Published in final edited form as:
Expert Opin Ther Targets. 2007 November ; 11(11): 1473–1491. doi:10.1517/14728222.11.11.1473.

Targeting selectins and selectin ligands in inflammation and cancer

Steven R Barthel, **Jacyln D Gavino**, **Leyla Descheny**, and **Charles J Dimitroff**†
Harvard Skin Disease Research Center, Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA

Abstract

Inflammation and cancer metastasis are associated with extravasation of leukocytes or tumor cells from blood into tissue. Such movement is believed to follow a coordinated and sequential molecular cascade initiated, in part, by the three members of the selectin family of carbohydrate-binding proteins: E-selectin (CD62E), L-selectin (CD62L) and P-selectin (CD62P). E-selectin is particularly noteworthy in disease by virtue of its expression on activated endothelium and on bone-skin microvascular linings and for its role in cell rolling, cell signaling and chemotaxis. E-selectin, along with L- or P-selectin, mediates cell tethering and rolling interactions through the recognition of sialo-fucosylated Lewis carbohydrates expressed on structurally diverse protein-lipid ligands on circulating leukocytes or tumor cells. Major advances in understanding the role of E-selectin in inflammation and cancer have been advanced by experiments assaying E-selectin-mediated rolling of leukocytes and tumor cells under hydrodynamic shear flow, by clinical models of E-selectin-dependent inflammation, by mice deficient in E-selectin and by mice deficient in glycosyltransferases that regulate the binding activity of E-selectin ligands. Here, the authors elaborate on how E-selectin and its ligands may facilitate leukocyte or tumor cell recruitment in inflammatory and metastatic settings. Antagonists that target cellular interactions with E-selectin and other members of the selectin family, including neutralizing monoclonal antibodies, competitive ligand inhibitors or metabolic carbohydrate mimetics, exemplify a growing arsenal of potentially effective therapeutics in controlling inflammation and the metastatic behavior of cancer.

Keywords

adhesion molecule; cancer; cutaneous lymphocyte-associated antigen; fucosyltransferase; hematopoietic cell E- and L-selectin ligand; inflammation; metastasis; sialyl Lewis X/A

1. Introduction

Movement of leukocytes from the circulation to infected or diseased tissue is an important component of both adaptive and innate immune responses [1,2]. Such recruitment is facilitated by a dynamic and coordinated multi-step paradigm that is initiated by the versatile family of carbohydrate binding proteins called selectins and transitions to the family of heterodimeric adhesion molecules called integrins [3-6]. Recently, a new class of proteins called junctional adhesion molecules (JAMs), belonging to the immunoglobulin superfamily, have been implicated as additional mediators of leukocyte transmigration. JAMs are expressed at endothelial intercellular junctions, where they are well-positioned to strategically promote

†Author for correspondence, Harvard Skin Disease Research Center, Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Harvard Institutes of Medicine, Room 669, 77 Avenue Louis Pasteur, Boston, MA 02115, USA, Tel: +1 617 525 5693; Fax: +1 617 525 5571; E-mail: cdimitroff@rics.bwh.harvard.edu

cellular diapedesis via heterotypic and homotypic binding interactions with other JAMs or integrins expressed on migrating leukocytes [7]. Identified nearly two decades ago, selectins expressed on postcapillary vessel linings mediate low-affinity binding interactions with ligands on leukocytes; integrins on rolling leukocytes become activated in response to cytokine stimulation leading to firm arrest of leukocytes on adhesive ligands. Leukocyte transmigration through the endothelial barrier is mediated by allosteric structural rearrangements of integrins in response to chemoattractants. The dynamic on/off bond rates between selectins and respective ligands, expressed on leukocytes, causes cells to torque and roll in response to the hydrodynamic shear flow in the vasculature. Platelet (P)-selectin (CD62P) stored constitutively within Weibel-Palade bodies of endothelial cells may be recruited to the cell surface within minutes, following stimulation with inflammatory mediators, including thrombin, leukotrienes, or histamine; expression may be enhanced on platelets following secretion by α-granules in response to activation [4]. Endothelial (E)-selectin (CD62E) is synthesized *de novo* by endothelial cells in response to IL-1, lipopolysaccharide, TNF-α, or G-CSF and is, therefore, detectable either after or concurrently with P-selectin to augment leukocyte recruitment [4,8]. Leukocyte (L)-selectin (CD62L), concentrated on the tips of microvilli of most leukocytes, promotes trafficking through binding interactions with carbohydrate ligands on high endothelial venules in lymph nodes or on activated endothelium at sites of inflammation [4]. Although selectins are often viewed as benign yet potent adhesion molecules for steering leukocytes into tissues to resolve infections and heal wounds, it is becoming clearer that selectins may play a detrimental role in inflammation and cancer [9,10]. In chronic or acute inflammatory pathologies, including asthma [11,12], psoriasis [13,14] or arthritis [15], aberrant homing of leukocytes to affected tissues, facilitated by selectins may result in exacerbation of symptoms. Even more recently, selectins have been implicated in the progression of cancer. In fact, several types of tumor cells express functional ligands of selectins and contact selectins expressed on blood vessel walls [16-18]. In other words, tumor cells might harness and exploit the selectin-dependent mechanisms used by migrating leukocytes to metastasize in a process that may operationally resemble leukocyte trafficking, conceptually referred to as 'leukocyte mimicry' [16,18]. To this end, the study of the role of selectins in leukocyte and tumor cell extravasation merits particular attention in understanding the pathophysiology of inflammation and cancer.

