

SCIENCE BEHIND THE STUDY

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JAK Inhibition Immunotherapy for APS-1

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Autoimmune polyendocrine syndrome type 1 (APS-1) is a life-threatening, multiorgan autoimmune condition for which immunotherapeutic treatments have not been established. In this issue of the *Journal*, Oikonomou et al.¹ report the effects of an inhibitor of Janus kinase (JAK) 1 and 2 (JAK1 and JAK2) in a mouse model of APS-1 and a cohort of five patients with the disease. In line with previous reports,²⁻⁴ the authors showed a key role for interferon- γ signaling in disease pathogenesis. Because interferon- γ signals through JAK1 and JAK2, these findings provide the rationale for testing the effects of a JAK1 and JAK2 inhibitor (ruxolitinib) in APS-1. Treatment of the mouse model of APS-1 and patients with APS-1 resulted in protection from a remarkably diverse array of disease manifestations. These results support the testing of JAK inhibitors as potential first-line immunotherapies for APS-1 in clinical trials.

WHAT IS APS-1?

Also known as autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy (APECED), APS-1 is a rare, monogenic autoimmune disease that results from autosomal recessive variants in *AIRE*, which encodes the autoimmune regulator protein. Patients typically have a clinical triad of mucocutaneous candidiasis, adrenal insufficiency, and hypoparathyroidism in childhood, with development of multiple additional immune-mediated diseases throughout their lifetime. Some pathogenic *AIRE* variants function in a dominant manner to incite autoimmune disease and are associated with more restricted, later-onset disease manifestations.^{5,6}

Currently, the goals of medical management center on regular screening for the development of new clinical manifestations, hormone replacement for endocrine disease, and immunotherapies targeted at specific nonendocrine autoimmu-

mine conditions (i.e., hepatitis, pneumonitis, and pancreatitis).⁷ However, an immunotherapeutic approach is not yet available that broadly treats the many disease manifestations associated with *AIRE* deficiency.

HOW DOES AIRE DEFICIENCY CAUSE APS-1?

AIRE is a transcriptional activator and enforces **central T-cell tolerance** (see Key Concepts), a mechanism for preventing autoimmunity. Within medullary thymic epithelial cells (mTECs), *AIRE* up-regulates expression of a wide array of peripheral self-antigens.⁸ These self-antigens (e.g., insulin) are typically tissue-restricted (e.g., to pancreatic beta cells) and are “ectopically” expressed in mTECs by *AIRE*. How *AIRE* targets a large number of tissue-specific antigens for mTEC expression has been an area of intense interest, and recent work suggests that *AIRE* functions in a large macromolecular complex to induce expression of genes with specific DNA sequence motifs in their promoters⁹ (Fig. 1). Expression of *AIRE*-regulated self-antigens by mTECs allows their presentation to developing T cells in the thymus, and T cells recognizing these self-antigens with high affinity undergo negative selection. Thus, self-reactive T-cell clones are removed before they can be released into the periphery to cause tissue-specific autoimmune disease.¹⁰ At the same time, self-reactive T cells can also be tolerized by their diversion into the immunosuppressive regulatory T-cell lineage.¹¹ Cell types other than mTECs that express *AIRE* may contribute to the enforcement of self-tolerance.¹²

WHY RUXOLITINIB?

In patients with APS-1 and in mouse models of the disease, self-reactive T cells that escape central tolerance incite tissue destruction through the production of interferon- γ .¹³ Oikonomou et al. found up-regulation of interferon- γ and

interferon- γ signaling proteins in serum and multiple affected tissues (including liver, lung, stomach, and ileum) of patients with APS-1. The identity of cell types in which interferon- γ signaling is critical remains unclear, and it is possible that they include both immune cells and target tissue. However, it is known that binding of interferon- γ to the interferon- γ receptor at the cell surface results in activation of the **JAK–signal transducer and activator of transcription (STAT) signaling cascade** that ultimately alters transcription.

