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Immune-phenotyping IRF5 genetic risk and therapeutic strategies to target IRF5 hyper-activation in SLE

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Statement of the Problem: The transcription factor interferon regulatory factor 5 (IRF5) is a central mediator of innate and adaptive immunity. Genetic variations within IRF5 associate with risk of systemic lupus erythematosus (SLE), amongst other autoimmune diseases, and mice lacking Irf5 are protected from lupus onset and severity, but how IRF5 functions in the context of SLE disease progression remains unclear. The purpose of this study is to determine how IRF5 genetic risk contributes to SLE disease onset and severity, and whether targeting IRF5 with select inhibitors will alleviate disease severity and mortality.

Methodology & Theoretical Orientation: Studies were performed in blood from genotyped healthy donors, SLE patients and the NZB/W F1 model of spontaneous murine lupus.

Findings: Using the NZB/W F1 model of spontaneous murine lupus, we show that murine Irf5 is already hyper-activated before clinical onset in a cell type-specific manner. In healthy donors carrying IRF5 genetic risk, we detect IRF5 hyper-activation in the myeloid compartment that drives an SLE immune phenotype. In SLE patients, IRF5 hyper-activation correlates with SLEDAI and dsDNA titers. To test whether IRF5 hyper-activation is a targetable function, we developed novel inhibitors that are cell permeable, non-toxic and selectively bind to the inactive IRF5 monomer. Treatment of NZB/W F1 mice with inhibitor attenuated lupus pathology by reducing serum ANA and dsDNA titers and reducing the number of circulating plasma cells and age- or autoimmune-associated B cells (ABCs), which alleviated kidney pathology and improved overall survival. In ex vivo human studies, the inhibitor blocked SLE serum induced IRF5 activation in healthy immune cells and reversed basal IRF5 hyper-activation in SLE immune cells.

Conclusion & Significance: This study provides the first *in vivo* pre-clinical support for treating SLE patients with an IRF5 inhibitor.

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