawrence et al., 1987). In this sense, IFN-I levels are a heritable trait in SLE and juvenile dermatomyositis (DM) families (Niewold et al., 2007, Niewold et al., 2011), supporting the idea that there is a genetic component influencing the activation of t IFN-I pathways.

Several functional gene variants known to impact IFN-I production and response associate with an increased risk of several autoimmune disorders (Ghodke-Puranik and Niewold, 2015) (Figure 1). For example, gain-of-function variants in IFIH1, the gene encoding the RNA cytosolic sensor MDA5, are associated with psoriasis and SLE (Harley et al., 2008, Robinson et al., 2011, Strange et al., 2010). Similarly, functional polymorphisms affecting the IRFs that modulate the induction of IFN-I transcripts downstream of TLRs and cytosolic nucleic acid receptors have been found to heighten susceptibility to systemic autoimmunity (Matta et al., 2017). Genetic variants in IRF5 are not only associated with overt SLE and progression to clinical disease in asymptomatic ANA-positive individuals (Alarcón-Riquelme et al., 2016, Cherian et al., 2012), but also with Sjogren's syndrome, systemic sclerosis, dermatomyositis, and certain organ-specific autoimmune disorders such as cutaneous lupus (Chen et al., 2014, Graham et al., 2006, Ito et al., 2009, Järvinen et al., 2010, Miceli-Richard et al., 2007, Radstake et al., 2010). In addition, IRF5 and IRF7 or IRF7/PHRF1 risk haplotypes associate with the presence of autoantibodies and high serum IFN-alpha activity in patients with SLE (Fu et al., 2011, Harley et al., 2008, Niewold et al., 2008, Salloum et al., 2010). Interestingly, an even greater effect on IFN-I levels is seen in patients with SLE-associated autoantibodies and IRF5 or IRF7 polymorphisms, as an example of gene-environment interaction in autoimmunity (Niewold et al., 2012, Salloum et al., 2010). Genetic variants of IRF7 have also been described in systemic sclerosis (Carmona et al., 2012). Rare variants in BLK and its epistatic partner BANK1 are also associated with SLE *via* impaired repression and nuclear translocation of IRF5, and subsequent enhancement of IFN-β expression (Jiang et al., 2019). Furthermore, genetic

variation near the *IFNK* locus has been shown to have sex-specific associations with SLE susceptibility and specific skin genotypes (Harley et al., 2010).

Most commonly, autoimmune rheumatic diseases such as SLE, DM, and Sjogren's syndrome, are considered complex polygenic diseases. However, several monogenic conditions involving IFN-I pathway hyperactivation have been described in the last decade (i.e., monogenic interferonopathies). For example, Aicardi–Goutieres syndrome (AGS) is caused by functional mutations in genes related to nucleic acid degradation or sensing mechanisms, including *TREX1,* the gene encoding the intracellular 3'−5' repair exonuclease 1, and *IFIH1* (Oda et al., 2014, Rice et al., 2007). AGS manifests as an early-onset encephalopathy and chilblain lesions in distal extremities and ears. Interestingly, a heterozygous missense mutation in *TREX1* was identified in individuals with familial chilblain lupus, which also manifests with ulcerating acral skin lesions but without the neurologic affectation of AGS (Lee-Kirsch et al., 2007). Similarly, a heterozygous gain-of-function mutation in *TMEM173* (the gene encoding the protein STING) was also recently found as a monogenic cause of familial chilblain lupus (König et al., 2017). Germline dominant gain-of-function mutations in *TMEM173* are also responsible for the development of STING-associated vasculopathy with onset in infancy (SAVI), another form of monogenic interferonopathy which manifests as cutaneous vasculopathy and interstitial lung disease (Jeremiah et al., 2014, Liu et al., 2014).

