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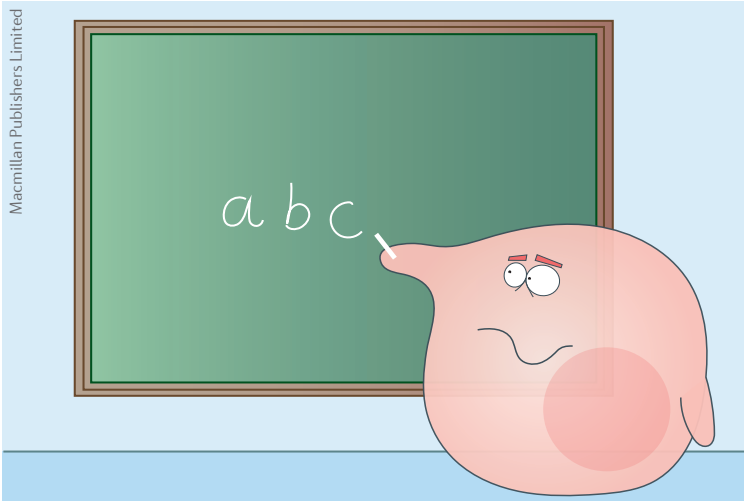

AUTOIMMUNITY

The ABCs of autoimmune disease

First identified in mice in 2011, a subset of B cells that expands with increasing age termed age-associated B cells (ABCs) is receiving increased attention as a potential driver of autoimmune disease. A new study published in *Nature Immunology* advances our knowledge of ABCs in the setting of autoimmunity, providing insights into their potential role in murine lupus-like disease, as well as hints towards a possible role in human autoimmune disease.

ABCs express classic murine B cell markers (such as B220, CD19 and IgM) and markers of myeloid cells (such as CD11c) as well as the transcription factor T-bet, and expand in response to IL-21. Intriguingly, these cells accumulate in ageing mice to a higher degree in females than in males, and expand prematurely in murine models of lupus. "Of particular interest, expansion of B cells with features similar to ABCs has also been detected in several human autoimmune disorders, including systemic lupus erythematosus (SLE) and rheumatoid arthritis," states corresponding author Alessandra Pernis.

> "ABCs express classic murine B cell markers … and markers of myeloid cells … and expand in response to IL-21"

On the basis of previous studies, the researchers identified a protein called DEF6, one of only two members of a family of Rho GTPase–regulatory proteins termed SWEF proteins that have an immunoregulatory role, and demonstrated that mice deficient in both SWEF proteins (double knockout mice) developed a lupus-like disease that occurred predominantly in females. "Notably, *DEF6* has recently been identified as a new risk variant for human SLE, supporting the idea that this family of proteins controls pathways that are directly relevant to human SLE," explains Pernis. These double knockout mice also had a prematurely expanded population of ABCs that could produce anti-nucleic acid autoantibodies and were therefore potentially pathogenic.

"The molecular mechanisms that control ABCs are largely unknown," says Michela Manni, first author on the study. "To gain broad insights into this new population, we employed genome-wide transcriptional and epigenetic analyses." Using these techniques on cells from double knockout mice, Manni and colleagues unravelled the mechanism by which SWEF proteins regulate ABCs. "In the absence of the SWEF proteins, B cells exhibit increased ABC formation in response to IL-21 due to increased activity of a specific interferon regulatory family member, IRF5, which can then cooperate with T-bet at selected ABC-specific regulatory regions," states Manni.

IRF5 and IL-21 are both implicated in the pathogenesis of murine lupus and human SLE, but the two molecules had not been connected in a single pathway before. The promising parallels for this mechanism between mice and humans have prompted the authors to begin investigations into potential roles for ABCs in human autoimmune diseases. "Importantly, we plan to extend our findings to patients with SLE," says Pernis. "We also plan to extend our mechanistic studies with the hope of understanding how best to target this pathway from a therapeutic point of view."

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ORIGINAL ARTICLE Manni, M. et al. Regulation of age-associated B cells by IRF5 in systemic autoimmunity. *Nat. Immunol.* https://doi.org/10.1038/s41590-018-0056-8 (2018)