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Evidence That the Autoimmune Regulator Gene Influences Thymic Production of Ovarian Antigens and Prevents Autoimmune-Mediated Premature Reproductive Senescence

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Commentary

Evidence That the Autoimmune Regulator Gene Influences Thymic Production of Ovarian Antigens and Prevents Autoimmune-Mediated Premature Reproductive Senescence[1]

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The importance of the ovarian reserve, defined as the supply of primordial follicles in the mammalian ovary, to women's health [1, 2], mammalian fertility [3, 4], and mammalian assisted reproductive technologies [5, 6] has been the subject of much research. Depletion of the ovarian reserve is considered to be a major factor influencing reproductive senescence in female mammals, and menopause is associated with a number of health risks in women [2, 7]. Premature ovarian failure (POF; also known as premature ovarian dysfunction or primary ovarian insufficiency) causes premature menopause (also known as premature reproductive senescence), defined as menopause before age 40 in women [8]. Recent research has demonstrated both genetic predisposition [9] and autoimmune disorders [10] to be major factors contributing to the occurrence of POF.

The thymus is the organ responsible for T cell development and establishment of central tolerance, the process that allows the immune system to recognize self and prevent autoimmune disorders. T cells are derived from hematopoietic precursors that arise in the bone marrow and migrate to the thymus, where central tolerance is promoted by both positive and negative selection [11]. Positive selection sets the baseline T cell receptor (TCR) signaling threshold; negative selection occurs when the T cells migrate to the thymic medulla, where thymocytes with strong self-reactive TCRs undergo apoptosis, preventing them from initiating an autoimmune response in the peripheral tissues.

First discovered in 1997, the autoimmune regulator (*Aire*) gene codes for a 545-amino-acid glycoprotein that has a critical role in the process of central tolerance. It is predominantly expressed in the medullary thymic epithelial cells (mTECs) and functions as a transcriptional coactivator, controlling both intra- and extrathymic transcription of tissue-specific antigens. Microarray analysis identified a number of tissue-specific-genes that were depressed in the thymus of *Aire*-deficient mice, including preproinsulin II [12]. In a subsequent study, targeted deletion of the insulin gene in the mTECs of mice was sufficient to cause diabetes mellitus, although expression of insulin was normal in the pancreatic β cells [13], clearly demonstrating the requirement of low-level expression of tissue specific-antigens to promote central tolerance. More than 45 mutations in the *AIRE* gene have been identified, and most are inherited in an autosomal recessive manner [14].

The autoimmune polyglandular syndromes (APS) are a group of disorders that have a common pathology of multiple autoimmune disorders and/or immunodeficiencies [15]. APS type 1 (APS-1), also called autoimmune polyendocrinopathy candidiasis ectodermal dystrophy or Whitaker syndrome, is a monogenic multiorgan disease that is caused by functional mutations in the *AIRE* gene. The disorder manifests early in life and is diagnosed by at least two of the following three pathologies: 1) chronic mucotaneous candidiasis, 2) hypoparathyroidism, or 3) Addison disease. Alopecia and hypogonadism are also commonly associated with APS-1, and early reproductive senescence and/or infertility are common pathologies in women with APS-1.

In this issue of *Biology of Reproduction*, Jasti et al. [16] report the influence of the *Aire* gene on premature reproductive senescence in mice, because the expression of ovarian genes in mTECs is under the control of *Aire* and this may be critical for preventing ovarian autoimmune disease. *Aire*-deficient ($Aire^{-/-}$) mice had delayed puberty, although all eventually attained puberty. Ovulation rate and litter size were unaffected. However, only half of the *Aire*-deficient mice gave birth to a litter, and only 16% produced two litters. Histological evaluation of the ovaries revealed depletion of the ovarian reserve in 25% of virgin females by 8 wk of age; by 20 wk of age, 50% of *Aire*-deficient females had ovaries completely void of follicles. As would be expected, serum follicle-stimulating hormone concentrations were elevated in the *Aire*-deficient mice, most likely due to reduced negative feedback from the ovary.

Immunohistochemistry identified CD3+ T lymphocytes infiltrating the ovaries of *Aire*-deficient mice, suggesting that the depletion of the ovarian reserve was, indeed, due to an autoimmune response. Transcription of *Aire* in the ovary has

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been reported [12], although at much lower levels than in the thymus. Thus, Jasti et al. [16] needed to determine if follicular depletion occurred due to reduced *Aire* expression in the ovary without an immune response. To do this, they transplanted wild-type ovaries into the subrenal capsule of either *Aire*-deficient or wild-type mice. Two thirds of the wild-type ovaries displayed follicular depletion by 10 days after transplantation. Because *Aire* expression would have been normal in the wild-type ovaries, this clearly demonstrated that the follicular depletion was dependent on factors extrinsic to the ovary.

Evidence that the *AIRE* gene is involved in autoimmune disorders and could play a role in autoimmune-mediated POF has existed for some time, but the study by Jasti et al. [16] advances our understanding about the time course of follicular depletion and its correlation to hypergonadotropism and infertility in female mammals. The transplantation study clearly demonstrates that decreased *AIRE* expression in the thymus is the factor contributing to POF. Whereas a host of other genes have been shown to be associated with POF (e.g., *FMR1*, *FMR2*, *BMP15, FSHR, FOXO3*, and *FOXL2*) [9], only the *AIRE* gene has been linked to autoimmune-mediated POF. This work will have implications beyond the ovary, both by aiding in deciphering the molecular mechanisms involved in other tissues affected by APS-1 and by broadening our understanding of the mechanisms controlling autoimmune-mediated infertility.

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