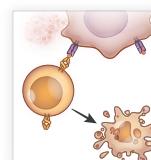
Binding of cytokines (including interferon- γ) and growth factors to their receptors results in phosphorylation and activation of JAKs, which ultimately phosphorylate and activate STAT transcription factors.¹³ Activated STATs then directly induce transcription of downstream proinflammatory genes that play a role in autoimmunity development. A combination of four JAK isoforms (JAK1, JAK2, JAK3, and tyrosine kinase 2) are specifically activated by particular cytokine receptors, and selective JAK inhibitors have been developed that interfere with particular JAK isoforms to varying degrees. Ruxolitinib, for example, inhibits JAK1 and JAK2, which are activated by interferon- γ signaling. On the basis of the strong evidence that interferon- γ signaling is critical in the pathogenesis of APS-1, inhibition of JAK1 and JAK2 by ruxolitinib was chosen as a potential immunotherapeutic candidate for APS-1.

In a mouse model of APS-1, ruxolitinib treatment was associated with prolonged survival and decreased T-cell infiltration in multiple tissues. In parallel, ruxolitinib treatment of five patients with APS-1 led to remission of multiple APS-1-associated conditions, including enteritis, alopecia, gastritis, and Sjögren's-like syndrome. Ruxolitinib treatment was associated with remission of oral candidiasis in mice and humans, a finding that supports a role for JAK–STAT signaling in the pathogenesis of APS-1 across species.

WHAT'S NEXT?

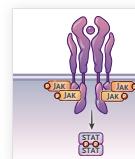
This study, along with a complementary report of the efficacy of ruxolitinib in patients with APS-1,¹⁴ provides compelling evidence that a clinical trial is warranted for testing JAK inhibi-

Key Concepts



Central tolerance

A means by which organ-specific autoimmunity is averted. For T cells, central tolerance refers to a process that occurs in the thymus. There, developing T cells that recognize self-antigens undergo clonal deletion so that they are not released into the periphery to cause autoimmune disease.



JAK–STAT signaling

A pathway through which cytokines and growth factors affect transcriptional changes important in the development of autoimmunity. Once a receptor is activated by ligand binding, phosphorylation and activation of Janus kinase (JAK) isoforms lead to phosphorylation and activation of signal transducer and activator of transcription (STAT) proteins. STATs then translocate to the nucleus, where they induce gene transcription.

tion in APS-1. Such a trial will be particularly important for delineating potential toxic effects, given the observation that infection with *Pneumocystis jirovecii* was noted in a patient with APS-1 and that the infection cleared with ruxolitinib discontinuation. Ruxolitinib is currently approved by the Food and Drug Administration (FDA) for multiple autoimmune and inflammatory indications (e.g., graft-versus-host disease). Thus, the safety and efficacy of ruxolitinib in these conditions is well known. The FDA recently issued a warning that certain JAK inhibitors may increase the risk of serious heart-related events, cancers, blood clots, and death,¹³ so it will be important to determine whether these toxic effects are seen in the treatment of patients with APS-1.

An additional implication of this study is that ruxolitinib may be effective in treating common forms of clinical manifestations, even outside of APS-1. For example, the remission of thyroiditis and Sjögren's-like syndrome suggests that ruxolitinib may be beneficial for isolated forms of these conditions. Finally, it is well documented that ruxolitinib and other JAK inhibitors have “off-target” effects in dampening additional signaling pathways.¹³ The mechanism through which ruxolitinib prevents disease manifestations in APS-1 therefore needs further investigation.