By focusing on IFN-I activity as a molecular sub-phenotype, additional susceptibility loci were discovered on GWAS when comparing patients with SLE and high versus low IFN-α activity (Kariuki et al., 2015), which had not been previously identified in case-control studies (Alarcón-Riquelme et al., 2016, Harley et al., 2008). The top susceptibility genes in European ancestry patients include the PNP rs7897633 risk variant, a loss-of-function polymorphism that induces IFN-I pathway activation in lymphocytes (Ghodke-Puranik et al., 2017), and the PRKG1 rs7897633 variant, for which mechanistic studies are needed to elucidate the connection to IFN-I production and signaling. Polymorphisms in various genes associated with high IFN-I activity in SLE have also been found in association with increased circulating IFN-α levels in juvenile DM, including the osteopontin (OPN or SPP1) and tumor necrosis factor (TNF)-α−308 G/A variants (Kariuki et al., 2009b, Niewold et al., 2010).

Gene variants affecting IFN-I downstream signaling pathways have also been described. TYK2 represents an independent susceptibility locus for SLE (Gateva et al., 2009, Sigurdsson et al., 2005). An epistatic interaction between the TYK2 and IRF5 genes has also been postulated in SLE (Hellquist et al., 2009, Suarez-Gestal et al., 2010, Tang et al., 2015). The STAT4 risk haplotype correlates with greater STAT4 expression and is strongly associated with SLE, rheumatoid arthritis, and systemic sclerosis (Dieudé et al., 2009, Gourh et al., 2009, Harley et al., 2008, Remmers et al., 2007, Rueda et al., 2009, Sigurdsson et al., 2008, Zheng et al., 2013). In SLE, the STAT4 rs7574865 polymorphism is associated with low circulating IFN-I, increased sensitivity to IFN-α, and a more severe SLE phenotype, whereas the rs7582694 risk allele is associated with the presence of anti-dsDNA antibodies and shows an additive effect with two independent IRF5 risk alleles (Kariuki et al., 2009a, Sigurdsson et al., 2008, Zheng et al., 2013). Furthermore, the STAT4 rs7574865 and IRF5

rs2004640 alleles have an additive effect for susceptibility to systemic sclerosis and systemic sclerosis-associated interstitial lung disease (Dieudé et al., 2009). In DM, the ISG IFI35 has also been proposed as a potential risk locus (Bianchi et al., 2021).

3.2 Sex bias in IFN-I-related pathways

Accumulating evidence seems to suggest that the X chromosome is at least partially responsible for the female bias in certain autoimmune diseases (Weckerle and Niewold, 2011). An X chromosome gene-dose effect is supported by the increased risk of developing SLE and Sjogren's syndrome in patients with numerically abnormal karyotypes, such as trisomy X (47, XXX) and Klinefelter syndrome (47, XXY) (Harris et al., 2016, Liu et al., 2016, Scofield et al., 2008). In addition, mammalian X chromosomes are enriched for immune-related genes, and several of these escape X chromosome inactivation (Mousavi et al., 2020), including the TLR7 gene. In this sense, the role of the X chromosome complement is illustrated by an enhanced TLR-7 induced IFN-I production by pDC in females, which is exacerbated by estrogens (Laffont et al., 2014, Seillet et al., 2012). Similarly, the CXorf21 gene, which commonly escapes chromosome X inactivation (Zhang et al., 2013), is overexpressed in females compared to males (Odhams et al., 2019). The CXorf21 gene encodes for the TLR adaptor interacting with SLC15A4 on the Lysosome (TASL), a necessary adaptor for the recruitment and activation of IRF5 induced by ligand binding to the endosomal TLRs (Heinz et al., 2020).

Additional mechanisms of the sex bias in autoimmunity have been proposed. In a recent study, the transcription cofactor vestigial like family member 3 (VGLL3), which is enriched in the epidermis of women compared to men's (Liang et al., 2017), was postulated as key orchestrator of the female bias in autoimmunity. Overexpression of VGLL3 in mice was associated with enhanced IFN-I signaling and inflammatory changes that mimicked cutaneous lupus, as well as SLE-like features including autoantibody production and immune complex deposition in the kidneys (Billi et al., 2019). In agreement with these observations, Skopelja-Gardner, et al. demonstrated that UV light-irradiated mice skin showed an early IFN-I response that was approximately 10-fold higher in females compared to male mice (Skopelja-Gardner et al.). Altogether, these findings provide a plausible explanation for the female predominance of cutaneous, and possibly systemic, autoimmune diseases.

