A switch of integrin ligand specificity by distinct chemokine signaling

With the support by the National Natural Science Foundation of China and the Ministry of Science and Technology of China, Prof. Chen Jianfeng's laboratory from the Institute of Biochemistry and Cell Biology, Shanghai Institute for Biological Sciences, Chinese Academy of Sciences, revealed a novel mechanism by which integrin selects between different binding ligands to maintain the tissue specificity of lymphocyte homing, which was published in *Developmental Cell* (2014, 30(1): 61—70) as a cover story.

The immune surveillance and host defense depend on the precisely regulated trafficking of lymphocytes. The interaction between integrin and its ligand enables the targeting of lymphocytes to different tissues. Integrin $\alpha_4\beta_7$ mediates lymphocyte homing to gut-associated lymphoid tissues through its interaction with MAdCAM-1, which is specifically expressed in the gut; whereas it also binds VCAM-1 which is widely expressed in other tissues. In order to maintain the specificity of lymphocyte homing to tissues that express either MAdCAM-1 or VCAM-1, $\alpha_4\beta_7$ needs to distinguish one ligand from the other. Prof. Chen's group demonstrated the switch of integrin $\alpha_4\beta_7$ ligand-specificity by different chemokines to mediate selective adhesion of lymphocytes to either MAdCAM-1 or VCAM-1, and also importantly, the molecular mechanisms involved. CCL25 stimulation promotes $\alpha_4\beta_7$-mediated lymphocyte adhesion to MAdCAM-1 but suppresses cell adhesion to VCAM-1, whereas CXCL10 stimulation has the opposite effect. Using separate pathways, CCL25 and CXCL10 lead to different phosphorylation of the β_7 tail and distinct talin and kindlin-3 binding patterns, resulting in different integrin conformations and unique affinities for different ligands. This study provides a novel concept for keeping the tissue specificity of lymphocyte homing.

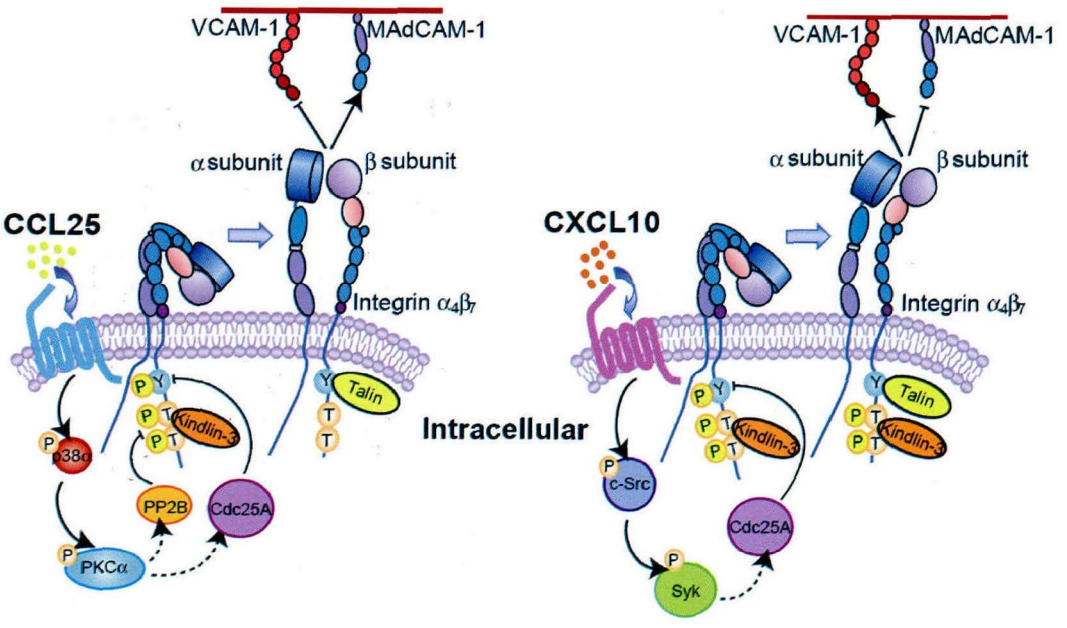

Figure Schematic of integrin ligand specificity switch by distinct chemokine signaling.