UNIVERSITYOF **BIRMINGHAM**

University of Birmingham Research at Birmingham

A different view on immunity

Dempsey, Claire M; Jones, Nick D

DOI:

10.1097/TP.00000000000000738

License:

None: All rights reserved

Document Version Peer reviewed version

Citation for published version (Harvard): Dempsey, CM & Jones, ND 2015, 'A different view on immunity: spatial mapping of human T cells over a lifetime', Transplantation, vol. 99, no. 5, pp. 896-7. https://doi.org/10.1097/TP.0000000000000738

Link to publication on Research at Birmingham portal

Publisher Rights Statement:
Final version published as: Dempsey, Claire M., and Nick D. Jones. "A Different View on Immunity: Spatial Mapping of Human T Cells Over a Lifetime." Transplantation 99.5 (2015): 896-897. Available online at: http://dx.doi.org/10.1097/TP.0000000000000738

Checked October 2015

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

•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.
•User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)

•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.

Download date: 05. May. 2024

A different view on immunity: Spatial mapping of human T cells over a lifetime

Claire M Dempsey¹ and Nick D Jones^{1,2}

1 Current Address: MRC Centre for Immune Regulation, Medical School, University

of Birmingham. Edgbaston, Birmingham. UK. B15 2TT

2 To whom correspondence should be addressed – n.d.jones@bham.ac.uk

Key words: transplantation; T cells; memory; life-course

The authors declare no funding or conflicts of interest.

Alloreactive T cells are widely accepted as the main driving force in the induction and progression of allograft rejection and as such are frequently analysed to ascertain a patient's immune reactivity to a transplant. Antigen-experienced T cells formed either *de novo* following a period of suboptimal immunosuppression or previously generated subsequent to sensitizing events or through heterologous immunity contribute significantly to rejection ¹. Thus far, studies of human T cells have been limited to sampling peripheral blood, which contains less than 3% of total T cells ². This raises the question as to how accurately peripheral blood lymphocytes reflect the immune status of transplant patients.

A seminal paper by Farber and colleagues published in *Cell*, provides important insights into the localisation, phenotype and trafficking of different T cell subsets in humans through a unique collaboration with New York Organ Donor Network ³. Their utilisation of tissue and blood samples from deceased donors allowed for a systematic analysis of T cell subsets across a broad range of anatomical locations, ages and races resulting in a comprehensive picture of memory T cell distribution as a function of time and space.

The term memory T cell encompasses several subsets of antigen-experienced cells that differ in their homing capacities and effector functions. Each of these subtypes may play distinct roles in immunity, and can be defined by the expression of CD4 or CD8 co-receptors and the differential expression pattern of CD45RA and chemokine (C-C motif) receptor 7 (CCR7) ⁴. Using this approach the authors sub-divided CD4⁺ and CD8⁺ T cells into naive or antigen-experienced TEMRA (short-lived, terminally differentiated cells), central memory (TCM) and effector memory (TEM) T cells. In

addition, they also analysed tissue resident memory cells (TRM), that are located and retained in the skin, liver and mucosal tissues. This elegant and comprehensive study has significantly increased our understanding of memory T cell subsets, their localisation and the dynamic changes that occur during the lifetime of an individual with a number of clear implications for the analysis of T cell immunity to transplanted tissue.

This work provides clear evidence that different memory T cell subsets are resident in, or circulate through distinct lymphoid and non-lymphoid locations in humans. For example, CD4⁺ TEM clones were found to be differentially compartmentalized amongst lymphoid tissues whereas CD8⁺ TEM tended to be circulating with more clones being present in multiple lymphoid tissues. Findings such as these challenge the current reliance on peripheral blood to evaluate human T cell responses, and suggest that studies that rely on peripheral blood as a source of recipient T cells should be interpreted with caution. Whilst peripheral blood is readily accessible and may give valuable insights into T cell immunity in transplant recipients, at best it is likely to provide a select window of immunity while potentially underestimating the participation of critical memory T cell subsets, T cell clones and specificities in alloimmunity.

