In Guidebook to the Extracellular Matrix, Anchor, and Adhesion Proteins
Second Edition, Edited by Thomas Kréis and Ronald Vale
1999

LFA-1

LFA-1 (lymphocyte function associated-1) is an adhesion receptor on leukocytes that is a member of the integrin family.[1] LFA-1 was originally identified by monoclonal antibodies that inhibit T lymphocyte mediated antigen-specific-killing.[2–4] LFA-1 participates in a wide variety of cell adhesion interactions of leukocytes by binding intercellular adhesion molecules[5,6] and provides an important model for regulation of adhesion molecule function through changes in receptor activity.[7]

Synonyms

CD11a/CD18, integrin $\alpha L\beta 2$.

Protein properties

The α subunit of LFA-1 (CD11a, integrin αL) is a type 1 transmembrane glycoprotein of 180 000 Da. The β

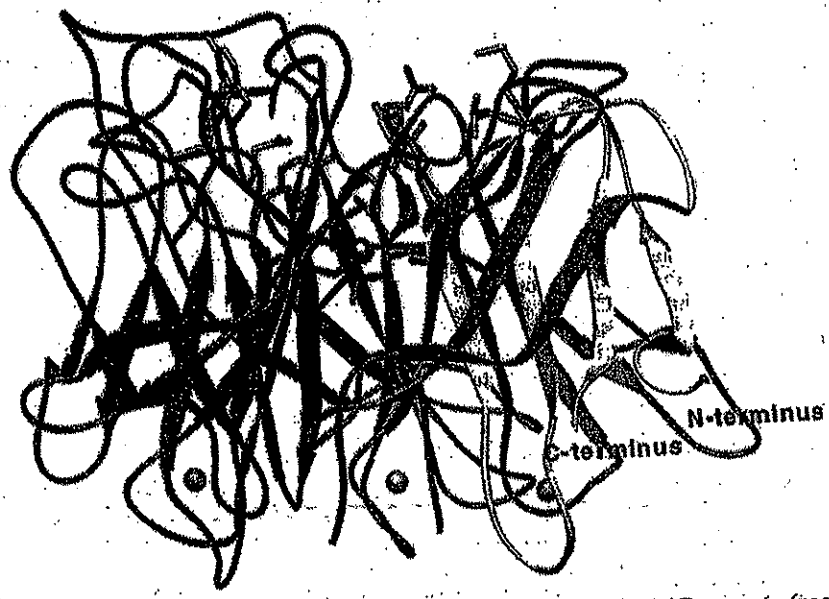

Figure 2. Model of the β-propeller domain of the integrin $\alpha 4$ subunit. The seven FG-GAP repeats (residues 1–452) are predicted to fold up into a β-propeller domain with seven anti-parallel β-sheets. The ribbon diagram shows each sheet in a different tint. Three Ca^{2+} ions shown as spheres are bound to loops on the bottom of the domain. Ligands are predicted to bind to the upper surface. From T. A. Springer (1997) *Proc. Natl Acad. Sci. USA*, **94**, 65–72.

the membrane. Many of the disulfide bonds in the α and β subunit have been determined for the integrin platelet glycoprotein IIbIIIa (αIIbβ3).[53,54] Many of the disulfides are conserved and are likely to form similarly in LFA-1.

The LFA-1 I domain has been characterized functionally in terms of ICAM-1 binding.[55] The I domain binds ICAM-1 with a k_d of ~150 μM. This is similar to the k_d for binding of ICAM-1 to the low affinity form of LFA-1.[25] These data suggest that the I domain interaction with ICAM-1 provides the low affinity interaction of intact LFA-1 with ICAM-1. The interaction of an isolated I domain with ICAM-1 mediates rolling adhesion in flow.[55] This indicates an off-rate of > 1 s^{-1} and strain resistance of the bond. The ability of the I domain to interact transiently with ICAM-1 may account for the role of ICAM-1 in regulation of leukocyte rolling velocities in mice.[18]

A protein that interacts with the cytoplasmic tail of $\beta 2$ is implicated in regulation of LFA-1 avidity. The cytoplasmic tail of the β subunit of LFA-1 is critical for LFA-1 function; when the $\beta 2$ tail is truncated, but a putative salt bridge between the α and β subunit cytoplasmic tails is left intact,[56] the molecule is inactive with respect to inside-out signalling.[57] Furthermore, the single chain transmembrane glycoprotein CD4 with the cytoplasmic domain of $\beta 2$ acts as a dominant negative inhibitor of LFA-1 function in transfected T and B cells.[53] This suggests that there are limiting factors that interact with the $\beta 2$ cytoplasmic domain to augment LFA-1 avidity. Recently, a protein referred to as cytohesin-1 or B2–1 and a related protein have been shown to bind the $\beta 2$ cytoplasmic domain and to activate LFA-1 on a T cell line.[58,59] This protein binds the $\beta 2$ cytoplasmic tail through a sequence with homology to yeast Sec7. This domain turns out to have binding activity for low molecular weight G proteins including ARF-1, a factor involved in protein secretion.[60] Cytohesin-1 also has a pleckstrin homology domain which has been shown to bind phosphatidylinositol 3,4,5-trisphosphate.[61] It is possible that this protein links activation of phosphatidylinositol 3-kinase, a critical signal for integrin activation,[62] to the ligand-induced association of the integrin with the actin cytoskeleton. The protein structure coordinates for the LFA-1 I domain with different cations bound in the MIDAS site are available: PDB accession codes 1ZOP, 1ZOO, 1ZON, and 1LFA.

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