Unique cellular sources of CXCR3 ligands direct intranodal T cell positioning and interactions following viral infection

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The lymph node microarchitecture is a reticular network which provides a mechanical framework and restricts immune cells into structurally distinct regions. Recent discoveries have expanded our understanding of how T cells are positioned within lymph nodes during infection. Upon activation by dendritic cells (DCs) in the paracortex of a draining lymph node, the chemokine receptor CXCR3 is rapidly upregulated on the surface of antigen-specific T cells. CXCR3 binds two ligands in C57BL/6 mice, CXCL9 and CXCL10, which are produced in the cortical ridge, interfollicular and medulla regions of draining lymph nodes and provide chemotactic signals to newly activated CXCR3+ T cells. While it has been established that CXCR3+ T cell repositioning within these peripheral regions is required to mount an optimal immune response, the cellular partners that regulate CXCR3+ T cell location during activation and memory formation are still poorly understood.
Combining chemokine reporter mice with viral infection, we have extensively characterised the cellular sources of CXCR3 ligands. We show that CXCL9 and CXCL10 chemokines are produced by distinct DC and stromal cell populations. Specifically, we show that CXCL9 is produced by type 1 conventional DCs (cDC1) whereas CXCL10 production is produced by type 2 cDCs (cDC2), inflammatory monocytes and stromal cells. We have cleared and imaged intact lymph nodes using lightsheet microscopy to identify the location of chemokine expressing DC and stromal populations. We quantified how DC and stromal populations influence T cell positioning in chemokine reporter and knock-out bone marrow chimeras. Finally we correlate T cells position with the formation of T cell effectors and memory precursors and dissect how this is influenced by specific CXCR3-mediated interactions. This work highlights the finely regulated choreography of T cell migration and interactions following viral infection and will inform new vaccine strategies.

Keywords : CXCR3 ligands, conventional dendritic cells, T cells, stromal cells, intranodal positioning
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