2. Topology of selectins

Tethering and rolling of leukocytes is mediated by the family of adhesive lectins (from the latin *legere*, meaning *to select*) called selectins. Cell rolling may also occur through interactions of integrin α4β1 (CD49d/29,VLA-4) with endothelial-expressed vascular cell adhesion molecule 1 (VCAM-1, CD106) to facilitate slowing of selectin-initiated rolling cells and promotion of firm adhesion [19]. The selectins are a family of calcium-dependent, type I transmembrane glycoproteins [20]. Three members cloned almost simultaneously in 1989 comprise the selectin family: E-selectin, P-selectin and L-selectin. They share a similar topology consisting of an N-terminal lectin-like domain, an epidermal growth factor (EGF)-like domain, a variable number of consensus repeats (CRs), a single transmembrane domain and a short cytoplasmic tail [9]. The function and specificity of each selectin in relation to a particular ligand appears to be regulated predominantly by three physicochemical parameters: the length of the CRs of the selectin, the unique structure of the N-terminal lectin-like domain of the selectin and the particular post-translational carbohydrate modification displayed on the ligand that is recognized by the selectin [4,21]. Residues of the EGF domain are involved, to at least some extent, in selectin binding and selectin ligand specificity [22-26]. Recognition of selectins is facilitated by the length and number of CR repeats, which extend the selectin beyond the glycocalyx (*glykos* = sweet, *calyx* = cup), the dense coating of negatively charged glycoproteins, proteoglycans, glycosaminoglycans and associated plasma proteins that

enshroud and cloak the endothelium [27]. Therefore, the structural features of selectins may conceivably be exploited in the rational design of selectin antagonists in disease.

3. Selectins and their ligands

E-selectin, formerly known as ELAM-1, is a heavily glycosylated transmembrane protein. If calculated purely from the sequence, the relative molecular weight of E-selectin is 64 kDa but has been observed in the range of 107 - 115 kDa, depending on the nature and extent of glycosylation [28]. E-selectin, recognizes several diverse and structurally distinct glycoconjugates on various hematopoietic and carcinomatous cells in affinity or binding assays. These ligands may include cutaneous lymphocyte-associated antigen (CLA; a distinct glycoform of P-selectin glycoprotein ligand-1 [PSGL-1]) [29-31], L-selectin [32,33], E-selectin ligand-1 [34], CD43 [35,36], hematopoietic cell E- and L-selectin ligand (HCELL; a specialized glycoform of CD44) [37], β2 integrins [38], and glycolipids [39]. Recently, death receptor-3 (DR3) expressed on colon carcinoma cells has been identified as a new E-selectin ligand [40]. Of these ligands, PSGL-1, the 240 kDa sialomucin disulfide-linked homo dimer, is the most extensively characterized at the molecular, cellular and functional level [20]. Such detailed characterization may be explained by the realization that PSGL-1 is the most important ligand for L-selectin or P-selectin [9]. If appropriately glycosylated, PSGL-1 may bind E-selectin, the only known selectin ligand capable of binding all three selectins [30]. In binding assays performed *in vitro*, radioiodinated PSGL-1 purified from membranes of human neutrophils binds with at least 50-fold lower affinity to immobilized recombinant E-selectin than P-selectin [29]. In this respect, E-selectin is special among selectins by virtue of its preference for ligands other than, and in addition to, PSGL-1. In fact, many ligands of E-selectin are not even identified [41,42].

