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Structural alterations of leukocyte integrin, LFA-1

The mechanism through which adhesiveness of lymphocyte function-associated antigen-1 (LFA-1) is the consequence of highly coordinated structural rearrangements within both α and β subunits yet, atomic details of LFA-1 conformations remain to be investigated. Here we determined the crystal structures of the LFA-1 headpiece that shows coordinations of cations in the closed conformation. The external ligand binding (αI) domain provides striking inter domain flexibility, which potentially plays a pivotal role for greater accessibility in ligand recognition. Loops at the αI and β-propeller interface for the αL and αX differ in length, orientation and post-translational modifications. Moreover we also characterize in atomic details of how a shape-shifting pathway of the β2 I-domain regulates its affinity for the internal ligand, which occurs in a different order than in β1, β3 and β6 integrins. Small angle X-ray scattering (SAXS), negative stain electron microscopy (EM) and adhesion assays here show that LFA-1 activation requires headpiece opening event. Mn2+, universal integrin activator together with the high-affinity ICAM-1 ectodomain was examined for the effect on the equilibrium between the open and closed LFA-1 headpiece conformations. Mn2+, relative to the Mg2+ shifted the equilibrium toward the open conformation. Addition of ICAM-1 substantially stabilized the open headpiece. The observed headpiece opening upon addition of Mn2+ and ICAM-1 is consistent with our previous structural studies and headpiece-opening model. Furthermore, our adhesion assays revealed that an activating and inhibiting βI mutations stabilized the open/extended and bent/closed integrin states, respectively, which provides a structural mechanism into a leukocyte adhesion deficiency (LAD-I) mutation.

Biography

Mehmet Sen has completed his PhD from the University of Houston, Department of Biology and Biochemistry with Glen Legge and Postdoctoral studies from Harvard Medical School, Department of Biological Chemistry and Molecular Pharmacology with Timothy Alan Springer. His research interests lie in the structural and functional basis of receptor/ligand interactions, which are relevant to human health and disease. Structural studies by proten NMR spectroscopy, X-ray Crystallogaraphy and Electron Miscroscopyare complemented by functional approaches using molecular biology and protein engineering to dissect structural information, design proteins/peptides/small molecules with modified specificities and activities and ultimately contributes to the development of biologics with therapeutic potential.

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