

Breaking and making B cell tolerance to ubiquitous autoantigens

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A long history of study has demonstrated that autoreactive B cells are eliminated through a process of tolerance. Elegant use of conventional Ig transgenic mouse models initially indicated that medium/high avidity autoreactive B cells are eliminated by clonal deletion, however these studies also uncovered a different tolerance mechanism, receptor editing, which operates through secondary V(D)J recombination events that inactivate the gene(s) encoding the autoantibody. This process leads to the generation of novel genes encoding non-autoreactive antibodies. From the initial observation as a curious pathway in a small population of Ig transgenic B cells, receptor editing is now appreciated as a major physiological mechanism of central B cell tolerance. Using various mouse models, we have demonstrated that all immature B cells reacting with ubiquitous membrane-bound autoantigen undergo receptor editing and not clonal deletion during their development. In these mice, clonal deletion is only observed as a secondary event in cells that are unable to undergo editing and only when receptor editing is artificially inhibited or abolished. These data support a model in which clonal deletion is not induced by antigen binding, but is a default pathway in developing B cells that are unable to express non-autoreactive antigen receptors.

A secondary effect of receptor editing is the generation of allelically/isotypically included B cells through Ig gene rearrangement events occurring at the previously non-rearranged alleles. We have found that through receptor editing high avidity autoreactive B cells can acquire non-autoreactive antigen receptors that promote their differentiation despite the co-expression of autoreactive receptors. These cells appear superficially tolerant as they retain the autoreactive antibodies within the cell through continual antigen-mediated receptor internalization. We propose that tonic signal(s) transduced by non-autoreactive antigen receptors can, in some circumstances, lead to the development of dual antibody-expressing autoreactive B cells. Moreover, these cells have the potential to contribute to the development of autoimmunity when interacting with foreign antigens via their non-autoreactive antigen receptor and differentiate into plasma cells that secrete both foreign- and self-antigen specific antibodies.

Selected Publications:

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- Halverson, R., R.M. Torres, and R. Pelanda, 2004. Receptor editing is the primary mechanism of B cell tolerance toward membrane antigens. *Nature Immunology*, 5(6):645-50.
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