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The transition of leukocyte-function-associated antigen-1 (LFA-1), expressed on T cells, from an inactive into an activated state depends on the presence of extracellular Mg^{2+} and/or Ca^{2+} ions. We investigated the Ca^{2+} occupancy of LFA-1, reported by an antibody (NKI-L16) that recognizes a Ca^{2+} dependent epitope on LFA-1. We found that Ca^{2+} can be bound by LFA-1 with different affinities (weak or strong). LFA-1 on resting T cells shows weak binding of Ca^{2+}, whereas LFA-1 expressed on activated T cells shows strong binding of Ca^{2+}. In addition we observed that stable binding of Ca^{2+} to LFA-1 is associated with cluster formation of LFA-1 on the cell surface, thereby facilitating the interaction with its ligand. In contrast, if Ca^{2+} is only weakly bound, T cells exhibit a dispersed LFA-1 distribution, and hardly respond to stimuli known to activate LFA-1. Of all divalent cations, only Sr^{2+} can replace Ca^{2+} to form the L16 epitope, and to induce LFA-1 cluster formation. Ca^{2+} binding, and clustering of LFA-1 on the cell surface does not change upon activation of LFA-1 by PMA. We furthermore observed that activation of LFA-1 by certain activating anti-LFA-1 antibodies induces the L16 expression, which is associated with a transition of weak binding of Ca^{2+} into strong binding of Ca^{2+} by LFA-1, and an increase in LFA-1 avidity.

These data indicate that high affinity Ca^{2+} binding to LFA-1, as reported by NKI-L16 binding, induces a clustering of LFA-1 on the cell surface, and enhances the avidity of LFA-1 - ligand interaction.