The primordial thymus
Anderson, Graham; Baik, Song

DOI:
10.1016/j.immuni.2014.07.012

License:
Other (please provide link to licence statement)

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Link to publication on Research at Birmingham portal

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

• Users may freely distribute the URL that is used to identify this publication.
• Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
• Users may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (7)
• Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.
exerted by AhR is somehow more prevalent than the one exerted by enzymes generating its physiologic ligands, e.g., L-kynurenine. There are at least two possible and non-mutually exclusive explanations for this. The first is that the enzymes involved in tryptophan catabolism are to some extent redundant in their ability to produce the AhR ligand L-kynurenine. Alternatively, it is possible that additional AhR ligand(s) are produced physiologically via other host catabolic pathways that support the protective effects of AhR. Candidate AhR ligands include those produced by heme oxygenases (HOs), a stress-responsive enzyme that confers disease tolerance to polymicrobial infections (Larsen et al., 2010). Heme catabolism by HOs produces several putative AhR ligands including biliverdin (a direct end-product of HO activity) and bilirubin (a potent antioxidant generated from biliverdin catabolism by biliverdin reductase that activates AhR) (Denison and Nagy, 2003). Moreover, heme catabolism by HOs also generates carbon monoxide, a gasotransmitter that can bind ferrous (Fe²⁺) iron contained in the heme group of AhR and modulate its activity. Whether regulation of disease tolerance by AhR acts via a mechanism involving the putative action of different end products of heme catabolism by HOs has not been established. If proven correct, this would argue for the integration of the AhR signal transduction pathways in a wider network of stress-responsive signaling pathways regulating disease tolerance to infection.

Although simple in its essence, the concept of disease tolerance should have major implications to our current understanding of the pathogenesis of infectious diseases. The study by Bessede et al. (2014) and future studies should provide the mechanistic insight, i.e., “nuts and bolts,” allowing for targeting this defense strategy therapeutically toward a much-needed supplement to the current clinical approaches available in the treatment of infectious diseases.

ACKNOWLEDGMENTS


REFERENCES


lymphocyte receptors type A [VLRA] and VLRC-type antigen receptors), but not B cells (VLRB-type antigen receptors). Thus, the anatomical separation of sites supporting lymphocyte production has existed for over 500 million years. In a recent issue of Cell Reports, by manipulating expression of Foxn1 and its ancient parologue Foxn4 in the context of vertebrate thymus development, Swann et al. (2014) discover that the primordial thymus represented a site that fostered both T and B cell development. Such findings are significant because they reveal the emergence of specialization in lymphoid tissues and suggest how the thymus developed away from a common site of lymphopoiesis toward a site specialized for T cell development.

To investigate the evolutionary origins of thymic tissue, Swann et al. (2014) analyzed the thymus of vertebrates (mouse), cartilaginous fish (catshark), and bony fish (zebrafish and medaka) for Foxn1 and Foxn4 expression, the latter an ancient gene that gave rise to Foxn1 by duplication. While expression of both genes was readily detectable in fish, Foxn4 was barely detectable in mouse thymus. Such findings suggested to the authors that TEC expression of Foxn4 was progressively lost during evolution, a scenario consistent with the lack of detectable Foxn4 in the thymus of jawless vertebrates. Moreover, while Foxn4 cannot compensate for the absence of Foxn1 in mice, further experiments showed the opposite: that Foxn4-mediated thymus development in teleost fish occurs in the absence of Foxn1. Such findings define an important functional role for the ancient gene Foxn4 during thymus development in early vertebrates, prior to the gene duplication giving rise to Foxn1. Next, the authors adopted a transgenic approach in which either Foxn1 or Foxn4 expression was introduced into nude mice, which lack normal thymus development due to disruption of the endogenous Foxn1. As expected, reintroduction of Foxn1 rescued thymus development in nude mice. Most striking was the impact of introducing Foxn4 in the context of Foxn1 deficiency. Here, thymus development occurred, including the generation of cortical and medullary TEC that supported T cell development.

Swann et al. (2014) report the reconstruction of the primordial thymus and show that it represents a tissue with dual T and B lymphopoietic function. The study of Swann et al. (2014) is important in several respects, including understanding the current specialization of the thymus for T cell development. While the thymus represents the unique site for T cell production in all vertebrates, several tissues share the capacity to support B cell development. That the primordial thymus represented a site of combined lymphopoietic activity suggests that changes in expression of the Foxn1 and Foxn4 gene family, notably the gene duplication that generated Foxn1, limited the ability of the thymus to support B cell development. Thus, high amounts of FOXN1-dependent Dll4 increased the T lymphopoietic properties of the thymus at the expense of B lymphopoiesis. This is compatible with studies demonstrating that when the NOTCH-DLL4 axis is compromised, there is an increased ability of the thymus to support B cell development (Shah and Zühlig-Pflücker, 2014). Relevant to this is comparison of the microenvironmental requirements of T and B lymphopoiesis. While the latter requires stromal support from mesenchyme, the former requires a combination of both mesenchymal and epithelial interactions (Anderson et al., 1993). Thus, the increasing efficacy of intrathymic T cell development caused by the appearance of Foxn1 might have led to increased competition for mesenchyme support between developing T and B cell progenitors, and the progressive decline in B lymphopoiesis. Whatever the mechanism that caused restriction of the dual lymphopoietic properties of the thymus, it is still not clear how this process led to the fetal liver and bone marrow emerging as sites of B cell development in mammals. An additional possibility raised by the findings of Swann et al. (2014) is whether the presence of effective B cell development in the primordial thymus could have benefitted aspects of
intrathymic T cell development. In mammals, B cells have been linked to the negative selection of autoreactive T cell specificities in the establishment of T cell tolerance (Perera et al., 2013). Additionally, they can express tumor necrosis factor superfamily (TNFSF) ligands that regulate thymic microenvironments (Anderson and Takahama, 2012). Thus, the development and organization of the bifunctional thymus might have benefitted from signals from both lymphocyte development programs.

Despite their important findings, Swann et al. (2014) do not tackle the relationship between alterations in the lymphopoietic capacity of the thymus and the nature of thymus colonizing lymphoid progenitors. This is important as the developmental properties of cells recruited to the thymus remain unclear (Zhang and Bhandoola, 2014). For example, while studies report thymus colonization by progenitors with restricted lineage potential, others detect the presence of common lymphoid progenitors. Thus, as with studies in mice, the ability of the ancient thymus to act as a site that either imposes, or reveals, T lineage commitment remains unclear.

In summary, Swann et al. (2014) provide a glimpse of the evolutionary history of the thymus. Reconstruction of the primordial thymus as a bipotent tissue that supports both T and B lymphopoiesis underlines similarities in the developmental programs of both cell types and identifies how alterations in TEC gene expression led to the effective and highly specialized thymic tissue seen in modern vertebrates.

REFERENCES