3.3 Non-genetic contributions to IFN-I dysregulation in autoimmunity

Although the genetic contribution to IFN-I-related autoimmune diseases is widely accepted, it is generally insufficient for the development of clinical autoimmunity. Environmental triggers such as infections, cigarette smoking, occupational exposures, as well as the microbiome are likely to play an important role in the development and heterogeneity of autoimmune diseases (Barbhaiya and Costenbader, 2016, Björk et al., 2020, De Martinis et al., 2016, Li B. et al., 2018). Epigenetic modifications have been proposed as a link between environmental exposures and modulation of expression in immune-related genes. Hypomethylation and overexpression of ISGs such as IFIT1, MX1, and USP18 have been identified in T cells from patients with primary Sjogren's syndrome, SLE, and systemic sclerosis (Altorok et al., 2014, Chen et al., 2019, Coit et al., 2013, Imgenberg-Kreuz

et al., 2016). Although some epigenetic modifications are cell-specific, genes related to IFN-I pathway activation can be hypomethylated in more than one cell type; for example, hypomethylation of IRF7 has been identified in both myeloid and lymphoid cells from SLE patients (Absher et al., 2013). Interestingly, the hypomethylation at ISGs has been shown to be more pronounced in patients with active SLE compared to those with inactive disease, and in patients with Sjogren's syndrome (Imgenberg-Kreuz et al., 2018). Given the lack of prospective epigenetic data assessing the progression from preclinical to established clinical autoimmunity, it remains unclear whether the observed DNA methylation changes are a cause or a consequence of increased IFN-I signaling. Moreover, genetic ancestry, risk polymorphisms, and certain medications such as glucocorticoids may alter DNA methylation patterns and be important confounders in epigenetic studies in autoimmunity (Lanata et al., 2018).

Recent studies have provided a link between intestinal dysbiosis and the pathogenesis of several autoimmune diseases (Rosser and Mauri, 2016). It is thought that a restricted intestinal microbiota and impaired enteral barrier could lead to bacterial translocation and consequently to increased IFN-I levels and autoantibody production (Silverman, 2019). Compared to healthy individuals, patients with SLE or primary Sjogren's syndrome have been found to have a less diverse gut microbiota (van der Meulen et al., 2019). Furthermore, a specific pattern of intestinal dysbiosis characterized by a greater representation of *Ruminococcus gnavus* and restrictions in taxonomic diversity was recently found to be associated with higher SLE disease activity scores, particularly in lupus nephritis (Azzouz et al., 2019). In this study, there was also a significant correlation between the levels of serum IgG against a specific non-protein bacterial antigen and IFN-α2 levels, providing a potential mechanism linking intestinal dysbiosis and enhanced IFN-I pathway activation in SLE.

4. IFN-I in systemic autoimmune disorders

4.1 SLE

Multiple lines of evidence have implicated IFN-I in the pathogenesis of SLE (Postal et al., 2020). Up to 80% of patients with SLE show overexpression of IFN-I-related genes in circulating immune cells (i.e., IFN signature), and about 50% have chronically elevated IFN-I levels that are detectable in plasma or serum (Baechler et al., 2003, Weckerle et al., 2011). Patients with SLE and evidence of high IFN-I activity tend to have higher disease activity scores and a greater risk of relapse while in remission (Kirou et al., 2005, Mathian et al., 2019). Increased circulating IFN-I levels also associates with specific organ involvement in SLE, including lupus nephritis, cutaneous manifestation, and arthritis, as well as autoantibody patterns (Hua et al., 2006, Oke et al., 2019).

The source of IFN-I in SLE has been debated. pDCs are best known for their ability to effectively produce IFN-α in response to endosomal TLR activation (Reizis, 2019). In SLE, immune complexes formed by autoantibodies and endogenous nucleic acids are thought to result in pDC stimulation and subsequent production of IFN-I, which could contribute to the early break in tolerance and disease initiation (Mavragani et al., 2016, Munroe et al., 2016, Niewold et al., 2007). Abnormalities in the processing and clearance of extracellular DNA, such as it occurs in genetic or acquired cases of DNAse1L3 deficiency, affect tolerance to

self-DNA and associate with anti-dsDNA antibody production and clinical manifestations of SLE (Hartl et al., 2021, Soni and Reizis, 2019). Interestingly, the generation of antibody-forming cells in this setting is facilitated by IFN-I in a pDC-dependent manner, further confirming the essential role of these cells in triggering and perpetuating autoimmunity (Soni et al., 2020). Accordingly, in early phase studies, pDC depletion has been shown to correlate with decreased IFN-I activity and improved disease activity (Furie et al., 2019, Karnell et al., 2021).

