part of FcgRIIA reducing the phagocytic capacity while promoting progression into NETosis. Importantly, ex vivo isolated neutrophils from SLE patients demonstrated increased shedding of neutrophil FcgRIIA ($p < 0.0001$), which was correlated with neutrophil activation ($r = -0.73$, $p = 0.003$) and the presence of anti-Sm/RNP antibodies ($p < 0.001$).

Conclusions Neutrophils are not terminally differentiated cells but could shift into phagocytic or NETosing cells, partly regulated by a cross-talk between TLR8 and FcgRIIA. SLE patients have ongoing shedding of neutrophil FcgRIIA related to neutrophil activation and anti-RNA antibodies, demonstrating the in vivo relevance of our observation. Therapeutic approaches aimed at degrading the TLR8 ligand would be predicted to increase uptake of circulating ICs, while disarming their inflammatory potential and ability to induce NETs.

II-05 INTERFERON REGULATORY FACTOR 5 PROMOTES THE EFFECTOR PHASE OF IMMUNE COMPLEX-MEDIATED GLOMERULONEPHRITIS

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Background Lupus nephritis is a serious manifestation of lupus for which treatment is only partially effective. It is characterised by the deposition of immune complexes in the kidney, activation of the complement cascade, cellular injury with the release of necrotic cell debris and the development of glomerular inflammation. However, the signalling pathways leading to the glomerular inflammation are incompletely defined. Interferon regulatory factor 5 (IRF5) polymorphisms are strongly associated in human genetic studies with an increased risk of developing lupus and, in mouse models, IRF5 has been shown to play an important role in the early phases of lupus pathogenesis including B cell autoantibody production and T cell activation by dendritic cells. IRF5 is a transcription factor that acts downstream of Toll-like receptors (TLRs) and other innate immune receptors to induce inflammatory responses. As necrotic cell debris has the potential to activate innate immune receptors, we hypothesised that IRF5 may also play a role in the later phases of lupus pathogenesis by promoting glomerular inflammation and lupus nephritis.

Materials and methods We developed a novel model of immune complex-mediated glomerulonephritis in which glomerulonephritis can be induced without exogenous adjuvant, making it possible to study the role of innate immune system activation by endogenous ligands. We induced nephritis using an endotoxin-free IgG1 fraction of sheep nephrotoxic serum (NTS) administered intravenously to wildtype (WT), IRF5-deficient ($IRF5^{-/-}$) and TLR7-deficient ($TLR7^{-/-}$) Fc gamma receptor IIB-deficient mice. Five days later, we euthanized the mice and measured nephritis severity.

Results WT mice developed severe glomerulonephritis characterised by glomerular necrosis and crescents in 28 ± 6% of glomeruli and a marked mononuclear cell infiltrate. $IRF5^{-/-}$ mice developed significantly less severe disease with glomerular crescents and necrosis seen in only 6 ± 2% of glomeruli ($p < 0.01$) and a substantial reduction in mononuclear cell infiltration. $TLR7^{-/-}$mice exhibited an intermediate phenotype. All mice had similar amounts of IgG and complement deposition in the kidney indicating that the differences in disease severity observed were not due to differences in the initial deposition of IgG1 NTS.

Conclusions IRF5 signalling plays an important role in the pathogenesis of the effector phase of immune complex-induced glomerulonephritis. This is likely mediated, at least in part, by the role of IRF5 downstream of innate immune receptors involved in the sensing of endogenous ligands released from injured cells. The reduction in disease in $TLR7^{-/-}$ mice suggests that RNA may be one such endogenous ligand involved.

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II-06 THERAPEUTIC BLOCKADE OF IMMUNE COMPLEX-MEDIATED GLOMERULONEPHRITIS BY HIGHLY SELECTIVE INHIBITION OF BRUTON'S TYROSINE KINASE

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Background Lupus nephritis (LN) is a potentially dangerous end organ pathology that affects upwards of 50% of patients with systemic lupus erythematosus (SLE). Classical treatments for this condition have targeted the adaptive immune response and/or autoantibodies, rather than the inflammatory process itself. Besides its role in B cell development, Bruton's tyrosine kinase (BTK) is important for Fc receptor signalling and macrophage polarisation. Furthermore, increasing evidence points to the role of the innate immune system, and particularly macrophages, in the pathogenesis of lupus nephritis.

Materials and methods In this study, we investigated the effects of a novel, highly selective and potent BTK inhibitor, BI-BTK-1, in an inducible model of LN in which female 129/SvJ mice receive nephrotoxic serum (NTS) containing anti-glomerular antibodies. Mice were treated once daily with vehicle alone or BI-BTK-1 (0.3–10 mg/kg, n = 16/group), either prophylactically or therapeutically.

Results When compared with control treated mice, NTS-challenged mice treated prophylactically with BI-BTK-1 exhibited significantly attenuated disease which was dose dependent, as measured by proteinuria, serum creatinine, and serum BUN. Histological assessment confirmed marked renal protection in the BI-BTK-1 treatment groups. BI-BTK-1 treatment resulted in decreased recruitment of inflammatory monocytes from the splenic reservoir, and a decrease in infiltrating IBA-1+ cells as well as C3 deposition within the kidney. RT-PCR on whole kidney RNA and serum profiling indicated that BTK inhibition significantly decreased levels of LN-relevant inflammatory cytokines and chemokines. Renal RNA expression profiling by RNA-seq revealed that BI-BTK-1 dramatically modulated pathways related to inflammation and glomerular injury. Importantly, when administered therapeutically, BI-BTK-1 reversed established proteinuria and improved renal histopathology. Moreover, preliminary results confirm the efficacy of BI-BTK-1 in the spontaneous MRL-lpr/lpr murine lupus model as well.

Conclusion Our results highlight the important role for BTK in the pathogenesis of immune complex-mediated nephritis. These results, together with additional studies by our group showing comparable efficacy with other small molecule macrophage inhibitors in nephrotoxic serum nephritis and spontaneous lupus, point to macrophage modulation as a promising therapeutic target for LN and possibly other immune related glomerulopathies.