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Anatomy of the lymphocyte function-associated antigen-1

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Abstract

The β_2-integrin lymphocyte function-associated antigen-1 (LFA-1, $\alpha_L\beta_2$, CD11a/CD18) is made of the association of the CD11a and CD18 subunits that each possesses a large extracellular region and short transmembrane and cytoplasmic parts. A general comparison among species enlights the importance of especially conserved functional regions, as well as their role in folding and heterodimerization. This review also focuses on providing insights into structural aspects that lead to lymphocyte function-associated antigen-1 ability, central to its critical role in the molecular interactions responsible for leukocyte adhesion and migration in the immune system, to modulate dynamically its adhesiveness through avidity (affinity and valency)-based mechanisms.

Keywords: LFA-1; Integrin; Interspecies; Folding; Modulation

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, as the formation of tight associations with neighboring cells is a prerequisite to build cell layers, tissues, and organs [1–3]. Therefore, multicellular organisms express specialized surface receptors (not found in prokaryotes or unicellular eukaryotes) that not only support the structural integrity of cells and tissues, but also contribute to the transduction of signals. These receptors can be subdivided into several groups, most importantly the

Abbreviations: EGF, epidermal growth factor; ICAM, intercellular adhesion molecule; LFA-1, lymphocyte function-associated antigen-1; MIDAS, metal ion-dependent adhesion site; PMA, phorbol myristate acetate; PSI, plexin semaphorin integrin.

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integrins, the cadherins, the immunoglobulin superfamily cell adhesion molecules, and the selectins [3,4].

2. β_2-integrins

The historical perspective of the emergence of integrins has been recently reported [5]: they are transmembrane receptors that play an important role in cellular adhesion even if their recognition as surface receptor family is only dated from 1987 [4,6]. Because they were extensively studied (more than 30,000 articles to date) and appear to be implicated in many biological, physiological, and pathological processes. These cell surface glycoproteins typically function as receptors for extracellular matrix molecules or recognize membrane-bound counter receptors [7]. As heterodimeric receptors, they consist of a 120–180 kDa α subunit and a 90–110 kDa β subunit that are noncovalently associated single-pass transmembrane proteins [2,7,8], both containing a large extracellular domain, a single transmembrane stretch and, with the exception of integrin β_4, a short cytoplasmic tail [3]. Integrins are expressed by all multicellular organisms but their diversity varies widely among species; for example, in mammals, 19 distinct α subunits can combine with 8 β subunits to form 25 receptors, whereas the *Drosophila* and *Caenorhabditis* genomes encode only 5 and 2 integrin α subunits, respectively [8].

In mammals, the 8 β subunits define 8 subfamilies, each one associating with different α subunits. The β_2-integrins, that share the common β_2 subunit CD18 [9], include 4 different heterodimers [2,10,11]: the lymphocyte function-associated antigen-1 (LFA-1), also known as CD11a/CD18 or $\alpha_L\beta_2$, that predominates [12,13]; CD11b/CD18 ($\alpha_M\beta_2$ or Mac-1 or CR3) [14,15]; CD11c/CD18 ($\alpha_X\beta_2$ or P150/95 or CR4) [9,16], and CD11d/CD18 or $\alpha_D\beta_2$ [17,18]. The CD11a chain is expressed on virtually all leukocytes and many leukocyte-derived cells, such as macrophages. T and B lymphocytes normally express only CD11a/CD18 [19], whereas polymorphonuclear neutrophils express CD11b/CD18 at a significant higher level than CD11a/CD18 and CD11c/CD18 [20,21]. The most prominent CD11 chains on activated granulocytes and tissue macrophages are CD11b and CD11c, respectively [19]. Lastly, CD11d/CD18 is abundant on the $CD8^+$ lymphocyte subpopulation in peripheral blood and on macrophages present in specialized tissue compartments [17,18].

The CD11a–d/CD18 heterodimers whose expression is restricted to white blood cells mediate high-affinity adhesion to a variety of cell types that display one or more of the β_2-integrins ligands, intercellular adhesion molecules (intercellular adhesion molecule [ICAM]-1 to -5) [20,22–36]. The adhesion process mediated is a critical step of a wide range of immunological activities, including cytolysis of target cells, cross-interaction and cross-stimulation between lymphocytes, phagocytosis of complement-coated targets, neutrophils clearance from inflamed tissue, and the regulation of leukocyte traffic between the bloodstream and tissues [37–40].

3. LFA-1 (CD11a/CD18, $\alpha_L\beta_2$)

As stated above, LFA-1 (CD11a/CD18, $\alpha_M\beta_2$) is the predominant β_2-integrin. The receptor plays a critical role in the complex and well-orchestrated molecular interactions