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Leukocyte integrins: Role in leukocyte recruitment and as therapeutic targets in inflammatory disease

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ABSTRACT

Infection or sterile inflammation triggers site-specific attraction of leukocytes. Leukocyte recruitment is a process comprising several steps orchestrated by adhesion molecules, chemokines, cytokines and endogenous regulatory molecules. Distinct adhesive interactions between endothelial cells and leukocytes and signaling mechanisms contribute to the temporal and spatial fine-tuning of the leukocyte adhesion cascade. Central players in the leukocyte adhesion cascade include the leukocyte adhesion receptors of the β2-integrin family, such as the αLβ2 and αMβ2 integrins, or of the β1-integrin family, such as the α4β1-integrin. Given the central involvement of leukocyte recruitment in different inflammatory and autoimmune diseases, the leukocyte adhesion cascade in general, and leukocyte integrins in particular, represent key therapeutic targets. In this context, the present review focuses on the role of leukocyte integrins in the leukocyte adhesion cascade. Experimental evidence that has implicated leukocyte integrins as targets in animal models of inflammatory disorders, such as experimental autoimmune encephalomyelitis, psoriasis, inflammatory bone loss and inflammatory bowel disease as well as preclinical and clinical therapeutic applications of antibodies that target leukocyte integrins in various inflammatory disorders are presented. Finally, we review recent findings on endogenous inhibitors that modify leukocyte integrin function, which could emerge as promising therapeutic targets.

Contents

Abbreviations: BBB, Blood–brain barrier; CCL, CC-chemokine ligand; CAMs, cell adhesion molecules; CNS, central nervous system; CD, Crohn's disease; CXCL, CXC-chemokine ligand; DCs, dendritic cells; Del-1, Developmental endothelial locus-1; EGF, epidermal growth factor; EAE, experimental autoimmune encephalomyelitis; GDF, Growth Differentiation Factor; GALT, gut-associated lymphoid tissue; IBD, inflammatory bowel diseases; LAD-I, I leukocyte adhesion deficiency; ICAM-1, intercellular cell-adhesion molecule 1; JAM, Junctional Adhesion Molecule; LFA-1, lymphocyte function-associated antigen 1; Mac-1, macrophage-1 antigen; MAdCAM1, mucosal vascular addressin cell-adhesion molecule 1; MS, multiple sclerosis; PTX-3, pentraxin-3; PECAM-1, platelet/endothelial-cell adhesion molecule 1; PML, progressive multifocal leukoencephalopathy; PSGL-1, P-selectin glycoprotein ligand-1; RAGE, receptor advanced glycation end products; Treg, regulatory T cells; RA, rheumatoid arthritis; TLRs, Toll-like receptors; UC, ulcerative colitis; VCAM, vascular cell-adhesion molecule; VLA, very late antigen.

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1. Introduction

Leukocyte trafficking to sites of injury or infection is tightly regulated by the leukocyte adhesion cascade. The cascade starts with selectin-dependent leukocyte rolling, followed by chemokine-induced leukocyte activation and leukocyte slow rolling, mediated by the collaboration between selectin and integrins and the interactions thereof with their respective ligands. Slow rolling paves the way for the integrin-dependent steps comprising firm leukocyte adhesion/arrest, adhesion strengthening and leukocyte crawling on the endothelium, that finally enable the transendothelial migration of leukocytes mostly through endothelial junctions to the subendothelium (Fig. 1) (Ley et al., 2007; Chavakis, 2012). The present review will focus particularly on the function of integrins in the leukocyte adhesion cascade, endogenous factors and molecular mechanisms contributing to the regulation of integrin activity, animal models, in which the role of integrins in the context of leukocyte recruitment has been studied, as well as therapeutic approaches targeting leukocyte integrins in inflammatory diseases.

2. Integrins; an overview

Integrins are a family of adhesion molecules that exist as transmembrane heterodimers, consisting of one α- and one β-subunit (Moser et al., 2009; Hogg et al., 2011). In mammals, eighteen α and eight β subunits have been described, forming 24 different integrin heterodimers (Hynes, 2002; Herter & Zarbock, 2013).

Activated integrins participate in mediating cell adhesion; the strength of integrin-mediated cell adhesion is defined as integrin avidity (Carman & Springer, 2003). Both integrin affinity and integrin valency contribute to integrin avidity (Carman & Springer, 2003). Affinity represents the strength of the individual bond between a single integrin and its ligand and is regulated by the conformational status of integrin subunits, whereas integrin valency is mediated by the clustering of integrin receptors on the cell surface, thereby bringing together several individual bonds (Carman & Springer, 2003). In the absence of activating signals, integrins have an inactive, bent conformation (Askari et al., 2009). Upon activation by different signals, e.g., deriving from chemokines, or PSGL-1 ligation, integrins undergo major conformational changes, which results in exposure of their ligand-binding site in the extracellular domains (Arnaout et al., 2005; Wegener et al., 2007; Moser et al., 2009; Hogg et al., 2011; Tiwari et al., 2011). Another feature of the process of integrin activation is its strong dependency on the presence of divalent cations, especially Mn^{2+} and Mg^{2+} ions, which control the conformational changes of the integrin molecules (Gailit & Ruoslahti, 1988; reviewed in Arnaout et al., 2002; Dransfield et al., 1992; Tiwari et al., 2011).