The consequences of sulfation of PSGL-1 and antibodies that target PSGL-1 serve only to accentuate further the special binding character of E-selectin in relation to other selectin members. More specifically, recognition of PSGL-1 by E-selectin is insensitive to sulfation of PSGL-1, whereas recognition by L-selectin or P-selectin is particularly sensitive, indicating that E-selectin recognizes an epitope of PSGL-1 that is distinct from that recognized by L-selectin or P-selectin [43-45]. In agreement with such differences in selectin recognition by PSGL-1, the KPL-1 antibody, which recognizes the YEYLDYD tyrosine sulfation motif in residues 5 - 11 near the N terminus of propeptide-cleaved human PSGL-1 (46 - 52 of non-cleaved PSGL-1) [43] and the PL-1 antibody, which binds the LPETE non-tyrosine sulfated sequence contained within residues 8 - 21 of propeptide-cleaved PSGL-1 (49 - 62 of non-cleaved PSGL-1) [46], block binding of P-selectin [43,47,48] or L-selectin [43,49], but are less inhibitory of E-selectin [43,48,50]. PL2 antibody, which recognizes an epitope further away from the N-terminus than KPL-1 or PL1 within residues 147 - 194 of propeptide-cleaved PSGL-1 (188 - 235 of non-cleaved PSGL-1), has no effect on binding E- or P-selectin [46]. Mouse and human E-selectin share high sequence similitary in the lectin-like domain and EGF-like domain [9]. In fact, mouse E-selectin mimics human E-selectin in that it too is refractory to inhibition by antibodies that target the N terminus of PSGL-1 and block P-selectin binding, including 2PH1 or 4RA10 [51-53]. The 2PH1 antibody raised against an N-terminal peptide of mouse PSGL-1 and the 4RA10 antibody generated against recombinant mouse PSGL-1 recognize epitopes within amino acids 1 - 9 of propeptide-cleaved PSGL-1 (42 - 60 of uncleaved PSGL-1) [51,53]. This region overlaps the KPL-1 and PL-1 recognition sites. In total, these findings support a scenario by which E-selectin is mostly resistant to inhibition by anti-PSGL-1 antibodies. Sulfated residues near the N-terminus of PSGL-1 are involved in binding L- and P-selectin, and may play less of a role in binding E-selectin. Thus, therapeutics that target the interaction between PSGL-1 and E-selectin should be designed to overcome such resistance to inhibition.

4. Glycosyltransferases associated with biosynthesis of selectin carbohydrate-binding determinants

Selectins exhibit a preference for ligands modified with particular carbohydrate motifs. These ligands include protein or lipid scaffolds bearing sialyl Lewis X (sLe^X or CD15s) or sialyl Lewis A (sLe^a) [39,54-56]. The sLe^X and sLe^a carbohydrates are found at the terminus of O-glycans (mucins), N-glycans or neolactosphingolipids expressed on the surface of leukocytes or tumor cells [57]. sLe^X and sLe^a are linked to these glycoconjugates in the Golgi compartment by sequential action of *N*-acetylglucosaminyl-, galactosyl-, sialyl- and fucosyltransferases [58]. Figures depicting the role of these enzymes in Lewis carbohydrate synthesis can be found in the following references [59-62]. The terminal step in the synthesis of sLe^X or sLe^a involves the transfer of fucose to *N*-acetylglucosamine. The fucosylation is facilitated by members of the fucosyltransferase (FT) family; enzymes that harness the exergonic free energy released in hydrolysis of the phosphoester bond of GDP-fucose to drive fucose transfer reactions [63]. In the case of Le^X or sLe^X, the α1,3 glycosidic bond linking fucose to *N*-acetylglucosamine may be catalyzed by FT3-FT7 or FT9 [63]. FT3 and FT5 exhibit dual specificity such that these FTs may generate, additionally, the α1,4-glycosidic bond of sLe^a [63]. The role of each FT in Lewis carbohydrate antigen synthesis has largely been elucidated by *in vitro* assays with synthetic oligosaccharide substrates. Of the nine FT enzymes encoded in the human genome, FT3, FT4 and FT7 have been studied most extensively. In COS cells, most CHO cell lines and nearly all human leukemic cell lines studied, transfection with FT3 generates Le^X, sLe^X, Le^a or sLe^a, FT4 yields high levels of Le^X and lower levels of sLe^X, whereas FT7 produces high levels of sLe^X, but not Le^X [64-68]. Cytokines, such as G-CSF, IL-4 and IL-12, may regulate the expression level of glycosyltransferases that may, in turn, modulate expression of selectin-binding glycoforms of PSGL-1 and CD44 on distinct cellular subsets [69-71]. A consequence of such elevation may be generation of more sialyl Lewis antigen that enables leukocytes and tumor cells to better recognize selectins. In such diseases, sLe^X expressed on leukocytes is a potent mediator of selectin-binding in inflammatory settings and both sLe^X and sLe^a, expressed on various types of circulating cancer cells, may initiate attachment to endothelial linings of distant tissues. Thus, glycosyltrans-ferases synthesizing sialyl Lewis antigens may be exploited as potential therapeutic targets in dampening inflammation or tumor metastasis.

