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Bind another day: The LFA-1/ICAM-1 interaction as therapeutic target

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Abstract

Lymphocyte function-associated antigen-1 (LFA-1, CD11a/CD18, $\alpha_L\beta_2$) actively contributes to the molecular interactions responsible for normal functions of the immune system but is also associated to several diseases from various etiology (genetic, bacterial, viral, neoplastic, allergic, and autoimmune). In this way, the interaction between lymphocyte function-associated antigen-1 and its major ligand intercellular adhesion molecule-1 (ICAM-1 or CD54) has been extensively studied, leading to the development of therapeutic antibodies, peptides, and small inhibitory molecules.

Keywords: LFA-1; Disease; Therapeutic; ICAM; Binding

1. Introduction

Cell adhesion receptors are known to play an essential role in multicellular organisms by mediating the direct association of cells with each other and with proteins of the extracellular matrix [1,2]. Among these receptors is lymphocyte function-associated antigen-1 (LFA-1, CD11a/CD18, $\alpha_L\beta_2$) that actively contributes to the molecular interactions responsible for cellular adhesion and migration in the immune system [3–6].

Abbreviations: APC, antigen presenting cell; ICAM, intercellular adhesion molecule; IL, interleukin; JAM, junctional adhesion molecule; LFA-1, lymphocyte function-associated antigen-1; mAb, monoclonal antibody; MTX, methotrexate; NK, natural killer.

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In this context, LFA-1 needs to be tightly regulated, which occurs through conformational changes [7–11] and controlled association with the cytoskeleton [12,13] and various proteins such as its ligands, intercellular adhesion molecules (ICAMs)-1 to -5 and junctional adhesion molecule (JAM)-A.

2. Intercellular and Junctional Adhesion Molecules

2.1. Intercellular adhesion molecule-1

The first counterreceptor identified for LFA-1 was the ICAM-1 (CD54), a member of the immunoglobulin superfamily, providing the first example of an interaction between a member of the integrin family and a member of the immunoglobulin superfamily [14,15]. ICAM-1 is a cell surface glycoprotein that promotes adhesion in immunological and inflammatory reactions [15]. It is constitutively expressed on some tissues and induced on other by inflammatory cytokines such as interleukin-1 or interferon-γ [16]. It could thus be expressed on nonhematopoietic cells such as vascular endothelial cells, thymic and certain other epithelial cells, fibroblasts, and on hematopoietic cells such as tissue macrophages, mitogen-stimulated–T lymphocyte blasts, and germinal center dendritic cells in tonsils, lymph nodes, and Peyer's patches [17]. In these different cell types, ICAM-1 displays Mr heterogeneity with a Mr of 97,000 on fibroblasts, 114,000 on the myelomonocytic cell line U937, and 90,000 on the B lymphoblastoid cell JY [17]. Electron micrographs show that ICAM-1 is a bent rod, 18.7-nm long, suggesting a model in which its 5 immunoglobulin-like domains are oriented head to tail at a small angle to the rod axis. The amino-terminal 2 immunoglobulin-like domains appear to interact conformationally and domain 1 contains the primary site of contact for LFA-1 [18–21].

ICAM-1 has been shown to also bind Mac-1 (CD11b/CD18) [22] through its domain 3 [23]. These findings provide a function for the tandem duplication of immunoglobulin-like domains in ICAM-1 and have implications for other immunoglobulin superfamily members. Mutations at 2 sites in the third domain that destroy consensus sequences for N-linked glycosylation enhance binding to purified Mac-1, and agents that interfere with carbohydrate processing provide evidence that the size of the N-linked oligosaccharide side chains on ICAM-1 affects binding to Mac-1 but not to LFA-1, suggesting that the extent of glycosylation on ICAM-1 may regulate adhesion to LFA-1 or Mac-1 in vivo [23].

ICAM-1 domain 1 residues Glu34 and Gln73 have been identified as critical for binding of LFA-1 as an intact receptor [18], and interaction between isolated I domain and domain 1 of ICAM-1 is inhibited partially by mutation of Glu34 but not by Gln73, which correlates with divalent cation dependence (Mg^{2+} and Mn^{2+} promote binding), indicating that this residue might be in direct contact with the metal ion-dependent adhesion site. On the cell surface, ICAM-1 exists predominantly in a dimeric form that binds more efficiently to LFA-1 than does its monomeric form [24]. However, a single ICAM-1 monomer contains the ''fully competent'' LFA-1–binding surface [25]. The X-ray crystal structure of domains 1 and 2 of ICAM-1 shows that the N-terminal of domain 1 functions as the interface of the dimer formation [26]. Also, the residues that bind to LFA-1 are oriented with the critical Glu34 residue pointing away from each other in the dimer, which is ideal for simultaneous binding of