

Visualizing Dynamic Microvillar Search and Stabilization during Ligand Detection by T Cells

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During immune surveillance, T cells survey the surface of antigen-presenting cells (APCs), which may display mainly nonstimulatory peptide-loaded major histocompatibility complexes (pMHCs) and only rare cognate antigen in a process involving close membrane apposition. Thus, T cell must solve a classic trade-off between speed and sensitivity. It has long been supposed that microvilli on T cells act as sensory organs to enable search, but their strategy has been unknown. We used lattice light-sheet microscopy and quantum dot-enabled synaptic contact mapping microscopy to show how microvilli on the surface of T cells search opposing cells and surfaces before and during antigen recognition. We uncovered fractal organization of the microvilli on T cell surfaces. We found that microvilli survey the majority of opposing surfaces within one minute through anomalous diffusion, which is equivalent to the roughly one-minute half-life of T cell-APC contacts in vivo. Individual microvilli dwell times were long enough to discriminate pMHC half-lives. TCR recognition resulted in selective stabilization of receptor-occupied protrusions as seen by longer microvilli dwell times in synapse regions with pMHCs and increased persistence of TCR-occupied contacts. Stabilization was independent of tyrosine kinase signaling and the actin cytoskeleton, suggesting selection for avid TCR microclusters. This work defines the efficient cellular search process against which ligand detection takes place in T cells.