A comparison of the carbohydrate structures recognized by E-selectin in relation to L- or P-selectin may be a particularly important consideration for therapeutic intervention. Specifically, the enzyme that facilitates core 2 carbohydrate branching, β1,6-glucosaminyltransferase-I (C2GlcNAcT-I), is required for PSGL-1 recognition of L-selectin and P-selectin but not E-selectin, indicating that core 2 branches may be less important in recognition by PSGL-1 of E-selectin in comparison to L-selectin or P-selectin [59,72]. In CHO cells, transfection of cDNA encoding C2GlcNAcT-I dramatically enhances binding of P-selectin by PSGL-1, but has no effect on binding of E-selectin [73]. Such a finding may be significant, given that ligands of E-selectin, including glycolipids that express sLe^X or sLe^a, lack the core 2 structure. In other words, even in the absence of PSGL-1, CHO cells expressing E-selectin are competent to form stable rolling interactions on sLe^X presented on glycosphingolipids adsorbed to monolayers of phosphatidylcholine and cholesterol [74]. Indeed, sustained cell rolling on E-selectin may occur independently of PSGL-1 or core 2 carbohydrates and depend even more on FT3, FT4, FT7 and sialyltransferases of the ST3Gal family [75,76]. In support of this notion, transfection of cDNA encoding FT7 induces binding to E-selectin in virtually all lymphoid cell lines studied [20,77,78], indicating that FT7 is regulator of E-selectin binding. That recognition of E-selectin, but not P-selectin, is particularly dependent on FT7 and is consistent with the observation that T cells require much higher levels of FT7 for the generation of ligands of E-selectin compared with P-selectin [77,79]. Transfection of FT4, a potent fucosylator of glycolipids [80], confers E-selectin binding in

some, but not all cell lines [20,77]. Therefore, these findings merit further interest in novel therapeutics that target E-selectin ligands in addition to PSGL-1, namely glycolipids or several other counterreceptors.

5. Expression of E-selectin: E-selectin ligands correlate with disease

E-selectin may be of potential therapeutic value in inflammatory diseases and cancer by virtue of its unique temporal and spatial expression profile. E-selectin is expressed constitutively on skin and bone microvessels [81,82] andmay also be found in the vasculature of bronchial mucosa [83]. Chronic expression of E-selectin has been reported in skin microvessels at sites of local inflammation in delayed hypersensitivity reactions [84-86]. In most other organs and depending on endothelial cell type, expression of E-selectin can be induced by *de novo* synthesis on endothelium, peaking within 2 - 6 h in response to inflammatory stimuli, including IL-1, lipopolysaccharide or TNF-α and subsiding to basal levels within 10 - 24 h [20,87,88]. Abrogation of E-selectin expression is facilitated by the short half-life of E-selectin mRNA [89] and involves slow internalization from the endothelial surface to lysosomes for degradation [90]. Several global transcriptional regulators, including NF-κB and AP-1, regulate E-selectin gene expression [91-93]. The expression can be blocked by inhibitors of transcription, translation or cytokines, including actinomycin D, cyclohexamide or transforming growth factor-β (TGF-β), respectively [94,95]. The fact that expression of E-selectin can be chronic in the skin and transient in other organs may suggest a versatile role for E-selectin in both chronic and acute inflammatory diseases. Constitutive expression of E-selectin on bone marrow endothelium may indicate a further role in metastasis of breast and prostate tumor cells that selectively home to bone marrow [96-98].

Humans expressing a polymorphism of the E-selectin gene with serine replaced by arginine at position 128 exhibit early onset, severity and frequency of atherosclerotic disease [22,23]. The polymorphism, which occurs in the EGF domain of E-selectin, profoundly alters E-selectin ligand binding by enabling E-selectin to abnormally recognize heparin or the non-fucosylated sialyl lactosamine precursor of sLe^X or sLe^a [22,23]. A similar alteration in binding has been reported with an R84A mutation in E-selectin, which causes enhanced adhesion [99]. Humans with the rare and inherited genetic syndrome, leukocyte adhesion deficiency II (LAD II), express a defect in the GDP-fucose transporter and lack α1,3 fucosylated carbohydrate ligands that are needed to recognize selectins [100]. Leukocytes of such individuals display diminished selectin-binding and recruitment to infected foci, leading to severe chronic and recurrent infection [101]. In mice, a similar hypofucosylated state of selectin ligands may result from inactivation of the GDP-transporter gene and lead to impaired leukocyte adhesion and rolling on selectins [102]. Mice null for the fucose-generating FX enzyme, which supplie ~ 90% of cellular fucose [103,104], exhibit immunodeficiencies or impairments in leukocyte recruitment that are reminiscent of LAD II [103,105-107] and which may be ameliorated by oral administration of L-fucose [104]. Mice deficient in FT4 and/or FT7 display defects in leukocyte rolling and/or emigration of leukocytes to inflammatory sites [108-110]. Clearly, appropriately fucosylated selectin ligands, namely Lewis carbohydrate antigens, are critical in leukocyte recognition of selectins and in leukocyte trafficking to inflamed tissues.

