Estrogen turns down “the AIRE”

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Autoimmune disease: sex-dependent differences

The incidence of autoimmune disease is increasing worldwide; therefore, the need to understand the basis of autoimmunity has taken on a new urgency. Progress in identifying genetic contributors to autoimmunity has been made through the study of monogenic autoimmune diseases. Such an approach has identified critical immune-regulatory genes, such as the autoimmune regulator (AIRE), which encodes a nuclear protein that functions as a key regulator of thymic central tolerance (reviewed in ref. 1). AIRE enforces self tolerance by promoting the promiscuous expression of tissue self-antigens (TSAs) within medullary thymic epithelial cells (mTECs), a nonhematopoietic, stromal cell population (Figure 1A). Presentation of these TSAs within the thymus results in negative selection of autoreactive T cells (3), whereas the differentiation of immunoregulatory CD4+CD25+FOXP3+ T cells (3), whereas estrogen enhances survival of T cells in patients with autoimmunity (4). Thus, there is a plethora of evidence that sex hormones directly modulate T cells in the periphery.

Genetic alterations are known drivers of autoimmune disease; however, there is a much higher incidence of autoimmunity in women, implicating sex-specific factors in disease development. The autoimmune regulator (AIRE) gene contributes to the maintenance of central tolerance, and complete loss of AIRE function results in the development of autoimmune polyendocrinopathy syndrome type 1. In this issue of the JCI, Dragin and colleagues demonstrate that AIRE expression is downregulated in females as the result of estrogen-mediated alterations at the AIRE promoter. The association between estrogen and reduction of AIRE may at least partially account for the elevated incidence of autoimmune disease in women and has potential implications for sex hormone therapy.

Early clues that sex hormones may also modulate thymic stromal populations, including mTECs, came from elegant studies that utilized bone marrow chimeras (5, 6). These studies showed that thymic epithelial cells express estrogen receptor (ER) and androgen receptor (AR) and that expression of these hormone receptors in the stromal compartment is required for altering bone marrow–derived T cell subsets in the thymus (5, 6). In this issue, Dragin et al. confirm that sex hormones indeed act on receptors on thymic stromal cells to impinge upon T cell development within the thymus. Furthermore, this study demonstrates that sex hormones regulate AIRE expression in mTECs and, in particular, estrogen decreases AIRE to predispose females to autoimmunity (7).

Estrogen-mediated AIRE downregulation

Transcriptional control of AIRE is complex and involves cis-regulatory elements and epigenetic modifications (Figure 1A). Identified regulators include enhancer elements that contain NF-κB response elements (9); transcription factors, including activator protein-1 (AP-1), specificity protein 1 (Sp1), nuclear factor Y (NF-Y), and ETS family transcription factors (10); histone modifications (9); and DNA methylation (11). Dragin et al. report that direct binding of estrogen/ER complexes to the AIRE promoter is unlikely, as predicted estrogen response elements are lacking at this site. Instead, estrogen-dependent downregulation of AIRE transcription was determined to be dependent on DNA methylation, an epigenetic mark of gene silencing (Figure 1B). An inhibitor of DNA methyltransferases (DNMTs), 5-aza-2'-deoxycytidine, blocked estrogen-mediated modulation of AIRE, and addition of estrogen to primary human mTEC cultures increased DNA methylation at the AIRE promoter. Notably, it remains to be clarified exactly how estrogen promotes DNA methylation. One could speculate that estrogen/ER complexes may promote DNMT function to increase DNA methyla-

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described in other cell types. How do sex hormones (progesterone and the androgen dihydrotestosterone [DHT]) also affect AIRE transcription? Our data indicate that DHT/AR complexes bind directly to androgen response elements (AREs) in the AIRE promoter to upregulate AIRE transcription (18). Does progesterone act through its receptor to bind directly to the AIRE promoter? Or does progesterone function through an epigenetic mechanism?

Conclusions and future directions
The findings in the study by Dragin and colleagues provoke a number of follow-up questions. First, the authors show that, in addition to estrogen, other sex hormones (progesterone and the androgen dihydrotestosterone [DHT]) also affect AIRE mRNA levels. Progesterone, similarly to estrogen, decreased AIRE expression, while the androgen DHT increased AIRE. What are the mechanisms by which these hormones regulate AIRE transcription? Our data indicate that DHT/AR complexes bind directly to androgen response elements (AREs) in the AIRE promoter to upregulate AIRE transcription (18). Does progesterone act through its receptor to bind directly to the AIRE promoter? Or does progesterone function through an epigenetic mechanism?

Second, AIRE is expressed not only in mTECs, but also in extrathymic AIRE-expressing cells (eTACs), thymic B cells, and other cell types (1). How do sex hor-
mones influence AIRE expression in these alternative AIRE-expressing cell types? Furthermore, the transcription factor FEZF2 can regulate the expression of TSAs independently of AIRE (19). Do sex hormones also influence FEZF2 expression? Third, sex hormone profiles are not only different between males and females after puberty, but also in the first six months of life, when neonates undergo “mini-puberty” with adult levels of circulating sex hormones (20). Are differences in AIRE expression already present at this early time period? Testing AIRE expression in this neonatal window is of particular importance, because this time period has been reported to be crucial for AIRE function (21). On the opposite end of the age spectrum, sex hormone production decreases in older adults. What is the effect of decreased sex hormone levels on AIRE expression and autoimmunity risk? A recent study reported that there was no difference in the transcriptome, including Aire and AIRE-dependent TSAs, of mTECs from male versus female mice (22), a finding that appears to be in direct conflict with the findings of Dragin et al. A possible explanation for the discrepancy in the two studies is the differences in ages of the mice studied. Dumont-Lagacé and colleagues utilized 24-week-old mice, whereas Dragin et al. evaluated 6- to 8-week-old mice. Of note, thymic involution is considerable in 24-week-old animals; therefore, this additional factor may be important at this time point. Together, both of these reports raise the question of how age, sex hormone levels, and possibly thymic involution might act on AIRE expression in males and females.

Finally, whether sex hormone modulation can be utilized for therapeutic purposes is an intriguing question. In theory, SERMs or other therapies that antagonize the effects of estrogen might be useful for treatment of autoimmune disease. On the other hand, increasing estrogen’s effects, which would lower AIRE expression and allow escape of tumor-reactive T cells from negative selection, might be useful as a cancer immunotherapy. Proof of principle for the latter concept has been established by augmentation of antitumor immunity through transient blockade of AIRE function in adult mice (1). These effects would ideally be limited to mTECs in order to prevent unwanted side effects of sex hormone therapy. Such strategies will require examination in future studies.

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