Tissue specific surveillance strategies of memory CD8⁺ T cells

Nora Ruef

T cells play a central role in the adaptive immune response. Their remarkable motility is crucial for host defense because they rely on direct interaction with antigen presenting cells to exert their actions. Here we focus on the surveillance mechanisms of tissue resident memory CD8⁺ T cells (T_RM) in the submandibular salivary gland (SMG).

First, we describe that SMG T_RM dynamically follow tissue macrophage topology to efficiently surveil the tissue. We could not identify any specific molecular interaction between both cell types, suggesting that T_RM follow tissue macrophages because this represents the path of least resistance. In the absence of macrophages T_RM show a disrupted patrolling behavior and are not able to cluster in response to local inflammatory chemokines. Unlike naive and memory T cells from lymphoid tissues SMG T_RM show a robust intrinsic motility in the absence of chemoattractants and adhesion molecules. In this spontaneous mode of cell migration, we show that the force transmission for cell translocation can be mediated by friction or protrusion insertion.

Additionally, we uncover molecular pathways driving this intrinsic SMG T_RM motility. This is on the one hand Dock2 – Rac – Arp2/3 generated F-actin leading to elevated F-actin levels compared to other memory T cell subsets, and a spontaneous retrograde actin flow in the absence of chemokines. On the other hand, the nucleus senses the confinement which leads to a Ca²⁺-dependent cytosolic phospholipase A2 (cPLA2) activation promoting actomyosin contractility. We show that SMG T_RM show high levels of myosin IIA and phosphorylated myosin light chain (pMLC) compared to other memory T cell subsets, and that interfering with MLC phosphorylation abolishes spontaneous T_RM migration. We observed that the high cytoplasmic pressure mediated by cortical contractility also leads to the formation of membrane blebs at the leading edge. In sum, our findings uncover that memory CD8⁺ T cells adapt their surveillance strategies to the tissue of residence.

In additional projects we investigated i) the role of Flotillin-1 (Flot1) in CD8⁺ T cell immune surveillance, ii) a resource for the classification of cell migration patterns, iii) the role of Fam65b expression and phosphorylation in RhoA regulation, and iv) the fate of dendritic cells after forming productive immune synapses.

Jury:
Prof. Jens Stein (thesis supervisor)
Dr. Ana-Maria Lennon-Duménil (external co-examiner)
Prof. MichaelWalch (internal co-examiner)
Prof. Curzio Rüegg (president of the jury)