6. E-selectin signaling may promote leukocyte diapedesis

E-selectin natively expressed on endothelial cells may transduce signals by an ‘outside-in’ mechanism in response to ligation. In essence, the phosphorylation state of serine or tyrosine residues in the cytoplasmic tail of endothelial E-selectin can be regulated either by engagement of E-selectin by counter-receptors expressed on leukocytes, crosslinking by anti-E-selectin antibodies or with beads coated with PSGL-1 [111-113]. Phosphorylation of the cytoplasmic tail of E-selectin may cause physical interactions with cytoskeletal proteins [114] or changes

in the shape of endothelial cells [115]. Such rearrangements may even enhance the permeability of the endothelial barrier through the acquisition of stress fibers and by facilitating cellular diapedesis [116]. Ligation of E-selectin by L-selectin, PSGL-1 and/or CD44 expressed on leukocytes can induce activation, upregulation and clustering of αMβ2 (CD11b/CD18, Mac-1) on the leukocyte surface [117-121]. The crosstalk between E-selectin and integrins, involving phosphorylation of p38 and p42/44 MAPKs, may facilitate movement of neutrophils and other leukocytes through the endothelium to inflammatory foci [119-121].

7. Role of E-selectin: E-selectin ligand interactions in inflammation

Inflammation is associated with aberrant trafficking and/or hyperactive functioning of effector immune cells. Inappropriate immune activity has been implicated in the pathogenesis of a number of inflammatory disorders, including those of the respiratory system, such as asthma, allergic rhinitis and chronic obstructive pulmonary disorder and diseases of the skin, including psoriasis, atopic and allergic contact dermatitis, lichen planus and graft-versus-host disease [122-124]. Below, the authors outline the role of E-selectin in several such diseases.

7.1 Expression of E-selectin is enhanced in inflammatory disease

Expression levels of soluble E-selectin in the circulation or E-selectin expressed on endothelial surfaces often correlate with the duration and/or severity of inflammatory diseases, suggesting a role for E-selectin in disease etiology or progression. Soluble forms of E-selectin have been detected in supernatants of cytokine-activated endothelial cells [125] and are elevated in serum of subjects with bronchial asthma [126,127], eczema [128], psoriasis [129-131], atopic and allergic dermatitis [131-135], Kawasaki disease [136], Guillain-Barre syndrome [137] or Graves disease [138] compared with normal subjects. Soluble E-selectin is deficient in mice null for PSGL-1, suggesting a role for PSGL-1 in solubilization [139]. It may be that soluble E-selectin exacerbates symptoms in inflammatory disease through activation of β2 integrins, modulation of leukocyte movement and/or augmentation in release of reactive oxygen species through stimulation of the respiratory burst [140]. Intravenous administration of the CDP850 humanized anti-E-selectin antibody reduces levels of soluble E-selectin in plasma and of E-selectin expressed on lesional psoriatic skin in patients with moderate-to-severe chronic plaque psoriasis [141]. However, treatment with CDP850 does not significantly reduce the psoriasis area and severity index (PASI), calling into question the notion of a therapeutic strategy aimed solely at targeting only E-selectin and not additional pathways for leukocyte adherence. Elevation in native E-selectin has been observed further in skin biopsies of atopic patients, following application of house dust mite antigen [142], on dermal vasculature in response to LPS in an acute or delayed cutaneous inflammatory model involving rhesus monkeys [143], and on endothelium or submucosa of bronchial biopsies of allergic or intrinsic asthmatics [144,145]. Therefore, expression and upregulation of E-selectin is directly correlated with inflammation.

7.2 Role of E-selectin: E-selectin ligand interactions in the trafficking of effector leukocytes to inflamed tissues

E-selectin supports homing of immune cells in a variety of inflammatory settings. The role of E-selectin in leukocyte extravasation has been affirmed by studies in mice deficient in E-selectin or injected with anti-E-selectin antibodies [146-149]. In skin, E-selectin is critical for the recruitment of leukocytes associated with damaged skin [150], chronic inflammation [151-154] or autoimmunity [155]. In fact, the E-selectin ligand mediating leukocyte homing to skin, CLA, has been designated the ‘skin-homing receptor’. Ligands of E-selectin are prevalently expressed on specific subsets of lymphocytes, granulocytes and hematopoietic progenitor cells [31,37,156-166] and, to a greater extent, on leukocytes associated with cutaneous inflammation [109,167-169]. Of these ligands, PSGL-1, along with CD43, are

viewed as the predominant skin-homing receptor on T cells. PSGL-1-bearing sLe^X on T cells is designated as CLA by virtue of reactivity with anti-sLe^X monoclonal antibody HECA-452 [31,170]. Reactivity to HECA-452 on circulating T cells corresponds with skin-homing behavior [31,109,158,159,167-176]. Expression of FT7, a generator of sLe^X, is upregulated in $CD4^+$ cells recruited to the skin of dinitrofluorobenzene-sensitized mice [177]. FT7 can be induced in $CD4^+$ cells by TGF-β1 [178], by T_H 1 priming with IL-12 [71] or by antigen stimulation [177], indicating that glycosyltransferases are important regulators of T-cell recruitment. Indeed, deficiencies in glycosyltransferases result in a dampening of leukocyte recruitment and/or inflammation, indicating that carbohydrate ligands of E-, P- and L-selectin may be potential anti-inflammatory targets [78,108,109,179-182]. In mice deficient in FT7, contact hypersensitivity is reduced, whereas mice doubly deficient in FT4 and FT7 are virtually devoid of cutaneous inflammatory activity [109,180].

