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# LFA-1 and associated diseases: The dark side of a receptor

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**Abstract**

Lymphocyte function-associated antigen-1 (LFA-1, $\alpha_L\beta_2$, CD11a/CD18) plays a critical role in the complex and well-orchestrated molecular interactions responsible for cell adhesion events required for normal and pathologic functions of the immune system. This review focuses on the diseases from various etiologies (genetic, bacterial, viral, neoplastic, allergic, and autoimmune) that are associated to lymphocyte function-associated antigen-1 with a tremendous impact on human and animal health.


*Keywords:* LFA-1; Disease; Bacteria; Virus; Allergy; Cancer

## 1. Introduction

Lymphocyte function-associated antigen-1 (LFA-1, $\alpha_L\beta_2$, CD11a/CD18) is a protein made of the union of the CD11a and CD18 subunits that each possesses a large extracellular domain but short transmembrane and cytoplasmic regions. The N-terminal parts of both subunits associate to form the integrin headpiece, which contains the ligand-binding site, whereas the C-terminal segments traverse the plasma membrane and mediate interactions with the cytoskeleton and with signaling proteins [1,2].

LFA-1 plays an important role in cell migration and in interactions between T cells and antigen presenting cells (APCs). However, LFA-1 is also associated to several diseases from various etiologies that exhibit a tremendous impact on human and animal health.

*Abbreviations:* CDT, cytolethal distending toxin; ICAM, intercellular adhesion molecule; LAD, leukocyte adhesion deficiency; LFA-1, lymphocyte function-associated antigen-1; LKT, leukotoxin (from *M. haemolytica*); LTX, leukotoxin (from *A. actinomycetemcomitans*); mAb, monoclonal antibody; MIDAS, metal ion dependent adhesion site; TCR, T-cell receptor.

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## 2. Diseases associated to LFA-1

### 2.1. Genetic diseases

#### 2.1.1. Human leukocyte adhesion deficiency

Human leukocyte adhesion deficiency-1 is a genetic disease caused by mutations in the CD18 subunit. As the α and β subunits pair as precursors intracellularly and their transport to the cell surface is CD18 dependent, this leads to the lack of $\beta_2$-integrin cell surface expression and hence, clinically, to recurrent severe bacterial infections and other immune deficiencies [3–10]. Transfection of the $\beta_2$-integrin subunit complementary DNA into B lymphoblastoid cells from leukocyte adhesion deficiency (LAD) patients restored normal levels of LFA-1 to the cell surface as well as adhesion to intercellular adhesion molecule (ICAM)-1 [11]. The disease has been identified in man [3,8,12,13], dog [14,15], and cattle [16] and is viewed primarily as a failure of neutrophils function as (1) they are essential first arrivals at sites of tissue injury, and (2) they rely most heavily on $\beta_2$ integrins because they lack significant levels of other integrins, contrary to monocytes and lymphocytes that are able to express $\alpha_4\beta_1$ when $\beta_2$ integrins are missing [17]. In addition, a CD18 gene–targeted mouse model has been generated, displaying a disease phenotype similar to the human form of the disease [18,19].

Most LAD-1 cases involve single point ''missense'' mutations; most of them are located in the βI domain, a region coded for by exons 5–9, which is highly conserved in all β subunits and that has been modeled to ressemble the ligand-binding αI domain [9,17,20–22]. A second region of mutation of $\beta_2$ subunit centers on the last 2 cysteine-rich repeats coded for by exon 13, a heavily disulphide cross-linked region that is thought to provide structural rigidity for the β subunit and may influence either interdomain movement or the quaternary relationship between integrin subunits [17,22]. Rarer ''nonsense'' mutations can occur leading to an absence of transcription of the CD18 gene, to incorrect mRNA splicing and/or unstable mRNAs, and to truncated and often unstable proteins [8,21,22]. Two variant patients have also been described. The first one proved to be a heterozygote with one nonexpressing allele and the second allele that allowed normal expression but no $\beta_2$ integrin function due to a mutation in the metal ion dependent adhesion site motif [23]. The second variant was suspected to exhibit a mutation in a component of a critical signaling pathway leading to the activation of the $\beta_2$ integrins because no mutation was found in the CD18 gene [13].

Furthermore, a rare autosomal-recessive LAD-2 syndrome exists, which is characterized by a defect in fucosylation of glycoconjugates (such as ligands for the selectin family of adhesion molecules) caused by mutations in the gene for a GDP-fucose transporter of the Golgi [7,24–27]. LAD-2 is thus the first developmental and immune defect that is based on a malfunctioning nucleotide sugar transporter. LAD-2 patients suffer from problems with leukocytes adhesion and trafficking, severe psychomotor and growth retardation and have dysmorphic features, hypotonia, seizures, and strabismus [24,25,28,29].

Recent findings also indicate presence of a third form of LAD, a rare autosomal-recessive disease associated with severe defects in integrin activation by chemokine signals, despite normal ligand binding of leukocyte integrins. LAD III is caused by defects in G protein–coupled receptor–mediated integrin activation [10,30,31] as the small GTPase Rap1,