However, the isolation and identification of IFN-α-producing pDCs in patients with SLE have remained difficult (Der et al., 2019). Interestingly, SLE patients with high IFN-I have reduced circulating pDC numbers (Thanarajasingam et al., 2019). Furthermore, it was recently shown that circulating pDCs from patients with established SLE, Sjogren's syndrome, and patients in the preclinical stage are not only reduced in number but also are dysfunctional, with loss of all immunologic functions and features of senescence (Psarras et al., 2020). It is thus conceivable that pDC are not the only cell type involved in IFN-I dysregulation in SLE and other immune cells are also contributing. For example, monocytes are a source of IFN-I after UVB-triggered injury of mouse skin (Sontheimer et al., 2017). Follicular dendritic cells also produce IFN-α in response to self immune-complexes, mediated by TLR7 and IRF5 activation in murine models of lupus (Das et al., 2017). Neutrophils have been shown to mediate subclinical renal inflammation with transient proteinuria after UV light exposure to the skin, with evidence of reverse transmigration (i.e., after initially entering the irradiated skin, some neutrophils return to the bloodstream and infiltrate the kidney). Moreover, low-density granulocytes, a highly pro-inflammatory neutrophil subtype in SLE, have an enhanced ability to release neutrophil extracellular traps (NET), which can also trigger IFN-I production by pDCs (Garcia-Romo et al., 2011, Rahman et al., 2019).

Keratinocytes are also likely to play important roles in generating a robust IFN-I response in preclinical autoimmunity and established SLE *via* the production of large amounts of IFN-κ (and/or IFNβ) (Psarras et al., 2020, Sarkar et al., 2018). For example, increased levels of IFN-κ, which is seen in cutaneous and systemic lupus, may enhance the sensitivity of epithelia to IFN-α and UV irradiation (Sarkar et al., 2018). In addition, chronic ultraviolet B (UVB) light exposure-triggered IFN-I signaling has been shown to be independent of pDC recruitment in mice (Sontheimer et al., 2017). Interestingly, Skopelja-Garner et al. recently demonstrated that acute UVB exposure in the skin could trigger both local and systemic IFN-I responses via the cGAS/STING DNA sensing pathway, suggesting a potential rationale behind SLE flares induced by sunlight exposure in certain susceptible patients (Foering et al., 2013, Skopelja-Gardner et al.). These findings underscore the complex system linking IFN-I and various immune and non-immune cell types in the pathogenesis of SLE.

4.2 Systemic Sclerosis

Multiple studies have identified an IFN-I signature in whole blood or peripheral blood mononuclear cells from as many as 50% of patients with systemic sclerosis, even in early (pre-fibrotic) phases of the disease (Brkic et al., 2016, Duan et al., 2008, Higgs et al., 2011,

Rudnik et al., 2021, York et al., 2007). The presence of an IFN-I signature or increased circulating IFN-α levels have also been shown to correlate with serologic subtypes, specifically with anti-topoisomerase and anti-U1 RNP autoantibody positivity (Assassi et al., 2010), and more severe vascular manifestations and lung involvement (Eloranta et al., 2010, Liu et al., 2013). Target organs such as the skin and lung also demonstrate upregulation of ISGs in patients with systemic sclerosis (Christmann et al., 2014, Farina et al., 2010, Valenzi et al., 2021). Interestingly, as seen in SLE, there have been cases of systemic sclerosis developing as a complication of IFN-α therapy for myeloproliferative disorders or hepatitis C infection (Beretta et al., 2002, Solans et al., 2004).

