B CELLS

The pre-BCR shows its negative side

Given the well-established role of the pre-B-cell receptor (pre-BCR) in the positive selection of B cells, it comes as a surprise to learn that the pre-BCR also has a role in negative selection. A new study published in *Science* indicates that the pre-BCR censors the development of autoreactive B cells and that the absence of this checkpoint can result in the production of antinuclear antibodies (ANAs).

The BCR repertoire is generated by recombination of the immunoglobulin heavy- and light-chain genes. Recombination starts with the heavy chain in pro-B cells, producing a pre-BCR that consists of a recombined heavy chain and an invariant surrogate light chain (SLC). Signals through the pre-BCR positively select and lead to the proliferation of pre-B cells that have successfully rearranged the heavy chain. Mice that are deficient for SLC have decreased numbers of immature and mature B cells owing to the absence of positive selection.

Keenan *et al.* observed that the serum of SLC-deficient mice contained an increased concentration of ANAs, which indicates that some B cells in these mice had escaped the negative selection of BCRs that are specific for self antigens, such as DNA. Although the SLC-deficient mice had a decreased total number of splenic B cells compared with control mice, they had an increased proportion of mature CD21⁺CD23⁺ B cells, and this population was shown to produce ANAs after *in vitro* stimulation.

It had previously been observed that ANAs frequently contain at least one basic amino acid, such as arginine, in complementarity-determining region 3 of the heavy chain (HC-CDR3). CD21⁺CD23⁺ B cells from SLC-deficient mice often had two or more arginines in HC-CDR3 compared with an average of one arginine in CD21⁺CD23⁺ B cells from wild-type mice. In SLC-deficient CD21⁺CD23⁺ B cells,

one of the arginines was preferentially encoded by the D (diversity) gene segment, which, based on the position of the start codon, must be translated in the infrequently used reading frame 3 (RF3) to produce arginine. The use of RF3 and RF2 was increased in SLC-deficient CD21⁺CD23⁺ B cells compared with wild-type CD21⁺CD23⁺ B cells, which preferentially use RF1.

By comparing HC-CDR3 sequences in pro- and pre-B cells — before and after the postulated negative-selection checkpoint mediated by the pre-BCR — the authors showed that in SLC- and light-chain-deficient B cells, the high proportion of HC-CDR3 arginines and use of RF3 in pre-B cells was similar to that of control pro-B cells (as would be expected if negative selection is absent). This contrasts with the decrease in the proportion of arginines and use of RF3 between pro- and pre-B cells in wild-type mice (as expected due to negative selection).

These data indicate that the pre-BCR has a role in selecting against B cells expressing a HC-CDR3 with the potential to generate ANAs. However, SLC-deficient mice have not shown any evidence of autoimmune disease, which supports the presence of multiple negative-selection checkpoints.

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