Receptor editing: How B cells stay tolerant

In 1993, David Nemazee and Martin Weigert independently showed that autoreactive B cells could proofread, alter, and reexpress modified receptors to become nonautoreactive. This process, called "receptor editing," has since gained prominence as the main mechanism of B cell tolerance.

David Nemazee (left) and Martin Weigert

The immune system generates a diverse army of T and B cells to deal with pathogen diversity but usually manages to exclude self-reactive cells from its repertoire. To explain this phenomenon, McFarlane Burnet proposed the theory of clonal selection in 1959 (1). He hypothesized that cells that recognized self-antigens would be killed during development. Only nonautoreactive cells would then enter circulation and be called upon to provide protection during immune responses. His model remained unchallenged until the late 1980s, when investigators found that some autoreactive B cells survived the purge but did not respond to antigenic stimulation (2). At the same time, David Nemazee, then an immunologist at the National Jewish Center in Denver, CO, found evidence for a third mechanism for tolerance.

By this time, the generation of receptor diversity in developing B cells had been well-characterized. Others had shown that recombinase proteins first rearrange the B cell's heavy chain genes and then target the light chain genes. Checkpoints ensure that each B cell expresses only one receptor. It was therefore possible to force all the B cells in an animal model to express the same receptor by introducing prearranged antibody transgenes.

Death-defying B cells

Nemazee had been studying the deletion of autoreactive B cells in transgenic mice whose B cells all expressed receptors specific for a particular MHC molecule. When this transgene was bred onto mice that expressed that MHC protein, the developing B cells recognized it as an autoantigen. As expected, these mice lacked autoreactive B cells in the periphery. But to Nemazee's surprise, a large pool of autoreactive B cells persisted in the bone marrow (3).

B cells repair their receptors

To pinpoint the exact step at which the cells were escaping deletion, Nemazee and his team engineered strains in which the autoantigen was targeted to different anatomical locations. Expression of autoantigen in just the liver caused a near complete deletion of anti-MHC B cells, which were not replaced by non-autoreactive counterparts. Total B cell numbers were thus greatly reduced in the periphery. But when autoantigen was also present in the bone marrow, there were many more peripheral B cells that were no longer self-reactive. Nemazee discovered that these cells had escaped by switching antibody receptors—they had new light chains derived from a rearranged version of the endogenous gene. The alterations took place in immature B cells, as Nemazee only detected the rearrangements in bone marrow B cells.

Light chain replacement was simultaneously demonstrated in a different transgenic model by Martin Weigert and his team at the Fox Chase Cancer Center (Philadelphia, PA). While studying lupus, Weigert had designed mice that carried a transgene for an anti-DNA antibody. He found that these mice lacked autoreactive DNA-specific B cells. Younger mice had fewer B cells, suggesting that autoreactive clones had been deleted. But adult mice had normal numbers of B cells. These cells had substituted the transgene's light chain with endogenously rearranged light chains. Weigert and Nemazee published their seminal results in a series of papers in the *Journal of Experimental Medicine* in 1993 (4–6).

Improving on dogma

The studies were at first controversial, but numerous reports from other groups have since bolstered the case for receptor editing as a major mechanism for tolerance (7). It is now estimated that at least 25% of B cells in the repertoire have undergone receptor editing (8). Nemazee's anti-MHC transgenic mouse model has since been modified such that transgenes insert specifically into the heavy and light chain loci (9). These mice reveal that autoreactive B cells are rendered harmless mainly through receptor editing. Repairing its receptors rather than throwing away the whole cell might be the most efficient way to generate a diverse, non-self-reactive repertoire.

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