Circulating pDC numbers are reduced in patients with systemic sclerosis (Ah Kioon et al., 2018), similar to what has been described in SLE (Thanarajasingam et al., 2019). Conversely, pDCs infiltrate the skin of systemic sclerosis patients and demonstrate abnormal TLR8 expression, which likely leads to dysregulated IFN-α production by these cells (Ah Kioon et al., 2018). Furthermore, circulating and skin infiltrating pDCs have been shown to produce large amounts of the chemokine CXCL4, which exacerbates the TLR-mediated IFN-α response in pDCs (Ah Kioon et al., 2018, van Roon et al., 2014). In scleroderma mouse models, depletion of pDCs has also been associated with decreased IFN response in the skin and a reduction in skin fibrosis (Ah Kioon et al., 2018, Ross et al., 2021). Various IFN-I-related gene variants have also been associated with an increased risk of systemic sclerosis, including IRF5, IRF7, and STAT4 (Skaug and Assassi, 2020). Limited data on anifrolumab use in systemic sclerosis suggest that IFN-I blockade can suppress T cell activation and collagen accumulation (Guo et al., 2015). These findings support the idea that IFN-I pathway dysregulation represents a pathogenic driver in systemic sclerosis. Clinical trials involving direct or indirect IFN-I antagonists may benefit at least a subset of patients with systemic sclerosis, most likely in the early pre-fibrotic phases.

4.3 Dermatomyositis

A prominent IFN signature has been identified in the skin, muscle, and blood of patients with adult and juvenile DM (Bilgic et al., 2009, Chen et al., 2008, Greenberg et al., 2005, Higgs et al., 2011, Moneta et al., 2019, Wong et al., 2012). The IFN-I gene signature also seems to correlate with disease activity in adult DM (Bilgic et al., 2009, Walsh et al., 2007). Certain subsets of patients with DM, such as those with anti-melanoma differentiation-associated gene 5 (MDA5)+ disease, have been shown to have a lower level of ISG expression in muscle tissue compared to MDA5− patients (Allenbach et al., 2016). In contrast, MDA5+ patients seem to have a stronger IFN-I signature in blood and skin than MDA5− patients (Cassius et al., 2020, Ono et al., 2019, Zhang et al., 2019). As MDA5+ patients have relatively mild muscle involvement and worse skin and lung disease compared to MDA5− patients, it is plausible that the IFN-I signature differences identified in these studies relate to the degree of organ affectation. In addition, MDA5+ patients exhibit overexpression of the IFN-κ gene in the skin, suggesting keratinocytes as an important local source of IFN-I (Cassius et al., 2020).

pDCs are part of the inflammatory infiltrate in muscle and skin biopsies from DM patients, suggesting a potential local source of IFN-α, presumably induced by autoantibody-

containing immune complexes (Greenberg et al., 2005, McNiff and Kaplan, 2008, Shrestha et al., 2010). In this sense, serum IFN-α activity (measured with a sensitive bioassay) was found to be associated with elevation of muscle enzymes and shorter duration of untreated disease in patients with newly diagnosed juvenile DM (Niewold et al., 2009), as well as with anti-Ro, anti-La, and anti-Sm/RNP (Balboni et al., 2013). Conversely, elevated levels of circulating IFN-β (determined by ELISA), but not IFN-α, were found to correlate with blood IFN signature in DM patients (Liao et al., 2011). The contrasting findings are likely due to the limitations of measuring circulating IFN-I by ELISA, potential differences between local versus circulating levels of these cytokines, as well as differences in the timing of disease, serologic subtype, therapeutic agents used, and age at the time of diagnosis.