In the present review, we will focus on leukocyte integrins, in particular, β2-integrins as well as integrin α4β1 (very late antigen (VLA)-4; CD49d/CD29) and integrin α4β7 (LPAM-1), which play a role in leukocyte recruitment and in inflammatory disorders. The β2-integrins consist of a common β subunit (CD18) that associates with 4 different α subunits. They comprise the αLβ2-integrin (lymphocyte function-associated antigen 1 [LFA-1]; CD11a/CD18) and the αMβ2-integrin (macrophage-1 antigen [Mac-1] also designated complement receptor 3 [CR3]; CD11b/CD18), which are the most crucial β2-integrins for leukocyte recruitment, as well as the αXβ2 (CD11c/CD18; p150,95; CR4) and the αDβ2 (CD11d/CD18) integrins (Moser et al., 2009; Chavakis, 2012). LFA-1 is expressed by neutrophils, monocytes and lymphocytes, whereas Mac-1 is found mainly on neutrophils and monocytes and VLA-4 is expressed on monocytes and T lymphocytes (Chan et al., 2001; Hyun et al., 2009; Moser et al., 2009; Chavakis, 2012). αXβ2 is present on macrophages and dendritic cells (DCs) (O'Doherty et al., 1994; Wu et al., 2009), and αDβ2 is expressed on monocytes/macrophages, especially foam cells, which are macrophages found in atherosclerotic lesions (Van der Vieren et al., 1995).

3. The leukocyte adhesion cascade

The leukocyte adhesion cascade is initiated with leukocyte capture from the blood stream and rolling on the luminal surface of endothelial cells (Kunkel et al., 1998a,b). Rolling serves as a break for circulating leukocytes and is mediated by E-, P- and L-selectins (Kansas, 1996; Kuwano et al., 2010). E-selectin and P-selectin are expressed in endothelial cells. L-selectin is constitutively expressed on most leukocytes (McEver, 2002) and plays a significant role in the migration of naïve and central memory T cells to lymph nodes (von Andrian & Mempel, 2003). Upon inflammation, the abundance of P- and E-selectin on the luminal endothelial cell surface is enhanced. Elevated surface expression of endothelial selectins is mediated either by exocytosis mechanisms in

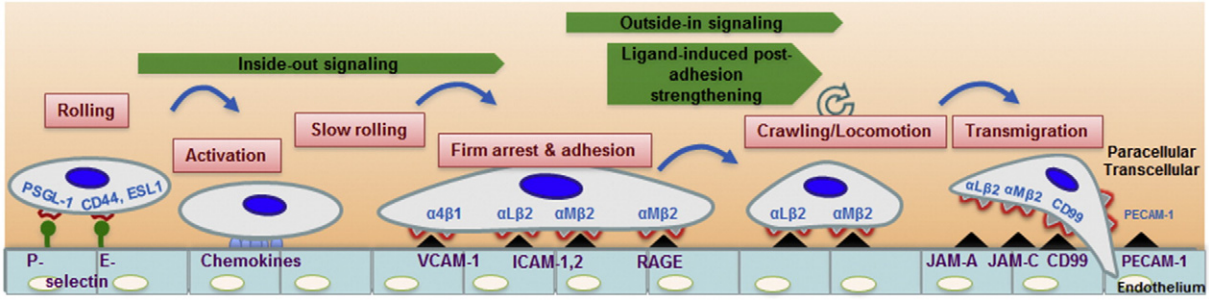

Fig. 1. The multistep model of leukocyte recruitment. The sequential steps of the leukocyte adhesion cascade and the adhesive interactions between endothelium and leukocytes are shown. The cascade is initiated with leukocyte capturing and rolling on the endothelium, followed by chemokine-induced leukocyte activation, slow rolling, firm leukocyte adhesion/arrest, adhesion strengthening induced by integrin ligation, crawling and leukocyte transmigration. Essential molecular players involved in the adhesive processes include: selectins and their glycoprotein ligands, chemokines and their receptors, integrins and adhesion receptors of the immunoglobulin-superfamily. α4- and β2-integrins play a critical role in the course of the cascade. Integrin activation occurs upon chemokine triggered signaling (inside-out signaling) in cooperation with selectin-activated pathways. Activated integrins contribute to slow rolling, firm adhesion, crawling and to transendothelial migration.