In respiratory syndromes, E-selectin supports recruitment of T cells to inflamed lungs [183, 184]. In E- and P-selectin double knockout mice, T-cell accumulation is reduced in a model of antigen-induced allergic pneumonitis [185]. Targeted deletion of E-selectin in mice results in reduced airway hyper-reactivity, peribronchial inflammation and eosinophil accumulation in response to challenge with cockroach allergen [186]. Mice lacking both E- and P-selectin show smaller atherosclerotic lesions compared with mice lacking either selectin alone [187, 188]. Therefore, E-selectin and its related selectin family members play a prominent role in numerous inflammatory pathologies.

8. Role of E-selectin: E-selectin ligand interactions in tumor metastasis

How tumor cells metastasize is not fully understood. It may be that the diameter of cancer cells, relative to the microvas-culature, causes cell arrest merely by size restriction [189]. Alternatively, specific interactions between receptors of tumor cells and ligands expressed on microvascular cells might explain the seeding and distinct tropism of cancer cell subsets. That tumor cells mimic and exploit similar mechanisms used by leukocytes in extravasation, through adhesive interactions with the vasculature, is substantiated by a number of recent studies [18, 190]. For one, several types of metastatic tumor cells isolated from subjects with cancer of the colon [40,74,116,191-211], prostate [212], breast [213-216], pancreas [217] or lung [218, 219] have acquired the capacity to roll and adhere to endothelial monolayers natively expressing E-selectin. In fact, prostate tumor cells, which selectively home to bone [96,220], adhere more avidly to human bone marrow endothelium in comparison with adhesion to endothelial cells derived from other organs, supporting the notion that adhesion is a key step in the metastatic cascade [221-224]. Indeed, highly metastatic colorectal tumor cells often adhere to endothelial cells with greater avidity than their less metastatic variants originating from the same tumor [225]. The notion that E-selectin expressed on activated endothelium can facilitate tumor cell seeding is validated by mice overexpressing E-selectin in the liver that causes a redirection of the metastasis from the lung to the liver [226]. Second, *de novo* expression of Lewis carbohydrates is often more pronounced on the surface of metastatic tumor cells in comparison with less aggressive neoplasms and is associated with poor prognosis. In other words, tumor cells of epithelial origin that are highly metastatic often appear to replicate the adhesive and surface phenotype of migrating leukocytes by upregulating protein or carbohydrate ligands of selectins, namely sLe^X or sLe^a [57,206,209,227-230]. Prostate tumor cells that are highly metastatic, express elevated surface levels of PSGL-1 [231] and HECA-452 antigen [212,232] compared with less aggressive or localized normal prostate cells. An additional example is HCELL, an E-selectin ligand that is prominently expressed on colon carcinoma cells [191,193]. Third, E-selectin expression is often enhanced on the surface of endothelial vessels at the site proximal to or directly at tumor metastases, indicating a synergy by which E-selectin expression may work in concert with E-selectin ligand expression to promote tumor cell extravasation [233-237]. Some tumor cells are even known to induce

expression of E-selectin on vascular endothelium through direct or indirect release of IL-1β [238]. Stable transfection of antisense sequences directed at FT3 into human colon carcinoma cells can inhibit expression of sLe^X, sLe^a, block tumor proliferation and tumorigenicity, and prevent colonization of the liver, further underscoring the important role of selectins and their respective ligands in cancer progression [198,199]. Overexpression of FT7 or its corresponding Lewis carbohydrate products is sufficient to cause colonization of the lung by lung adenocarcinoma cells [218,219]. There is growing awareness that platelets and leukocytes may potentiate and even enhance the hematogenous dissemination of cancer cells, suggesting a link between inflammation and cancer progression. Indeed, the tumor microenvironment often contains infiltrates of platelets, macrophages, dendritic cells and lymphocytes [239]. These cells may be critical sources of pro-inflammatory cytokines, including TGF-β, TNF-α, IL-1β and IL-6, all of which may promote the upregulation of selectin expression on the vascular wall and synergize with chemokines, such as IL-8, secreted by tumor cells. In addition, mucins released in soluble form or expressed on colon carcinoma cells can bind platelets or leukocytes through recognition of P- or L-selectin, respectively [204]. The binding may cause leukocyte agglutination, concomitant with enhanced adhesion of leukocytes to E-selectin, as well as stimulate platelet aggregation and endothelial binding [204]. Leukocytes and platelets attached to the inflamed vascular wall may, therefore, act as a bridge between the endothelium and tumor cells to enhance hematogenous spread into tissues. Further evidence linking inflammation and cancer progression is that platelets bind tumor cells via P-selectin, which may shield their recognition by immune cells [240,241].

