Autoimmune Disease: Fc Receptors, Epistasis and Augury

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Abstract

Part 1: FcγRIIb is an inhibitory Fc receptor, and defects in it are known to predispose to systemic lupus erythematosus (SLE) in both mouse and man. Mechanisms by which these deficiencies contribute to disease will be discussed, as will the role played in the pathogenesis of disease by genetic variation in FCGR2B. Data will be presented implicating malaria is an important evolutionary selection factor driving retention of these autoimmunity-associated polymorphisms in the gene pool. Gene copy number variation (CNV) has recently been recognised as a major source of genetic variation in the human population. FCGR3B CNV is very common in the population, and is associated with marked alterations in expression and function of the receptor on neutrophils. Low CNV can be demonstrated to the risk of some autoimmune diseases (such as SLE) but not others, shedding light on the functional role it plays. Novel data on interactions between FCGR3B CNV and FcγRIIb in driving autoimmunity will be discussed.

Part 2: We have performed detailed microarray-based analysis of gene expression in purified leucocyte subsets from patients with various autoimmune diseases. Analysis of the transcriptome of CD8 T cells in these diseases shows evidence of a transcriptional signature which correlates with long term disease outcome. The dysregulated genes which create the signature immediately suggest a mechanism by which it might drive CD8 T cell contribution to disease. This biomarker is now being assessed for its ability to guide therapy in autoimmune disease.