understand temporal patterns among relevant autoantibodies and the IFN signature in relation to disease flares. Our data suggest a potential role for microbial triggers in driving the immune system activation that leads to disease flares and support activation of the type I IFN as highly associated with disease flare in many patients.

Learning Objectives

- Describe potential mechanisms of type I IFN induction in SLE
- Describe individual temporal patterns in immune system activation based on longitudinal patient data
- Explain possible interpretations of longitudinal patient data with regard to triggers of lupus flare

REFERENCES

1. Crow MK. Type I interferon in the pathogenesis of lupus. *J Immunol.* 2014;**192**(12):5459–68.
2. Mavragani CP, Sagalovskiy I, Guo Q, *et al.* Expression of Long Interspersed Nuclear Element 1 Retroelements and Induction of Type I Interferon in Patients With Systemic Autoimmune Disease. *Arthritis Rheumatol.* 2016;**68**(11):2686–96.
3. Crow MK, Olfert M, Kirou KA. Type I Interferons in Autoimmune Disease. *Annu Rev Pathol.* 2019;**14**:369–93.
4. Barrat FJ, Crow MK, Ivashkin LB. Interferon target-gene expression and epigenomic signatures in health and disease. *Nat Immunol.* 2019;**20**(12):1574–83.

05

HOW INTERFERONOPATHIES INFORM SLE PATHOGENESIS

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Type I interferon (IFN) is a potent substance. As such, the induction, transmission and resolution of the type I IFN-mediated immune response are tightly regulated. The type I interferonopathies represent discrete examples of a disturbance of the homeostatic control of this system due to Mendelian mutations, and their molecular definition has the potential to dissect fundamental aspects of IFN control in the human context. Of note, the recognition of type I interferonopathies is becoming of increasing clinical importance as treatment options are developed based on an understanding of disease pathology and innate immune signaling. Definition of the type I interferonopathies indicates that autoinflammation can be both IFN and non-IFN related, and that a primary disturbance of the innate immune system can ‘spill-over’ into autoimmunity in some cases. Indeed, the fact that a number of non-Mendelian disorders, particularly systemic lupus erythematosus (SLE) and dermatomyositis, are also characterized by an upregulation of type I IFN signaling suggests the possibility that insights derived from this work will have relevance to a broader field of clinical medicine.

Learning Objectives

- Describe the phenotypic breadth of the type I interferonopathies
- Describe the molecular basis of the type I interferonopathies
- Describe the status of interferon signalling in the type I interferonopathies
- Describe the clinical link between the type I interferonopathies and SLE
- Describe the link between the molecular pathology of the type I interferonopathies and SLE

06

INTERFERON INHIBITION AND THE FUTURE MANAGEMENT OF SLE

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Type I interferon (IFN) is the term for a family of cytokines acting through a common receptor, known as IFNAR. Though functions are diverse, broadly speaking IFNs act in the innate immune system, providing rapid early host response to viral infection. Viruses activate IFN production largely through activating nucleic acid sensors including toll-like receptors (TLRs) 7–9 as well as other intracellular pathways, which have evolved to detect the presence of nucleic acids in the cytoplasm. Ligation of IFNAR leads to a cascade of inflammatory responses and enhances activation of the adaptive immune system.

It is now understood that these pathways of response to nucleic acid can be activated in diseases ranging from hereditary interferonopathies to acquired autoimmune interferonopathies, of which SLE is the archetype. Evidence of activation of the IFN system through increased expression of sets of IFN-regulated genes, known as the IFN signature, was first detected in SLE over 20 years ago. Other evidence for the role of IFN in SLE includes exacerbation of animal models of lupus by IFN treatment and induction of lupus-like clinical phenotypes in humans treated with IFN for other diseases.

Early clinical trials of IFN-blocking therapies had limited success, associated with incomplete suppression of the expression of IFN signatures. More recently, a monoclonal antibody to IFNAR, anifrolumab, demonstrated efficacy in a Phase 3 trial, after prior success in Phase 2 and positive results against all but the primary endpoint in another Phase 3 study.^{1–3} Broadly, anifrolumab treatment resulted in reduced disease activity, improved skin, joint and flare outcomes, and increased rates of glucocorticoid tapering, with acceptable safety notwithstanding included increased rates of herpes zoster reactivation.⁴

The potential applications of IFN blocking treatments in the management of systemic lupus erythematosus (SLE) driven by this evidence base will be explored.

Learning Objectives

- Describe the biology of type I IFN in autoimmune disease
- Discuss the evidence for the role of type I IFN in the pathogenesis of SLE
- Explain early clinical trial data supporting the role of type I IFN in SLE
- Describe the efficacy and safety of anifrolumab in the treatment of SLE
- Discuss future directions in IFN inhibition in SLE

REFERENCES

1. Furie RA, Morand EF, Bruce IN, *et al.* Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. *The Lancet Rheumatology.* 2019;**1**(4):e208–e19.
2. Furie R, Khamashta M, Merrill JT, *et al.* Anifrolumab, an Anti-Interferon-alpha Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. *Arthritis Rheumatol.* 2017;**69**(2):376–86.
3. Morand EF, Furie R, Tanaka Y, *et al.* Trial of Anifrolumab in Active Systemic Lupus Erythematosus. *New England Journal of Medicine.* 2019;**382**(3):211–21.
4. Tummala R, Abreu G, Pineda L, *et al.* Safety profile of anifrolumab in patients with active SLE: an integrated analysis of phase II and III trials. *Lupus Sci Med.* 2021;**8**(1).