

Antonio Peixoto

Harvard Medical School – Boston USA

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"LFA1 integrin, a key modulator of T cell crawling on HEVs, T-DC interactions and effector/memory commitment during LCMV infection "

The initiation of a cellular immune response in secondary lymphoid organs is dependent on 2 major events: first naive T cells need to migrate from blood and into the inflamed lymph node (LN). Second, once in the LN parenchyma, T cells need to "find" and interact with mature dendritic cells (DCs) carrying cognate antigen. Thus giving rise to effector cells that will eliminate antigen and memory cells that will confer long term protection. Both phenomena are characterized by multiple steps which are important for the immuno-surveillance provided by T cells: T cell migration involves initially their rolling on High Endothelial Venules (HEVs) mediated by selectins; followed by firm adhesion promoted by integrins that then leads to the transendothelial migration of T cells into the LN parenchyma⁽¹⁾. On the other hand T cell and DC interaction occurs in 3 distinct phases: transient serial encounters during the first activation phase (lasting several hours) are followed by a second phase of stable contacts culminating in cytokine production, which makes a transition into a third phase of high motility and rapid proliferation^(2,3). Although much is known about the molecular switches that trigger such transitions in T cell migration into lymph nodes,⁽¹⁾ less is known about the transmigration step. Instead these mechanisms remain largely unknown in the case of the phases of T-DC interactions during T cell priming.

Here we have addressed the role of adhesion/signaling, mediated by LFA1, in the regulation of T cell transmigration into lymph nodes and T-DC interactions by multi-photon microscopy (MP-IVM). Next we explored LFA1 function as a key modulator of immune responses in vivo. For this we used polyclonal or transgenic T cells specific for GP₃₃₋₄₃ protein of Lymphocytic Choriomeningitis Virus (LCMV) (P14)⁽⁴⁾, that are either LFA1 WT (normal adhesion), deficient in LFA1⁽⁵⁾ (LFA1^{-/-}, no adhesion) or genetically modified LFA1 in a activated configuration (LFA1^{ki/ki}, high adhesion)⁽⁶⁾. First, we show that during transmigration LFA1 adhesion has to be properly regulated after firm adhesion to HEVs. In fact, LFA1^{ki/ki} T cells adhered strongly to HEVs but crawled poorly and were impaired in finding a suitable exit site for transendothelial migration. In contrast, T cell motility of LFA1^{ki/ki} T cells in LN parenchyma was comparable to WT T cells. Second we found that both lack of, or aberrantly activated LFA1 on P14 T cells significantly decreases the T-DC interaction time measured by MP-IVM. In consequence adoptive transfer of P14 LFA1^{-/-} or LFA1^{ki/ki} T cells into WT recipients generated reduced effector cell numbers and poor cytokine producers upon LCMV infection, when compared to P14 WT cells. Surprisingly the numbers of memory precursor cells (IL7R^{high} KLRG1^{low})⁽⁷⁾ was not changed in the different conditions. Instead memory precursor numbers were greatly reduced upon adoptive transfer of P14 LFA1^{-/-} into ICAM1⁽⁷⁾ (LFA1, CD11b and CD11c ligand) deficient mice suggesting an alternative receptor on T cells that is crucial for memory precursor generation.

In summary, our results show that proper regulation of LFA1 is crucial for both T cell migration into LN and prolonged T-DC interactions, but not interstitial T cell motility. Furthermore LFA1 mediated signals regulate the number and differentiation of effectors cells upon LCMV infection, whereas ICAM1 on opposing cells regulates the generation of memory cells.

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Contact : Jean-philippe Girard