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Review

Selectin-mediated leukocyte trafficking during the development of autoimmune disease

Stefano Angiari *

Department of Pathology and Diagnostics, Section of General Pathology, University of Verona, Strada le Grazie 8, 37134 Verona, Italy

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ABSTRACT

Tissue inflammation is a finely regulated process that controls wound healing and allows the clearance of damaged cells, pathogens and irritants. However, excessive or uncontrolled inflammation is detrimental, causing tissue damage and leading to autoimmunity. The recruitment of circulating leukocytes to the target tissue is a key stage in the inflammatory process, and is controlled by a multistep cascade in which adhesive receptors known as selectins mediate initial leukocyte tethering and rolling along vascular surfaces, which is required for their subsequent adhesion and arrest. This review considers the role of selectins and their ligands in the recruitment of circulating leukocytes to peripheral tissues during inflammatory responses that lead to the development of autoimmunity, focusing on data from animal models and clinical trials suggesting that selectins may offer valuable therapeutic targets for the treatment of autoimmune diseases.

Contents

Abbreviations: SLO, secondary lymphoid organ; TNF-α, tumor necrosis factor-α; sLe^x, sialyl Lewis x antigen; Treg, regulatory T cells; ESL-1, E-selectin ligand-1; MPO-EL, myeloperoxidase-E-selectin ligand; TIM-1, T cell immunoglobulin and mucin domain-containing molecule-1; Th, T helper; PNAd, peripheral node addressin; HEV, high endothelial venule; MAdCAM-1, mucosal vascular addressin cell adhesion molecule-1; MS, multiple sclerosis; CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; RR-MS, relapsing–remitting multiple sclerosis; CLA, cutaneous lymphocyte antigen; AD, atopic dermatitis; LP, lamina propria; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; DSS, dextran sodium sulfate; FucT-VII, fucosyltransferase-VII; SAMP, senescence-accelerated prone mouse; T1D, type 1 diabetes; NOD, non-obese diabetic; RA, rheumatoid arthritis; SLE, systemic lupus erythematous; SSc, systemic sclerosis.

* Corresponding author. Tel.: +39 045 8027551; fax: +39 045 8027127.
E-mail address: stefano.angiari@univr.it.

1. Introduction

The homing of immune cells to secondary lymphoid organs (SLOs) and their recruitment into peripheral tissues are necessary for immune surveillance and are key events during the mounting and effector phases of inflammatory responses [1,2]. In both cases, circulating leukocytes interact under flow conditions with specialized vascular endothelia expressing a specific combination of cell adhesion molecules and chemoattractants that allow defined subsets of leukocytes to be recruited to the surrounding tissue [3,4]. This interaction between leukocytes and the vessel wall, promoting their transmigration into the tissue, is

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a complex multistep process comprising the phases of tethering (capture), rolling, activation, arrest and crawling of leukocytes on the vascular bed [4]. Among several families of adhesive receptors controlling interactions between leukocytes and the endothelium, selectins and their ligands mediate the primary capture and rolling of circulating leukocytes under both homeostatic and inflammatory conditions [5,6]. This step is necessary for leukocytes to detect and bind chemoattractants on the vessel wall that activate integrins and induce firm arrest, even though selectin–ligand interaction can directly induce intracellular signals that increase the affinity of integrins for their ligands [4,7].

Selectins are Ca^{2+}-dependent (C-type) lectins that recognize specific carbohydrate modifications on mucin-like glycoproteins [6,8]. The selectin family has three members, P-selectin, L-selectin and E-selectin, which comprise an N-terminal carbohydrate-recognition domain, an epidermal growth factor-like domain and a variable number of short consensus repeats, a transmembrane region and a C-terminal intracellular tail [5,8]. P-selectin is stored in the Weibel–Palade bodies of endothelial cells and in platelet α-granules, but is also constitutively expressed on the surface of some vascular endothelia (e.g., in the lung and choroid plexus). E-selectin is found on skin endothelial cells under steady-state conditions, but its expression can be induced on most endothelial cells by inflammatory stimuli such as tumor necrosis factor-α (TNF-α). Uniquely, L-selectin is constitutively expressed on the surface of most leukocytes, but not on endothelial cells [5,8].

Selectins play an important role in the interaction between circulating leukocytes and the vessel wall, and are therefore known to be involved in the development of inflammatory responses. However, individual selectins modulate leukocyte capture and rolling on different vascular beds, and they also bind specific ligands that are not always shared among the three selectins. This review highlights the importance of individual selectin–ligand interactions for the trafficking of specific leukocyte subsets to peripheral tissues, and discusses the importance of these interactions during the development of autoimmune diseases.

