CXCR4 transmembrane region VI governs its actin-dependent dynamic clustering, signaling and cell response

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A current challenge in cell motility studies is to understand how the dynamics and spatiotemporal organization of chemokine receptors at the cell membrane influences their function. Using single-particle tracking and super-resolution microscopy, we found that CXCR4 forms monomers, dimers and small nanoclusters on the T cell membrane, which became larger after binding of its ligand, CXCL12. The actin cytoskeleton and the co-receptor CD4 acting in an orchestrated fashion regulate the lateral mobility of CXCR4 and signaling strength. In CXCR4 transmembrane region VI, we identified the structural residues crucial for receptor clustering, and generated an oligomerization-defective CXCR4 mutant that did not cluster in response to CXCL12 and showed severely impaired signaling. We demonstrate that structural motifs of CXCR4 and local organizers of the cell membrane regulate the distribution, cluster size and function of this receptor and define new targets to intervene in the in vivo functions associated to these inflammatory mediators.