5. Available therapeutic agents targeting IFN-I-related pathways in autoimmunity

Most therapeutic agents targeting IFN-I that have entered clinical development were initially aimed at treating SLE (Paredes and Niewold, 2020). Anifrolumab, a monoclonal antibody against IFNAR1, has been shown to be superior to placebo in reducing disease activity, glucocorticoid dose, and severity of skin disease in SLE (Furie et al., 2017, Furie et al., 2021, Morand et al., 2020). Previously, the anti-IFN-α monoclonal antibody rontalizumab failed to achieve its primary and secondary endpoints in SLE (Kalunian et al., 2016). Other anti-IFN-α agents, sifalimumab and AGS-009, were assessed in early phase clinical trials but did not enter further development stages despite promising preliminary findings on safety and efficacy (Khamashta et al., 2016, Tcherepanova et al., 2013). The IFN-α kinoid, an immunotherapeutic vaccine aimed to elicit high titers of anti-IFN-α neutralizing antibodies, also failed to meet its primary endpoint in SLE, but met clinically relevant secondary outcomes, including prednisone daily dose reduction and a greater proportion of patients in lupus low disease activity state compared to placebo (Houssiau et al., 2020). However, anifrolumab is likely superior to anti-IFN-α-directed therapies given the broader IFN-I antagonism in the former, since all IFN-I molecules signal through IFNAR. Various other agents targeting IFN-I dysregulation currently being assessed in clinical trials for safety and efficacy in SLE, systemic sclerosis, and DM are shown in Table 1.

6. Conclusion

In summary, IFN-I dysregulation is a cornerstone of several systemic autoimmune diseases. Although multiple studies have proposed mechanisms by which IFN-I contribute to the pathogenesis of autoimmunity, many unanswered questions remain. The exact source and triggers of IFN-I, the specific role of genetic variation and interactions between genetic and environmental factors that lead to dysfunctional IFN-I responses are, in many cases, unknown. The heterogeneity of disease manifestations, medication use, exposures, and genetic background in autoimmunity further complicates the interpretation of study findings. As we better understand disease pathogenesis and its role on immune dysregulation and clinical heterogeneity, the role of precision medicine in IFN-I-related autoimmune diseases

seems promising. Reassuringly, various therapeutic agents that target IFN-I pathways are in different phases of development or testing for various autoimmune diseases.

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Conflicts of Interest:

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Abbreviations:

AGS	Aicardi–Goutieres syndrome
BAFF	B-cell activating factor
BILAG	British Isles Lupus Assessment Group
BICLA	BILAG-based Composite Lupus Assessment
DM	Dermatomyositis
JAK	Janus kinase
IFN-I	Type I interferon
IFNAR	Interferon alpha/beta receptor
ILT7	Immunoglobulin-like transcript 7
ISG	Interferon-stimulated gene
IRF	Interferon regulatory factor
MDA5	Melanoma differentiation-associated protein 5
pDC	Plasmacytoid dendritic cell
PRR	Pattern recognition receptor
RIG-I	Retinoic acid-inducible gene I
SAVI	STING-associated vasculopathy with onset in infancy
SLE	Systemic lupus erythematosus
STAT	Signal transducer and activator of transcription
STING	Stimulator of interferon genes
TASL	TLR adaptor interacting with SLC15A4 on the Lysosome
TLR	Toll-like receptor

TYK2	Tyrosine kinase 2
VGLL3	Transcription cofactor vestigial like family member 3

