SYSTEMIC LUPUS ERYTHEMATOSUS

IgG1 variant promotes autoimmunity

> the G390R variant lowers the threshold for BCR activation

A newly discovered variant of immunoglobulin G1 (IgG1) that can modulate B cell activation and differentiation is also a risk variant for systemic lupus erythematosus (SLE), according to a new study published in *Science*. These findings provide insights into the regulatory function of IgG-B cell receptor (IgG-BCR) signalling in the control of autoreactive B cell fate and SLE pathogenesis.

SLE is characterized by B cell dysfunction and the production of a wide spectrum of autoantibodies that can promote immune complex formation and deposition, leading to multi-organ damage. In healthy individuals, the autoreactivity of the IgG^+ plasma cell compartment is low, despite prevalent autoreactivity in the IgG^+ memory B cell pool. However, checkpoints that restrain plasma cell autoreactivity fail in autoimmune diseases such as SLE. "How autoreactive IgG^+ B cells are maintained in a quiescent state under normal immune homeostasis, but surmount the immune tolerance checkpoints in pathological conditions is still not clear," remarks Zhanguo Li, one of the corresponding authors of the study.

In B cells, the cytoplasmic tail of membrane-bound IgG (mIgG-tail) can modulate IgG-BCR activation by amplifying downstream signalling of the receptor through its phospho-immunoglobulin tail tyrosine (ITT) motif and a signalling module involving the adaptor molecule GRB2 and the tyrosine-protein kinase BTK. "Based on the effects of the mIgG-tail on B cell activation and differentiation, and the prevalent autoreactivity in human IgG-BCR-expressing B cells, we proposed that the illegitimate activation of IgG-BCR might be involved in the pathogenesis of autoimmune diseases such as SLE," explains Wanli Liu, the co-corresponding author.

By scanning for potential mutations in the mIgG-tail that might be associated with autoimmune diseases, they discovered a single nucleotide polymorphism (SNP; rs117518546) that correlated strongly with SLE susceptibility. This SNP results in a glycine-to-arginine substitution at codon 396 in human IgG1 (G396R variant) and is also associated with a more severe disease phenotype.

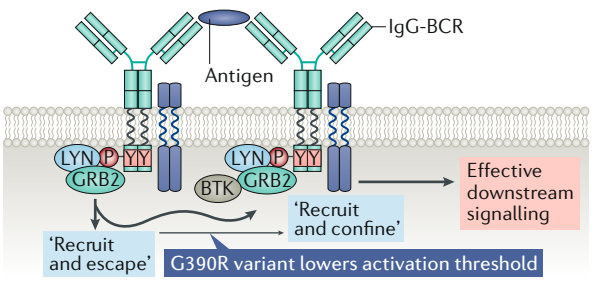
"Current genetic research on SLE indicates a strong genetic predisposition, mediated by multiple gene variants," says Liu. "As the patients with SLE who had this susceptible variant had exacerbated organ involvement, testing for this variant might help predict the patient prognosis."

To further study the mechanisms underlying this association, the researchers generated knock-in mice expressing the murine homologue IgG1-G390R (G390R mice). Under standard physiological conditions the mice had no apparent phenotype; however, in two mouse models of SLE (a bm12-inducible model and an apoptotic thymocyte-induced model) the G390R mice had higher IgG1 autoantibody levels than wild-type mice, as well as enlarged glomeruli and substantial deposition of $IgG1^+$ immune complexes. By further analysing the B cell compartment of the G390R mice, they also found evidence of increased plasma cell generation and changes in the $IgG1^+$ plasma cell population that were indicative of autoreactivity.

Using various imaging techniques and molecular dynamics simulations, the researchers found that the G390R variant lowers the threshold for BCR activation by promoting phosphorylation of the ITT motif via the LYN tyrosine kinase, resulting in enhanced recruitment of downstream signalling molecules GRB2 and BTK to the immunological synapses. The G390R ITT motif bound better to active LYN kinase than the wild-type ITT motif, which resulted in increased availability of the phospho-ITT motifs and promoted longer dwelling times of GRB2 in the immunological synapse. The researchers likened this effect to a 'recruit-and-confine' model. Following initial recruitment of GRB2 to the phospho-ITT motifs, GRB2 is released and recaptured rather than being released and escaping (as in the 'recruit-and-escape' model), leading to more effective downstream signalling.

"These findings deepen the understanding of the function of SLE susceptibility loci and emphasize the notion that autoreactive IgG^+ memory B cells are critical in SLE development and are a priority target for autoimmune disease treatment," remarks Li.

Jessica McHugh



Credit: Springer Nature Limited

ORIGINAL ARTICLE Chen, X. et al. An autoimmune disease variant of IgG1 modulates B cell activation and differentiation. *Science*. **362**, 700–705 (2018)