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T cell anergy as a strategy to reduce the risk of autoimmunity

Some self-reactive immature T cells escape negative selection in the thymus and may cause autoimmune diseases later. In the periphery, if T cells are stimulated insufficiently by peptide-major histocompatibility complex, they become inactive and their production of cytokines changes, a phenomenon called "T cell anergy". We explore the hypothesis that T cell anergy may function to reduce the risk of autoimmunity. The underlying logic is as follows: Since those self-reactive T cells that receive strong stimuli from self-antigens are eliminated in the thymus, T cells that receive strong stimuli in the periphery are likely to be non-self-reactive. As a consequence, when a T cell receives a weak stimulus, the likelihood that the cell is self-reactive is higher than in the case that it receives a strong stimulus. Therefore, inactivation of the T cell may reduce the danger of autoimmunity. We consider the formalism in which each T cell chooses its response depending on the strength of stimuli in order to reduce the risk of autoimmune diseases while maintaining its ability to attack non-self-antigens effectively. The numerical calculation reveals that T cell anergy is the optimal response when a T cell meets with antigen-presenting cells many times in its lifetime, and when the product of the autoimmunity risk and the number of self-reactive T cells has an intermediate value.