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

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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.

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