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An internal ligand-bound, metastable state of a leukocyte integrin, $\alpha_X\beta_2$

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The β_2 integrins, which are expressed only on leukocytes, must be activated rapidly to restrict integrin-dependent firm adhesion and emigration of leukocytes from the bloodstream only to sites where cues for inflammation or homing are locally displayed. All β_2 integrin subunits contain αI domains that bind ligand. Here, we describe two β_2 integrin structures: a cocked, metastable state of the leukocyte integrin $\alpha_X\beta_2$ ectodomain that primes it for rapid conformational change, and reveals how allostery is relayed to activate the αI domain, and a closed state of the leukocyte integrin $\alpha_L\beta_2$ headpiece.

The $\alpha_X\beta_2$ crystal structure reveals the $\alpha_X\beta_2$ ectodomainin a bent conformation; however, its ligand-binding $\alpha_X\alpha$I domain is in a high affinity, open conformation. Compared to the closed conformation, much of the αI α7-helix unwinds, loses contact with the αI domain, and reshapes to form an internal ligand that binds to a hydrophobic and metal ion-containing pocket at the interface with the $\alpha_X\beta$-propeller and $\beta_2\beta$I domains. An analogous pocket binds external ligand in integrins that lack αI domains.

In comparison of the the β2 subunits of the cocked $\alpha_X\beta_2$ and the closed $\alpha_L\beta_2$ structures, βI domain undergoes unexpected conformational change which reveals ratchet-like changes in positions of conserved hydrophobic residues located in the both N- and C-terminals of the α1-helix, despite absence of change in the neighboring βI domain α7-helix, which pistons in integrin headpiece opening. Mutations of these residues demonstrate a key role for ratchet residues in stabilizing active and inactive β_2 integrin states

Comparisons to other integrins suggest that the cocked state is a specialization of the β_2 integrin subunit. My two structures together with mutational analysis demonstrate the metastability of the cocked state, and suggest that it potentially catalyze rapid equilibrium between bent-closed, extended-closed, and extended-open states for rapid upregulation of leukocyte adhesiveness in β_2 integrins.

Biography

Mehmet Sen has completed his PhD from theUniversity of Houston, Department of Biology and Biochemistry with Glen Legge, M.D., Ph.D., and postdoctoral studies from Harvard Medical School, Department of Biological Chemistry and Molecular Pharmacology with Timothy Alan Springer, Ph.D.He is currently establishing his lab at the University of Houston. His research interests lie in the structural and functional basis of receptor/ligand interactions, which are relevant to human health and disease.

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