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Co-operative failure of thymic deletion and clonal anergy in the development of autoimmunity

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Abstract

Breakdown of self-tolerance in autoimmune diseases is poorly understood, as is the existence of so many different mechanisms for actively acquired tolerance. We find that failure of two tolerance mechanisms, thymic T cell clonal deletion to organ specific antigens mediated by Aire and the two-signal mechanisms of T cell tolerance in mature T cells imposed by the ubiquitin ligase Cblb, individually cause slow and subclinical autoimmunity but combine co-operatively to allow lethal T cell-mediated destruction of the exocrine tissue in the pancreas and salivary glands within weeks after T cells emerge from the thymus. Intriguingly, there was no evidence of autoimmunity in other tissues although Aire regulates deletion of T cells recognising huge numbers of self-antigens from multiple tissues. Varying the nascent T cell repertoire by substituting the B10.BR.H2k MHC in which the T cells were selected upon with the C57/B6.H2b MHC or introducing an unlimited source of transgenic T cells with a single specificity towards an alternative organ failed to redirect the autoimmunity in $Aire^{-/-}Cblb^{-/-}$ mice to other organs, albeit these strategies slowed down the intensity and tempo of the disease. This indicated that there was a unique feature of the "driver" T cells that escaped tolerance in $Aire^{-/-}Cblb^{-/-}$ mice. These "driver" T cells were identified using a novel multiplex nested RT-PCR method to simultaneously amplify transcripts encoding the TCRα and TCRβ chain recovered from single cells of $Aire^{-/-}Cblb^{-/-}$ adoptive transfer recipients. Based on amino acid sequence of the complementarity determining regions, several highly related CD8 clones were found to be selectively expanded in the pancreas. Expression of the most prominent CD8 T cell receptor in retroviral transgenic (retrogenic) chimeras was sufficient to recapitulate the pancreatitis and cachexia irrespective of the Aire or Cblb genotype. These findings support the hypothesis that organ-specific autoimmunity manifests only when a defect in thymic deletion is paired with a defect in peripheral T cell tolerance. Even then, only rare self-reactive CD8 T cells with particular TCR specificities escaped the other tolerance mechanisms, causing an extremely

rapid but very discrete pattern of organ-specific autoimmunity directed at the exocrine pancreas and salivary glands. The results illuminate the stringent nature of the mechanisms that protect the body from autoimmune diseases, and provide a framework and experimental approach for interpreting patterns of genetic and phenotypic variability in human autoimmune diseases.