Following E-selectin engagement, less is known about the mechanisms facilitating tumor cell diapedesis. There is evidence that E-selectin may promote movement through the endothelial wall by several mechanisms that may resemble the operations used by emigrating leukocytes. For example, T84 colon cancer cells adhere and spread on E-selectin-expressing endothelium and form pseudopodia that contact endothelial junctions [200]. The morphologic changes in cell shape are accompanied by phosphorylation of tyrosine residues within the tumor cell, rearrangements of actin and release of gelatinases involved in degradation of extracellular matrix. Adhesion of HT-29 colon cancer cells to E-selectin expressed on human umbilical vein endothelial cells activates stress-activated protein kinase-2 and causes tumor cell migration [196]. Similarly, soluble E-selectin is a chemotactic signal for T84 cells [200]. Several clinical studies have suggested that soluble levels of E-selectin in the serum of subjects with various cancers reflect tumor progression [242-248], whereas other studies have found no correlation [249-251]. In any case, the study of how E-selectin promotes tumor cell extravasation merits additional study.

9. Conclusions

The role of E-selectin and its ligands in inflammation and cancer has been advanced by studies involving E-selectin structure, expression and signaling, by identification of ligands for E-selectin, and by knowledge of the enzymatic machinery that regulates E-selectin ligand activity. E-selectin elicits cell tethering and rolling through recognition of several diverse glycans expressed on circulating lymphocytes, granulocytes, hematopoietic progenitor cells and carcinomatous cells. E-selectin binds ligands, including CLA, HCELL, CD43, E-selectin ligand-1 and sLe^X-bearing glycolipids, on leukocytes and tumor cells in a manner dependent on the catalytic activity of α2,3 sialyl- and α1,3fucosyltransferases. Constitutive expression of E-selectin in postcapillary venules of skin, bronchi and bone, and induction of E-selectin on vessels in inflamed tissues implicates E-selectin in inflammatory settings and in tissue-specific metastasis of carcinomas. Tumor cells can induce E-selectin expression on vascular walls through the release of cytokines that stimuate E-selectin gene transcription. Such a scenario is evidenced by the elevation in soluble levels of E-selectin in serum of patients with inflammatory diseases and malignancies. Soluble E-selectin may even be chemotactic for

migrating tumor cells. Signaling by E-selectin may promote leukocyte or tumor cell diapedesis through endothelial vessels. In the case of leukocytes, adhesion to E-selectin can activate αMβ2 and the respiratory burst via 'outside-in' signaling, induce phosphorylation of tyrosine residues in the cytoplasmic tail of E-selectin and augment the permeability of the vasculature. In the case of tumor cells, adhesion to E-selectin may also promote formation of pseudopodia, changes in cell morphology and release of matrix-degrading enzymes. Polymorphisms of E-selectin or genetic diseases in human or mouse, involving glycosyltransferases that regulate selectin ligand activity, including LAD II, affirm a role for selectins in inflammation and cancer. Indeed, levels of *N*-acetylneuraminic and fucose-bearing Lewis carbohydrate antigens, such as sLe^X or sLe^a, are elevated on the surfaces of migrating leukocytes and metastatic tumor cells. Selectin expression in the vicinity of the tumor microenvironment may be enhanced by pro-inflammatory cytokines secreted by infiltrates of immune cells, indicating a link between inflammation and cancer progression. P-selectin expressed by platelets and L-selectin on leukocytes may bind selectin ligands on tumor cells or mucin fragments released into the circulation by tumor cells, acting as a bridge between the tumor cells and the inflamed vasculature. To this end, targeting selectin-selectin ligand interactions represents a promising therapeutic endeavor to selectively interfere with the pathophysiology of inflammatory diseases and cancer.

10. Therapeutics targeting selectins and selectin ligands

The specificity of selectins for selectin ligands affords the opportunity to target these molecular entities to effectively alter the progression of inflammatory responses and cancer metastasis. As depicted in Figure 1, several modes of putative intervention have been developed and are being evaluated as anti-inflammatory/metastatic agents at present. Results from clinical trials involving therapeutics targeting selectin interactions, may be found in the following references [10,252].

