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SYSTEMIC LUPUS ERYTHEMATOSUS

B cell-derived IL-6 promotes disease

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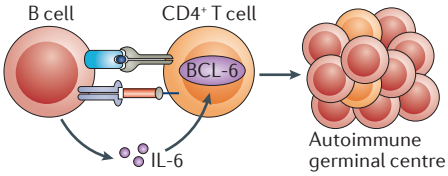
IL-6 production by B cells drives autoimmune germinal centre formation in a mouse model of systemic lupus erythematosus (SLE), promoting disease, according to a new study published in *The Journal of Experimental Medicine*. "Our findings emphasize the critical importance of B cells in the pathogenesis of SLE, and describe a new mechanism whereby B cells promote disease — namely via pro-inflammatory cytokine production," states co-corresponding author Shaun Jackson.

"Spontaneous, autoimmune germinal centres have been identified as an important source of autoantibody-producing plasma cells in SLE and other humoral autoimmune diseases," remarks co-corresponding author David Rawlings. To study the B cell-intrinsic signals underlying spontaneous germinal centre formation and SLE pathogenesis, the researchers developed a novel chimeric mouse model of SLE in which B cells lack the expression of Wiskott–Aldrich syndrome (WAS) protein. "In this model, *Was*$^{-/-}$ B cells initiate spontaneous humoral autoimmunity characterized by germinal centre formation, class-switched anti-nuclear antibodies and immune-complex glomerulonephritis, thus recapitulating several cardinal features of human SLE," describes Rawlings.



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Serum IL-6 levels were elevated in these mice, consistent with the high IL-6 levels typically observed in patients with SLE. B cell-specific deletion of IL-6 in this model abrogated T follicular helper (T_{FH}) cell expansion and spontaneous germinal centre development, which resulted in a loss of class-switched autoantibodies, and lupus nephritis. Furthermore, IFNγ promoted IL-6 production by both human and mouse B cells *in vitro*, an effect that was blocked by the JAK inhibitors ruxolitinib and tofacitinib, consistent with previous findings from the same group that demonstrated a key B cell-intrinsic role for IFNγ signals in autoimmune germinal cell formation.

"We propose a model wherein B cell-derived IL-6 facilitates transient expression of the T_{FH} cell master regulator B-cell lymphoma 6 protein (BCL-6) in cognate CD4$^+$ T cells, resulting in T_{FH} cell differentiation and spontaneous germinal centre formation. This process is enhanced by IFNγ, likely derived locally from activated T helper 1 (T_H1) cells," explains Jackson.

"In the future, we plan to study how genome-wide associatiation study-identified lupus polymorphisms might impact this process," says Rawlings. "In the long-term, we hope that improved understanding of the cellular mechanisms underlying autoimmune germinal centre formation will allow the development of effective targeted therapies in SLE," concludes Jackson.

Jessica McHugh

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