The differential distribution of memory T cell subsets amongst blood, lymphoid tissue and non-lymphoid tissues may also have ramifications for the development of biomarkers to predict rejection or tolerance. To date biomarkers relating to conventional T cell activity have been poorly predictive of tolerance while B cell and NK/ $\gamma\delta$ T cell gene signatures provided more robust data defining tolerant kidney and

liver transplant recipients, respectively ⁵⁻⁷. The work by Farber and co-workers offers a novel explanation, in that blood may not be the best place to look for biomarkers relating to certain subsets of alloantigen-experienced T cells. It is also interesting to speculate that, while the authors did not examine foxp3⁺ regulatory T cells (Tregs) in this paper, they too may be located in various anatomical locations, with varying distribution throughout life. Indeed, tissue tropic populations of Treg have been reported in the intestine and skin ^{8, 9}. Importantly, Tregs activated by recognition of organ-specific self-antigen form a residual population remaining in the target tissue that suggests that many alloantigen-reactive Treg reside in the graft rather than in the circulation ¹⁰.

Of additional importance, the distribution of certain T cell subsets varies with age, with ongoing dynamic changes occurring in both lymphoid tissues and in peripheral blood. To this end, an attrition of the naive T cell pool due to age-related antigen-mediated differentiation to TEM and TEMRA has been observed. In contrast, TEM and TEMRA populations at mucosal sites remained relatively stable with age as did the CD4⁺ TCM present in lymphoid tissues. This has obvious implications for clinical studies in which that frequently compare individuals with a relatively wide spread of ages. Based on the findings by Farber and co-workers, it may be worth considering that narrowing the upper and lower age limits of patient cohorts may reduce the intra-group variability caused by age-related changes in the T cell compartment of the assessed tissue.

In summary, by conducting detailed analyses of memory T cell subsets in tissues and blood from deceased donors, the authors have provided important and novel

insights into memory T cell subset localisation, maintenance and trafficking in lymphoid and non-lymphoid tissue throughout the human life course. This work highlights the importance of studying peripheral lymphoid tissue, as well as peripheral blood and where possible the graft itself for a detailed analysis of allograft rejection and acceptance.

References

- **1.** Brook MO, Wood KJ, Jones ND. The impact of memory T cells on rejection and the induction of tolerance. *Transplantation* 2006;82:1
- Ganusov VV, De Boer RJ. Do most lymphocytes in humans really reside in the gut? Trends in Immunology 2007;28:514
- 3. Thome JJC, Yudanin N, Ohmura Y, et al. Spatial Map of Human T Cell Compartmentalization and Maintenance over Decades of Life. Cell. 2014; 159:814
- 4. Sallusto F, Lenig D, Forster R, Lipp M, Lanzavecchia A. Two subsets of memory T lymphocytes with distinct homing potentials and effector functions. Nature 1999;401:708
- 5. Sagoo P, Perucha E, Sawitzki B, et al. Development of a cross-platform biomarker signature to detect renal transplant tolerance in humans. J Clin Invest 2010;120:1848
- 6. Newell KA, Asare A, Kirk AD, et al. Identification of a B cell signature associated with renal transplant tolerance in humans. *J Clin Invest* 2010;120:1836
- 7. Martinez-Llordella M, Puig-Pey I, Orlando G, et al. Multiparameter immune profiling of operational tolerance in liver transplantation. *Am J Transplant* 2007;7:309
- 8. Smigiel KS, Richards E, Srivastava S, et al. CCR7 provides localized access to IL-2 and defines homeostatically distinct regulatory T cell subsets. J Exp Med 2014;211:121
- Dudda JC, Perdue N, Bachtanian E, Campbell DJ. Foxp3+ regulatory T cells maintain immune homeostasis in the skin. J Exp Med 2008;205:1559

10. Rosenblum MD, Gratz IK, Paw JS, Lee K, Marshak-Rothstein A, Abbas AK.
Response to self antigen imprints regulatory memory in tissues. *Nature*2011;480:538