An expanded illustrated glossary is available at NEJM.org



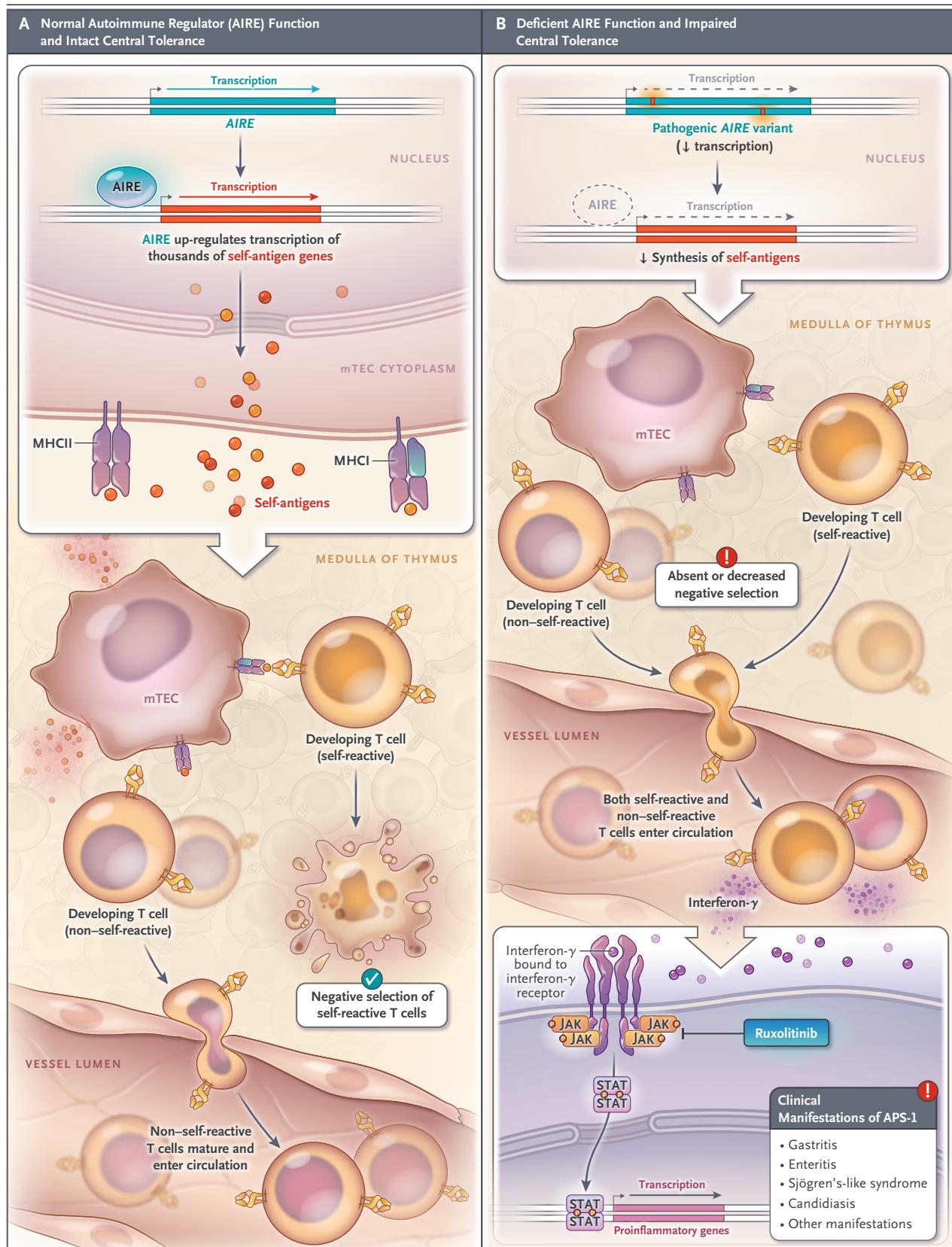


Figure 1 (facing page). AIRE Deficiency, Immune Intolerance, and Interferon- γ .

Within the thymus, AIRE normally functions to up-regulate thousands of tissue-specific self-antigens (Panel A). In autoimmune polyendocrine syndrome type 1 (APS-1), loss of AIRE function is associated with decreased self-antigen expression and escape of self-reactive T cells that recognize these self-antigens with high affinity (Panel B). On recognition of self-antigen outside the thymus, these T-cell escapees produce interferon- γ , which signals through Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathways to mediate tissue destruction. In this issue of the *Journal*, Oikonomou et al.¹ report that treatment of patients with APS-1 with the JAK inhibitor ruxolitinib induced remission of multiple autoimmune manifestations associated with APS-1. MHC I denotes major histocompatibility complex class I, and MHC II major histocompatibility complex class II.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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