AIRE's CARD revealed, a new structure for central tolerance provokes transcriptional plasticity

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Author(s) Ferguson, Brian J; Alexander, Clare; Rossi, Simona W; Liiv, Ingrid; Rebane, Ana; Worth, Catherine L; Wong, Joyce; Laan, Martti; Peterson, Pärt; Jenkinson, Eric J; Anderson, Graham; Scott, Hamish S; Cooke, Anne; Rich, Tina
Author(s) at UniBasel Rossi Girard, Simona ;
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Developing T cells encounter peripheral self-antigens in the thymus in order to delete autoreactive clones. It is now known that the autoimmune regulator protein (AIRE), which is expressed in thymic medullary epithelial cells, plays a key role in regulating the thymic transcription of these peripheral tissue-specific antigens. Mutations in the AIRE gene are associated with a severe multiorgan autoimmune syndrome (APECED), and autoimmune reactivities are manifest in AIRE-deficient mice. Functional AIRE protein is expressed as distinct nuclear puncta, although no structural basis existed to explain their relevance to disease. In addressing the cell biologic basis for APECED, we made the unexpected discovery that an AIRE mutation hot spot lies in a caspase recruitment domain. Combined homology modeling and in vitro data now show how APECED mutations influence the activity of this transcriptional regulator. We also provide novel in vivo evidence for AIRE's association with a global transcription cofactor, which may underlie AIRE's focal, genome-wide, alteration of the transcriptome.
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