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Perspectives

Aire's partnerships: An answer for many questions and new questions in search of answers

The focus of this perspective is the recent publication by Abramson et al. (1) on the role of the Aire (*A*uto*i*mmune *Re*gulator), which is a transcription factor involved in promoting the surveillance of self-antigens and the maintenance of immune tolerance. This protein is mainly expressed in the medulla of the thymus and is important in the prevention of autoimmune disease including Type 1 diabetes (T1D). In humans, a defective AIRE causes Polyglandular Autoimmune Syndrome (APS) type I or Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED), a rare autosomal recessive disorder involving multiple endocrine organs (4,5). APS-I is diagnosed when at least two of the following three clinical manifestations of this disease are identified: i) Chronic mucocutaneous candidiasis; ii) Hypoadrenocorticism iii) Hypoparathyroidism. APS-I has its peak of incidence in early childhood and its frequency is similar in both females and males, while APS-II is more frequent in middle age, more commonly associated with diabetes mellitus and without mutations in AIRE. Although less frequent in APS-I, other endocrine features of this syndrome include T1D as well as testicular or ovarian failure. Alopecia, vitiligo pernicious anemia and chronic active hepatitis can also occur in APS-I and all likely share a common autoimmune etiology. The relevance of Aire has been underscored by inactivating mutations of Aire in mouse models of a polyendocrine autoimmune disease (2, 3), which mimic the clinical features of APS-I.

Abramson's et al. publication (1) offers a new relevant insight to understand the pathophysiology of autoimmune endocrine diseases, including T1D. Whereas the paper addresses normal physiological interactions of Aire, it also becomes clear that modifications in these interactions can lead to loss of tolerance in autoimmune diseases. Although the specific role of Aire in T1D has not been completely elucidated, it is well documented that T1D is an autoimmune disease characterized by loss of tolerance to self-antigens; it is this loss of tolerance which leads to the T-cell mediated destruction of β cells. In this context, the work of Abramson and coworkers (1), when taken together with what is known in diseases related to Aire inactivation, provides a thought-provoking framework of information that can enlighten our understanding of the pathogenesis of T1D and provide eventual avenues for therapy.

Regulation of normal tolerance to potential self-antigens is essential for understanding the pathophysiology of autoimmune diseases. Negative selection of self-reactive T-cells in the thymus is critical for immune tolerance and requires surveillance of self-antigens. A key component of this tolerance is the function of thymic medullary epithelial cells (MECs), which possess the ability to ectopically transcribe "promiscuously" a large number of antigens normally expressed in peripheral organs. Nagamine and collaborators (6) and the Finnish-German APECED Consortium (7) independently identified the gene responsible for APECED and designated it *AIRE* (*A*uto*i*mmune *Re*gulator). However, the specific molecular interactions of Aire to modulate self-antigen expression have not been elucidated in detail. The publication by Abramson et al(1) addresses the potential multiple intracellular roles of Aire. As the authors state, and as also described in the accompanying commentary by Kyewski and Peterson (8), the pleiotropic effects of Aire, combined with the structure of Aire itself, strongly suggested that Aire does not act as a traditional transcription factor. The work presented (1), indicates that Aire acts through a variety of partners and pathways that can be grouped into four major functional mechanisms encompassing (i) nuclear transport, (ii) chromatin binding/structure, (iii) transcription and (iv) pre-mRNA processing. Their results (1) also imply that Aire interacts with expression of gene sequences through recognition of hypomethylated H3 tails. This suggests that Aire interacts with epigenetic processes in expression of self-antigens. Additionally, the data indicate that Aire

would promote stabilization of short-lived pre-mRNA through proper splicing and in turn, would contribute to increases in mature mRNA.

The broad range of actions and interactions of Aire may explain the diversity of phenotypes produced by its inactivation, as evidenced in mouse models of diverse backgrounds (2, 3, 9). There may be different susceptibilities to autoimmunity due to epigenomic structure. While the relevance of Aire mutations in Type 1 APS is established and constitutes a model for the loss of Aire function, the elucidation of role of Aire in Type 2 APS, which includes subpopulations with T1D, has proven elusive. There are gender-associated changes in incidence of type 1 diabetes in type 2 APS, where prevalence is higher in females (10, 11). Gender-related differences in methylation have been described in health (12) and in diseases such as cancer (13) and diabetes (14, 15). It is possible that epigenetic factors like methylation may influence Aire and autoimmune diabetes. Another possibility related to the action of Aire and to T1D is RNA stability promotion. RNA stability in pancreatic function has received growing interest (16). In Aire deficiency or impaired function, defective pre-mRNA processing and subsequent RNA instability may lower expression of relevant transcription factors. This could reduce T1D-associated gene expression and lead to autoimmunity if Aire-expressing MECs are affected.

The suggested mechanisms of action of Aire, described in Figure 7 of the publication by Abramson (1), depict a sequential multiplicity of interactions. These range from recognition of hypomethylated loci, to the optimization of transcription of DNA coding for weakly expressed self-antigens, to subsequent stabilization of mRNA transcripts. However, as the authors acknowledge, the figure describes a speculative model in need of testing and confirmation through rigorous research. Additionally, as indicated by the commentary by Kyweski and Peterson (8), the experimental work conducted by Abramson and coworkers (1), mainly describes stable molecular interactions and may have missed transient or weak molecular partnerships.

Conclusions

The article provides a set of data that can be extrapolated into thought-provoking and conceptually interesting possibilities to address the loss of tolerance in the development of T1D diabetes and also other endocrine-related autoimmune diseases. There is clearly much additional work that needs to be done before the role of Aire in autoimmunity can be fully elucidated. However, the work of Abramson and coworkers (1) reviewed here, does provide a fresh conceptual framework to help understand the complexities of maintenance of tolerance and the molecular epigenetic etiology of autoimmune diseases. This is another example along with previously published observations (17) suggesting that a diabetes-prone MHC genotype is not absolutely necessary to cause endocrine-specific autoimmunity including autoimmune diabetes. The ability to present ectopic autoantigens at sufficiently high levels to induce immunologic tolerance in the thymus could be a matter of threshold, and AIRE may play a crucial role in controlling this threshold. This concept begs for experimental demonstration.

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