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Editorial: New insights into interferons and proinflammatory cytokines in lupus

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Editorial on the Research Topic
New insights into interferons and proinflammatory cytokines in lupus

Systemic lupus erythematosus (SLE) is a highly heterogenous disease that we are still struggling to fully understand. The alterations to the immune system also impact non-immune cells such as endothelial cells and fibroblasts. The interactions of the various cell types are largely orchestrated by soluble mediators. In this collection, the investigators enhance our knowledge on some of these mediators, their intracellular signaling events and ways of using the new information for drug development and better patient stratification.

Nikolopoulos and Parodis reviewed the potential of targeting janus kinases (JAKs) for the treatment of SLE. JAKs are intracellular tyrosine kinases that along with tyrosine kinase 2 (TYK2) mediate signaling via phosphorylation of signal transducer and activators of transcription (STAT) proteins. Many cytokines use common JAK/STAT pathways; hence, JAK/STAT inhibition could potentially interfere with the production of several cytokine networks. The authors point out that TYK2 is part of the signaling cascade of several cytokines (IFNα, IL-6, IL-10 and IL-12/23) involved in the pathogenesis of SLE and that a selective inhibitor of TYK2 is currently in phase 3 trials in patients with non-renal lupus. This review discusses mouse model data of various drugs that inhibit different combinations of JAKs or TYK2. It also covers experimental data on human cell *in vitro* studies and results from the limited (to date) clinical trials.

Tang et al. reviewed the role of Th1 cells and associated cytokines in SLE. The authors summarize several studies demonstrating that SLE patients vary in the number and percentages of Th1 cells depending on different treatments and/or organ involvement. SLE patients have higher levels of Th1-related cytokines, such as IL-12 and IFN-γ, than healthy controls and higher levels are found in active than inactive disease. T-bet is also found in other immune cells including B cells. Patients with higher proportions of T-bet$^+$ naïve B cells had higher SLEDAI scores with higher ANA and anti-dsDNA levels associated with shorter disease duration. The authors also summarize the use of low dose IL-2 as a therapy for SLE. Interestingly, IL-2 therapy was associated with higher SRI-4 responses in patients with low baseline Tregs. The reduction in Tregs -commonly reported with prednisolone therapy- was not observed in patients who received low dose IL-2 treatment. These results, along with preliminary therapeutic

benefit of low dose IL-2, suggest that the role of Th1 immunity in SLE deserves further study.

In their original paper, Wang et al. show that the transcription factor FLI-1 promotes CXCL10 in endothelial cells and its receptor (CXCR3) expression in T cells. Elevated levels of FLI-1 are associated with active human lupus nephritis, whilst reduction of expression of FLI-1 in two lupus prone mouse strains decreased renal disease and prolonged mice's survival through a reduction in inflammatory cell levels. *In vitro* experiments using both human and mouse cells showed that transfection of FLI-1 siRNA greatly reduced CXCL10 expression. However, FLI-1 failed to directly activate the CXCL10 promotor, thus the exact mechanism of CXCL10 production remains unclear. Given FLI-1 is a key regulator of other inflammatory cytokines, a greater understanding of the possible therapeutic benefit of its inhibition is warranted.

The type I IFN pathway is known to be upregulated in a large proportion of SLE patients. However, its role in primary and secondary antiphospholipid syndrome (APS) is less understood. Cecchi et al. investigate the possible association between type I IFN dysfunction and the disease state in asymptomatic individuals with antiphospholipid antibodies (aPL) and APS patients. SLE patients and healthy subjects without aPL are used as control groups. Seven interferon stimulated genes (ISGs) were evaluated in whole blood to produce a composite IFN score. Significant IFN activation was observed across the APS spectrum, although the exact level of the individual gene expression and the IFN score varied. This was found even in patients who did not meet the clinical criteria of APS but had persistently positive aPL. SLE patients displayed the highest and most consistent activation. Thrombosis reoccurrence was positively associated with certain ISGs in patients with secondary APS (having both APS and SLE). The elevated presence of ISGs in patients only having aPL may represent a potential biomarker to stratify high risk for thrombosis patients.

An intriguing interplay of different type I interferons in cutaneous lupus erythematosus (CLE) was uncovered by Xu et al. The researchers had previously shown that IFN-κ was overexpressed in lesional and non-lesional CLE keratinocytes contributing to photosensitivity, but the key mechanisms for the reported IFN-κ production were unknown. After Poly (I:C) stimulation, keratinocytes rapidly produced IFN-β, but IFN-κ instead was only produced after a prolonged time delay. Blocking IFNAR only resulted in inhibiting IFN-κ. Similarly, inhibition of IFN-β decreased IFN-κ production. IFN-β knockout cell lines were incapable of producing IFN-κ after either Poly I:C or UVB stimulation. These results altogether demonstrate that IFN-κ is both an IFN gene and an IFN-simulated gene.

The work of Xia et al. assesses the effect of losing a mechanism of chemokine degradation in a model of lupus nephritis. The atypical chemokine receptor 2 (ACKR2) is found in the afferent lymphatics of many human tissues and can bind most of the CC chemokines. Through the expression of ACKRs, lymphatic vessels regulate chemokine levels and immune cell migration. The researchers used blood and tissues from ACKR2-deficient lupus-prone *B6lpr* and WT*B6lpr* mice to determine alterations to cellular patterns of inflammation and organ damage. In *B6lpr* mice that developed lupus nephritis, ACKR2 deficiency resulted in greater T and B cell tubulointerstitial inflammation, but these alterations were not associated with greater renal disease or higher levels of the assessed inflammatory mediators. These results show that the loss of ACKR2-mediated chemokine degradation can be compensated *in vivo* by other mechanisms.

The combined work of all these papers demonstrates the value of intracellular signaling events to *in vivo* mechanisms further shedding light on the complexity of SLE.

Author contributions

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Conflict of interest

WW is employed by AstraZeneca and owns stock in AstraZeneca.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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