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Journal club

MEDULLARY THYMIC EPITHELIAL CELL PROGENITORS: HIDDEN IN PLAIN SIGHT

By 2001, our understanding of intrathymic T cell development was in good shape. Key stages of thymocyte development, including positive and negative selection, were mapped out, and the roles of the thymic cortex and medulla in these processes were also appreciated. What was missing, however, was an understanding of how the cortical and medullary architecture of the thymus was established, and how different thymic epithelial cell (TEC) populations were generated to control thymocyte development. The 2001 paper by Hans-Reimer Rodewald and colleagues published in *Nature* provided a major advance in understanding thymus organogenesis by providing the first experimental evidence for the existence of TEC progenitors.

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Making use of blastocyst chimaeras and reaggregate thymus organ cultures (RTOCs), Rodewald *et al.* examined the building blocks of thymus compartmentalization in an unbiased way, in the absence of phenotypic indicators of potentially relevant cell types. They showed that medullary areas of the thymus form from cellular 'islets', with each adult thymic lobe containing approximately 300 of these structures. Importantly, each medullary islet was shown to arise from a single cell that did not contribute to the surrounding thymic cortex.

Thus, this study revealed the existence of lineage-restricted TEC progenitors that generate functionally important thymic microenvironments *in vivo*. Medullary TEC progenitors were born! This study remains important more than 15 years later for several reasons. First, when this paper was published, TEC progenitor activity had been proposed but had never been shown experimentally. Second, this study indicated the dynamic nature of TECs and their propensity for turnover and self-renewal. Finally, it represented the first *in vivo* use of RTOCs as an assay for TEC progenitors, an approach that has subsequently been used to identify bipotent and further lineage-restricted TEC progenitors (reviewed in Takahama *et al.*, 2017). TECs now represent an attractive cell therapy for thymic regeneration, and this stems from the discovery that their developmental programme involves precursor–product relationships that may be exploited to improve thymus function.

Graham Anderson
Institute for Immunology and Immunotherapy, University of Birmingham, UK.
G.Anderson@bham.ac.uk

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ORIGINAL ARTICLE Rodewald, H. R. *et al.* Thymus medulla consisting of epithelial islets each derived from a single progenitor. *Nature* **414**, 763–768 (2001)
FURTHER READING Takahama, Y., Ohigashi, I., Baik, S. & Anderson, G. Generation of diversity in thymic epithelial cells. *Nat. Rev. Immunol.* http://dx.doi.org/10.1038/nri.2017.12 (2017)