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INSIGHTS

The Aire family expands

Adrian Liston and James Dooley

T cell tolerance depends upon Aire-expressing cells to purge the T cell repertoire of autoreactive clones. Once thought to be the exclusive domain of thymic epithelial cells, a new study by Yamano et al. (https://doi.org/10.1084/jem.20181430) in this issue of *JEM* identifies ILC3-like cells in the lymph nodes with similar properties.

The transcription factor Aire is well characterized as a key player in T cell tolerance in the thymus. In the current issue of *JEM*, Yamano et al. identify the long-elusive peripheral counterpart, as innate lymphocyte cells (ILCs) join the Aire-expressing family. Aire has a critical function in thymic T cell tolerance as the driver of ectopic expression of tissue-restricted antigens (TRAs) in the thymic epithelium. This thymic expression of TRAs allows differentiating T cells to be exposed to the full range of peripheral antigens, purging the T cell repertoire of autoreactive T cells before entering the periphery (Anderson and Su, 2016). Mutations in AIRE disrupt this process, leading to autoimmune polyglandular syndrome type 1 (APS-1), a severe multi-organ autoimmune syndrome.

The mechanism of action of Aire in the thymic epithelium is now understood in stunning detail, from the molecular interactions occurring at TRA promoters through to the cellular processes of negative selection and regulatory T cell induction. Despite this wealth of knowledge, there have been clues from the beginning that we were missing part of the story. The known autoimmune targets following Aire mutation are mismatched from the set of Aire-dependent TRAs expressed in the thymus, hinting at mechanisms other than simple thymic expression. The key suspect has long been peripheral expression of Aire. Early studies identified Aire expression in peripheral lymphoid tissues (Nagamine et al., 1997). The generation of an Aire-reporter strain provided conclusive evidence for an Aire-expressing peripheral population (Gardner et al., 2008), however the identity of this population has proven elusive, being variously described as an atypical stromal cell (Gardner et al., 2008) or a novel dendritic cell–like population (Gardner et al., 2013).

The work by Yamano et al. (2019) elegantly identifies the true Aire-expressing peripheral cell as an ILC3-like resident of the lymph node. While diversity was observed among cells expressing Aire at the mRNA level, only ILC3-like cells expressed Aire protein (Yamano et al., 2019). This subset expressed Aire protein at a comparable level to that of Aire-expressing epithelial cells in the thymus. The other putative Aire-expressing peripheral cells, by contrast, demonstrated a clear discordance between Aire mRNA and protein, suggesting a biological basis for the long-simmering controversy in previous attempts to define peripheral Aire expression. The authors defined the Aire-expressing population as ILC3-like based on lymphoid morphology and phenotypic markers. Critically, the authors formally demonstrated the hematopoietic, Rag-independent, Rorg-dependent origin of these cells, placing them firmly within the ILC3 family. As with Aire-expressing thymic epithelial cells, Aire expression in ILC3-like cells is Rank dependent (Rossi et al., 2007), although intriguingly (and unlike the thymic counterpart), crosstalk with T cells is not required for Aire-expressing cells to emerge from the canonical ILC3 population.

The million-dollar question is whether Aire-expressing ILC3-like cells have any function. Do they express TRA, driving tissue-specific tolerance like their thymic counterpart? Or are they merely an epiphenomenon driven by a conserved Rank–

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Aire pathway in irrelevant cells? The jury is still out; however, this study provides two intriguing data points. First, the transcriptional impact of Aire on ILC3-like cells appears to be vastly different to that on thymic epithelial cells. While Aire expression in thymic epithelium drives TRA expression, Aire expression in the periphery drives largely nonoverlapping (or even opposing) transcriptional effects, without a bias for TRA (Yamano et al., 2019). In this respect, Aire-expressing ILC3-like cells cannot be seen to act as a peripheral safety net for thymic tolerance. The second point, however, strongly argues in favor of a functional role for Aire expression in ILC3-like cells. Expression of a neo-self antigen by this population resulted in efficient in vivo depletion of TCR-transgenic autoreactive T cells (Yamano et al., 2019). The ILC3-like cells are therefore not only effective antigen-presenting cells, but appear to be endowed with a strong tolerogenic function.

This study may close the book on the identity of Aire-expressing cells in the periphery, but, if anything, it raises more questions on the function of peripheral Aire expression. Is this peripheral expression

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required to avert autoimmunity? Does Aire expression impart the tolerogenic function of ILC3-like cells, or merely provide a set of antigens for these cells to present? Is the population dynamically regulated with age or during disease? Depending on the outcome of these questions, Aire-expressing ILC3-like cells may become a highly attractive target for therapeutic intervention. A peripheral population with parallel tolerogenic properties to thymic epithelial cells would provide several key advantages over the thymic counterpart, including accessibility and the ability to shape the post-thymic T cell repertoire. The identification of a suitable cellular host for tolerogenic vaccines has the potential to reshape how we treat autoimmune diseases.

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