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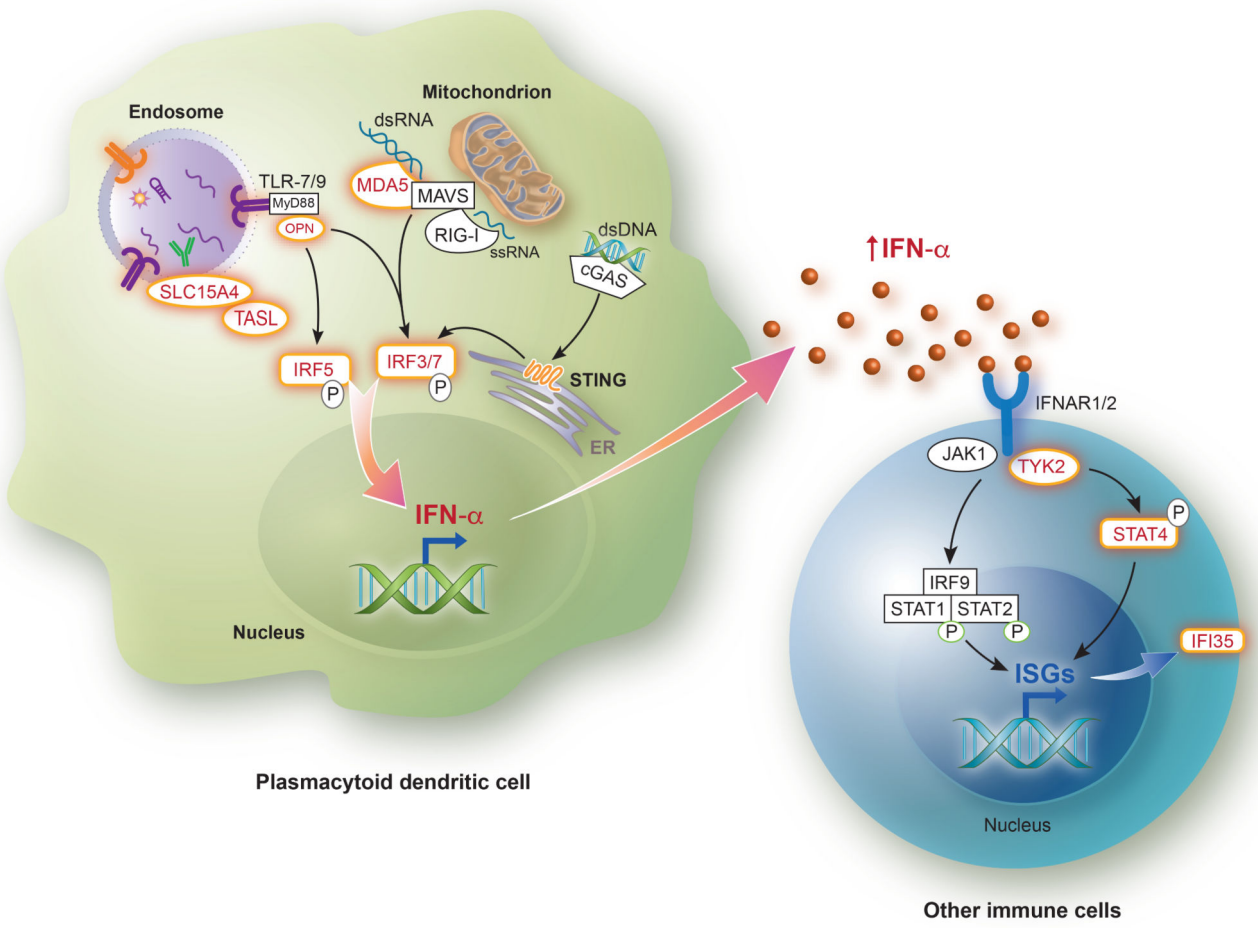

Figure 1. Risk alleles affecting type I interferon-related pathways in systemic autoimmune diseases.

Risk variants directly impacting the production of type I IFN or response that have been identified in SLE, Sjogren's syndrome, systemic sclerosis, or dermatomyositis are shown in red. Immune complexes containing autoantibodies and self nucleic acids (or antibodies and viral particles) are endocytosed by plasmacytoid dendritic cells, leading to ligand-triggered activation of endosomal Toll-like receptors. The adaptor interacting with SLC15A4 on the Lysosome (TASL, encoded by the CXorf21 gene) is necessary for the recruitment and activation of IRF5 induced by ligand binding to the endosomal TLRs. TASL escapes chromosome X inactivation and is overexpressed in females compared to males, whereas SLC15A4 has been identified as an SLE risk loci. Following TLR-7 and TLR-9 activation, MyD88 and OPN are recruited, which allows for subsequent phosphorylation and nuclear translocation of IRF5 and/or IRF7. Polymorphisms in SPP1 (OPN), IRF5, IRF7 have also been identified in various type I IFN-related autoimmune diseases. Cytosolic nucleic acids are recognized by cGAS (double-stranded DNA), MDA5 (double-stranded RNA) or RIG-I (single-stranded RNA), after which the adaptor proteins MAVS (for MDA5 and RIG-I) and STING (for cGAS) are recruited, allowing for IRF3 phosphorylation and translocation to the nucleus. Activation of IFNAR by type I interferons, including IFN-α, results in

phosphorylation of JAK1 and TYK2 and subsequent recruitment and phosphorylation of STAT proteins, which translocate to the nucleus and enhance expression of multiple interferon-stimulated genes (ISGs). TYK2 represents a susceptibility locus in SLE. STAT4 risk alleles have been identified in SLE and systemic sclerosis. The ISG IFI35, a negative regulator of the cytosolic nucleic acid sensor RIG-I, has been shown to be associated with dermatomyositis.

