**DELETION AND ANERGY RESTRAIN THE PRODUCTION OF AUTOANTIBODIES BY SELF-REACTIVE B CELLS**

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LAY ABSTRACT

The immune system is educated to distinguish between ‘self’ and pathogens such as bacteria and viruses. In healthy individuals, immune cells which recognise and respond to ‘self’ are purged by a process called ‘tolerance’. When these cells are not properly removed, they can initiate destructive responses against the body leading to the development of autoimmune disease. Despite an increasing incidence worldwide, there is no cure for autoimmune disease and limited therapeutic strategies are available. Effective therapies rely on a thorough understanding of the mechanisms of tolerance, however these are poorly understood. To address this, we have developed new tools and models to characterise how specific immune cells are educated. Together, our data provide new ways to design effective therapies for autoimmune diseases.

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SCIENTIFIC ABSTRACT

Failure to establish B cell tolerance underpins autoimmunity. Early studies using B cell receptor (BCR) transgenic models, where all B cells express a receptor recognising a single self-antigen, suggest that deletion and anergy are key but the precise timing and contribution of each vary depending on the model and setting. To resolve tolerance mechanisms active in a physiological setting, we developed a novel tetramer assay to monitor antigen-specific B cells within a normal repertoire. In a mouse model expressing ovalbumin (OVA) as a self-antigen (actin.mOVA), OVA-specific B cells (OB) were partially deleted from the peripheral repertoire. Surprisingly, in contrast to earlier models, deletion did not occur in the bone marrow and naïve self-reactive OB cells instead developed normally to a mature phenotype in the spleen before deletion was apparent. Residual naïve OB cells were functionally anergic because immunization of actin.mOVA mice with OVA failed to elicit activation and expansion of OB cells. Consequently, formation of OVA-specific plasma cells was blocked, preventing the induction of autoantibodies. In contrast, we also show that provision of diverse innate and T cell-mediated stimuli breaks tolerance, inducing the expansion of self-reactive OB cells accompanied by transient autoantibody production. Bone marrow chimeras revealed that self-antigen density dictates the stringency of B cell tolerance. Self-reactive OB cell responses were only modulated when self-antigen was expressed by more than 10% of donor cells. In sum, by using a physiological setting we refine for the first time the role of deletion and anergy in governing B cell tolerance.

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