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Control of chronic inflammation through elucidation of organ-specific autoimmune disease mechanisms

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Abstract

We are approaching the control of chronic inflammation through elucidation of organ-specific autoimmune disease mechanisms by investigating the function of Aire, a gene responsible for the hereditary type of autoimmune disease. The roles of Aire in the expression of the diverse arrays of tissue-restricted self-antigen (TRA) genes from mTECs and in organization of the thymic microenvironment are enigmatic. With the use of Aire/GFP-knockin mice, we suggested that Aire controls the differentiation program of medullary thymic epithelial cells (mTECs), thereby organizing the global mTEC integrity that enables TRA gene expression from terminally differentiated mTECs. We also assumed that the effect of Aire-dependent mTEC differentiation should have broader impact so that the developmental process of thymocytes might be also affected in Aire-deficient mice. Particularly, final maturation steps of thymocytes and/or their subsequent emigration might be controlled by Aire because of the anatomical location of $Aire^{+}$ mTECs. We examined these possibilities using Aire-deficient mice together with a novel mouse model in which a neo-self Ag expression is targeted to Aire-expressing mTECs. We also sought to monitor the production and maintenance of Aire-expressing mTECs by a fate-mapping strategy in which bacterial artificial chromosome transgenic mice expressing Cre recombinase under the control of the Aire regulatory element were crossed with a reporter strain for GFP expression. We found that, in addition to its well-recognized expression within terminally differentiated mTECs, Aire was expressed in the early embryo before emergence of the three germ cell layers. With the use of one transgenic line in which Cre recombinase expression was confined to mTECs, we found that $Aire^{+}CD80^{high}$ mTECs further progressed to an $Aire\text{-}CD80^{intermediate}$ stage(s), suggesting that Aire expression is not constitutive from after its induction until cell death but is temporally circumscribed at the beginning of terminal differentiation. Thus, the mechanisms underlying the autoimmune pathology caused by Aire deficiency are our focus of intense research aimed at answering the fundamental question of how the immune system discriminates between self and non-self within the thymic microenvironment.