cGAS, cyclic GMP–AMP synthase; dsDNA, double-stranded DNA; dsRNA, double-stranded RNA; IFI35, Interferon Induced Protein 35; IFN, Interferon; IFNAR, Interferon α/β receptor; IRF, Interferon regulatory factor; ISGs, Interferon-stimulated genes; JAK, Janus kinase; MAVS, mitochondrial antiviral-signaling protein; MDA5, Melanoma differentiation-associated protein 5; MyD88, myeloid differentiation factor 88; OPN, Osteopontin; RIG-I, Retinoic acid-inducible gene I; ssRNA; single-stranded RNA; STAT, Signal transducer and activator of transcription; STING, Stimulator of interferon genes; TASL, TLR adaptor interacting with SLC15A4 on the Lysosome; TLR, Toll-like receptor; TYK2, Tyrosine kinase 2.

Illustration assistance provided by Jan Ruvido Stebbins, Ruvido Medical Illustration, Dexter, MI.

Table 1.

Molecules in early-phase clinical trials targeting the type I interferon pathway in systemic autoimmune diseases.

Drug name	Mechanism of action	Clinical trial phase	Main outcomes	Disease focus	References
Tofacitinib	JAKi	Pilot study	All subjects met the IMACS group definition of improvement. Improvement in cutaneous disease activity by CDASI. Decreased IFN score in 5/8 patients (muscle only).	DM, refractory	(Paik et al., 2021)
VIB7734	pDC-depleting agent (anti-ILT7 mAb)	Phase 1	Unpublished results.	DM, SjS, SSc	Completed, pending results (NCT03817424)
VIB7734	pDC-depleting agent (anti-ILT7)	Phase 1	Adequate safety and tolerability. Rapid and durable depletion of pDCs. Reduction in type I IFN activity in skin and CLASI-A scores in CLE.	CLE, SLE, DM, SjS, SSc	(Karnell et al., 2021)
BIIB059	pDC-depleting agent (anti-BDCA2 mAb)	Phase 1	Tolerability and a favorable safety profile. Decreased expression of IFN response genes in blood. Reduction of immune infiltrates in skin and decreased CLASI-A scores in SLE.	SLE	(Furie et al., 2019)
Tofacitinib	JAKi	Phase 1	Adequate safety and tolerability. The effect of JAK inhibition was more robust in subjects with the *STAT4* risk allele. Improvement in cardiometabolic and immunologic parameters associated with premature atherosclerosis in SLE.	SLE	(Hasni et al., 2021)
Baricitinib	JAKi	Phase 2	More SLE patients achieved resolution of arthritis or rash with baricitinib (4 mg dosing) than placebo.	SLE	(Wallace et al., 2018)
BMS-986165	TYK2i	Phase 2	Unpublished results.	SLE	Active, not recruiting (NCT03252587) Recruiting (NCT03920267)
Filgotinib	JAKi	Phase 2	Unpublished results.	SjS	Completed, pending results (NCT03100942)
Anifrolumab (MEDI-546)	Anti-IFNAR mAb	Phase 1	Adequate tolerability and safety. Sustained inhibition of the type I IFN gene signature.	SSc	(Goldberg et al., 2014)

BDCA2, Blood dendritic cell antigen 2; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity score; CLE, Cutaneous lupus erythematosus; DM, Dermatomyositis; JAKi, Janus kinase inhibitor; IFN, Interferon; IFNAR, Interferon alpha/beta receptor; ILT7, Immunoglobulin-like transcript 7; mAb, Monoclonal antibody; pDC, Plasmacytoid dendritic cell; SjS, Sjogren's syndrome; SLE, Systemic lupus erythematosus; SSc, Systemic Sclerosis; TYK2i, Tyrosine kinase 2 inhibitor.