Receptor editing in developing T cells

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Receptor editing refers to the process whereby antigen receptor engagement leads to a secondary somatic gene rearrangement event and alteration of the receptor specificity. It has been well-described that immature B cells developing in the bone marrow undergo receptor editing in response to self-antigen. We recently provided evidence that immature T cells in the thymus can also undergo antigen specific receptor editing[1]. This response was observed in OT-I TCR transgenic mice that expressed the antigen in cortical epithelial cells of the thymus using the human K14 promoter.

The finding of receptor editing in cortical thymocytes was surprising, since it had previously been shown that these cells undergo apoptosis or clonal deletion upon antigen encounter. To test whether antigen presentation by cortical epithelial cells was key to receptor editing, we created two additional antigen transgenic strains using the hK14 promoter. Alternatively we studied OT-I mice that expressed the antigen broadly in all tissues. To our surprise, we observed receptor editing in OT-I mice regardless of where antigen was expressed, and observed "clonal deletion" in 2C and HY TCR transgenic mice even when antigen was expressed under control of the hK14 promoter. These data suggest that receptor editing is a property of certain TCR transgenic strains and not others. The mechanistic basis of this distinction will be discussed.

It is thought that secondary gene rearrangement does not necessarily favor the allele upon which the primary rearrangement occurred. Because of this secondary rearrangement events can give rise to cells that express two receptor chains, and therefore two potential receptor specificities. This is especially true in antigen transgenic models, where secondary rearrangement cannot physically delete the transgenic DNA. Thus, in OT-I mice expressing the antigen under control of the K14 promoter, the repertoire of mature T cells is largely composed of cells expressing two TCRa chains. Such dual-reactive T cells have previously been shown to have auto-immune potential. Interestingly, these mice experience a severe CD8 T cell dependent autoimmune disease. We used analysis of disease in various double transgenic and gene deficient strains to ask if dual reactive T cells contribute to the autoimmune disease observed in this model. Our data suggest that in this situation disease was not dependent upon dual reactive T cells. Other potential disease induction mechanisms will be discussed.

McGargill, M.M., Derbinski, J.M., and **K.A. Hogquist.** Receptor editing in developing T cells. *Nature Immunology,* 1:336 (2000)