Spatial dysregulation of T follicular helper cells impairs vaccine responses in ageing

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Abstract

Vaccination generates long-lived antibody-mediated immunity against (re-)infection. This humoral immunity is derived from memory B cells and long-lived antibody-secreting plasma cells via the germinal centre (GC) response. The magnitude and quality of the GC response declines with age, resulting in poor vaccine-induced immunity in older individuals, but the causal factor/s of this age-related decline are unknown. A functional GC requires the co-ordination of multiple cell types across time and space, in particular across its two functionally distinct compartments: the light and dark zones. We identified that the spatial organisation of the GC is altered in ageing, with CXCR4-mediated mislocalisation of T follicular helper (Tfh) cells in the dark zone and a compressed network of follicular dendritic cells (FDCs) in the light zone. By modulating the positioning of Tfh cells *in vivo*, we found that Tfh cell polarisation is critical for the quality of the antibody response, and, surprisingly, for the expansion of the FDC network upon immunisation. The smaller GC responses and defective FDC expansion in ageing were corrected by provision of Tfh cells that co-localise with FDCs via CXCR5:CXCL13-mediated interaction. This demonstrates that the age-dependent defects in the GC response are reversible and shows that Tfh cells have a dual role in B cell help and facilitating stromal cell responses to vaccines.