2. Selectins and their ligands: mediators of primary leukocyte adhesion on the vascular bed

Selectins are promiscuous molecules that can bind multiple glycoproteins by interacting with certain post-translational carbohydrate modifications, and distinct selectin ligands differentially control the interactions between particular leukocyte subsets and specific selectins. Most of the known selectin ligands need to display a peculiar glycan epitope, known as the sialyl Lewis x (sLe^x) tetrasaccharide, in which *N*-acetylglucosamine and galactose residues on core-2-*O*-linked glycans or *N*-linked carbohydrate chains are decorated with fucose and sialic acid [9]. In some cases, selectins may also recognize sulfated tyrosine residues for high-affinity binding to ligands [6,9,10]. However, selectin ligands do not always need to display the sLe^x epitope on their N-terminal domain for efficient binding [6,10]. The main selectin ligand is P-selectin glycoprotein ligand-1 (PSGL-1), a mucin-like protein expressed by all circulating leukocytes [11] that can mediate leukocyte capture and rolling on all three selectins [12–16]. PSGL-1 was initially described as the main rolling receptor for selectins expressed on neutrophils [13,14,16], but several studies have revealed the ability of this ligand to also control monocyte [17–19] and activated effector T cell [15,20–24] rolling on P-selectin and E-selectin under flow conditions. Furthermore, gamma–delta and regulatory T (Treg) cells can also use PSGL-1 to roll on both P-selectin and E-selectin in vitro [25–28], and PSGL-1 supports dendritic cell rolling on endothelial selectins and mediates their capture on activated platelets under flow [29–32]. PSGL-1 also controls basophil and eosinophil adhesion on P-selectin and mast cell rolling on P-selectin and E-selectin in vitro [33–35]. Finally, the interaction between PSGL-1 and P-selectin facilitates the capture and rolling of natural killer cells on activated platelets [36], confirming a broad role for this mucin in leukocyte rolling.

Several other more specialized selectin ligands have been identified and they are principally involved in leukocyte rolling on E-selectin. The CD44 glycoprotein mediates the rolling of neutrophils and activated T cells on E-selectin [37–39], whereas mucin CD43 is involved in effector T cell rolling [40,41]. CD43 expressed on neutrophils can also bind E-selectin, but whether this influences their rolling and trafficking is still unclear [42–44]. Another E-selectin ligand that plays a role in leukocyte rolling is E-selectin ligand-1 (ESL-1), which was shown to stabilize neutrophil rolling on E-selectin under flow conditions [37]. Finally, a variant of the enzyme myeloperoxidase (MPO) known as MPO-E-selectin ligand (MPO-EL) was recently described as a novel inducible E-selectin ligand on myeloid cells with a putative role in their recirculation [45].

Although rolling on E-selectin normally requires the cooperation of different receptors, few P-selectin ligands other than PSGL-1 play a significant role in immune cell adhesion. Mucin CD24 is expressed on myeloid cells, where it acts as a ligand for endothelial selectins [46] and mediates the rolling of some cancer cell lines on both P-selectin and E-selectin [47,48], but a role in myeloid cell rolling and trafficking has not been reported. Similarly, the CD34 family member endoglycan, which is expressed by T cells, B lymphocytes and monocytes, was initially reported as an L-selectin ligand [49] but was recently shown to support rolling on endothelial P-selectin and E-selectin [50]. However, its role in immune cell trafficking in vivo is currently unclear. Most recently, T cell immunoglobulin and mucin domain-containing molecule-1 (TIM-1) was identified as a P-selectin ligand involved in leukocyte rolling and trafficking in inflamed tissues [27]. The concurrent presence of PSGL-1 and TIM-1 was shown specifically to control the capture and rolling of pro-inflammatory T helper 1 (Th1) and Th17 cells on P-selectin, and their recruitment in inflamed tissues, with no role in the rolling and migration of naïve T cells, Th2 cells and Treg cells [27]. PSGL-1 and TIM-1 are so the only P-selectin ligands expressed by leukocytes with a clear role in their trafficking under homeostatic or inflammatory conditions.

Whereas endothelial P-selectin and E-selectin are required for leukocyte trafficking during inflammation, L-selectin is expressed on leukocytes and controls the homing of $CD4^+$ and $CD8^+$ T cells, B lymphocytes and monocytes to SLOs [1,5,19,51]. L-selectin binds to ligands of the peripheral node addressin (PNAd) family expressed by high endothelial venules (HEVs), but can also interact with PSGL-1 to support the secondary capture of circulating immune cells by leukocytes that have already adhered to the activated vascular endothelium, increasing their recruitment in inflamed tissues and potentiating the inflammatory immune response [16,52–56]. L-selectin also binds to mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1), which is constitutively expressed on HEVs in gut-associated lymphoid tissue and endothelial cells in the intestinal lamina propria [57,58]. In some models of chronic inflammation, L-selectin ligands such as PNAd can be expressed by the vascular endothelium [5,59,60], suggesting a potential additional role for L-selectin in immune cell trafficking to inflamed tissues.

3. Selectin–ligand interactions controlling immune cell trafficking during autoimmunity

Selectins and their ligands control leukocyte attachment and rolling on the vascular bed, and are therefore involved in the pathogenesis of inflammatory and autoimmune diseases. In this section, the importance of selectin-mediated leukocyte trafficking in several autoimmune conditions is comprehensively reviewed (Fig. 1).

3.1. Multiple sclerosis

Multiple sclerosis (MS) is a chronic and disabling autoimmune inflammatory demyelinating disease of the central nervous system (CNS) affecting mostly the young adult population. MS is characterized by the perivascular infiltration of inflammatory leukocytes in the CNS white matter, which causes myelin sheet destruction, neuronal death