A recombinant soluble form of PSGL-1 may competitively inhibit the interaction between PSGL-1 expressed natively on circulating leukocytes and tumor cells and E- and P-selectin expressed on endothelial blood vessels. Recombinant PSGL-1-immunogloblulin (PSGL-1-Ig) can be sulfated and glycosylated if expressed in cell lines prior to purification [253]. This bioactive, soluble form of PSGL-1 consists of the first 47 N-terminal amino acids of human PSGL-1 linked to the Fc portion of human IgG1 [254]. Recombinant PSGL-1-Ig directly inhibits rolling of murine leukocytes mediated by all three selectins in assays involving intravital microscopy [255] and prevents inflammation in a number of animal models [256-260]. Interestingly, the concentration of PSGL-1-Ig that dampens overall inflammation is 30-fold lower than the amount that inhibits selectin-mediated rolling [255], suggesting that PSGL-1-Ig may inhibit inflammation by mechanisms other than and/or in addition to leukocyte rolling. PSGL-1 is similar to chemokine receptors in its requirement for post-translational sulfation and glycosylation [261]. In fact, PSGL-1-Ig binds the CXC chemokine, KC [255], and has been shown recently to bind the CC chemokine, CCL21 [262]. Titration of chemokines with PSGL-1-Ig inhibits chemotaxis of mouse neutrophils in response to KC [255]. Production of PSGL-1-Ig for clinical trials is cost-prohibitive due to its production in mammalian cells co-transfected with FT and C2GlcNAcT-I. The high production costs, in combination with inadequate efficacy, may help explain why clinical trials have been discontinued [301].

Inhibitors targeting the α1,3- and α1,4-FTsthatgenerate sLe^X and sLe^a, respectively, are in development. Most such inhibitors are modeled after the structures of acceptor, donor and transition-state analogs of FT reaction components [263,264]. At least in theory, FT antagonists should be efficacious, given that mice with targeted deletions of FT7 exhibit a near absence in functional ligands of E- and P-selectin and display reduced leukocyte rolling in postcapillary venules [180]. Unfortunately, chemical synthesis of such small-molecule inhibitors has been

hampered by a number of technologic, pedagogic, or design issues. First, it is essential that FT antagonists penetrate two membranes: cellular and Golgi. Second, there is no available structural information about FTs, as evidenced by the absence of X-ray crystallographic or nuclear magnetic resonance models. Third, FTs have a low affinity for GDP-fucose and acceptor substrates, calling into question the practicality in designing inhibitors that are of sufficient affinity and potency [265-267]. At least one molecule, compound 24, was identified from a library of 85 different GDP-triazole compounds screened against FT6 [268]. Compound 24 is a non-competitive inhibitor of the *N*-acetyllactosamine acceptor molecule with potency in the nanomolar range [268,269]. Targeting only one FT alone may be insufficient in controlling disease as observed in one patient carrying a missense mutation of the FT7 gene. In this individual, FT4 compensated for the inactivity of FT7 in the synthesis of active selectin ligands [270]. In such a scenario, the use of compound 24 may be inadequate because it does not appear to potently inhibit FTs other than FT6, namely FT3 and FT5, both of which share high sequence identity with FT6 [268]. To this end, the authors and other co-workers have circumvented the problem of FT compensation with a novel fluorinated analog of *N*-acetylglucosamine: peracetylated-4-fluorinated-D-glucosamine (4-F-GlcNAc). 4-F-GlcNAc is a metabolic inhibitor of lactosamine (Galβ1,4GlcNAc) biosynthesis, which involves a series of steps that precedes and is even independent of FTs. The hydroxyl that is normally present in the 4′ position of GlcNAc has been replaced by fluorine in the 4-F-GlcNAc mimetic. Fluorine leads to a block in the addition of galactose and results in premature termination of lactosamine elongation and absence of sLe^X [176]. Radiolabeled 4-F-GlcNAc is incorporated directly into lactosamine natively expressed on purified T cells and abrogates expression of sLe^X [176]. 4-F-GlcNAc does not incorporate into some E-selectin ligands, including glycolipids, which may explain why E-selectin is a less sensitive target than P-selectin in response to 4-F-GlcNAc intervention [271]. Nonetheless, 4-F-GlcNAc is effective at inhibiting allergic contact hypersensitivity responses dependent on T cell E- and P-selectin ligand expression in mice [272].

Pan selectin competitive inhibitors, including sLe^X oligosaccharides [273], sLe^X mimetics [274], multivalent sLe^X ligands [275] or diverse molecular weight species of heparin have been developed. A few such carbohydrates have shown some success in the treatment of psoriasis (Bimosiamose or TBC-1269 and Efomycine M) or asthma (Bimosiamose) [276-278]. Unfractionated heparin and low molecular weight heparins have been shown to inhibit lung metastasis in experimental mouse models, presumably by inhibiting tumor cell binding of L- and P-selectin [279,280]. An alternative approach to competitive inhibition, is to divert native glycosylation away from the lactosamine backbone of Lewis antigens with carbohydrate decoys that compete with the backbone as substrates for FTs. Thus, structural derivatives of Galβ1,3GlcNAc or Galβ1,4GlcNAc added exogenously to cells can efficiently enter the Golgi compartment and downregulate the synthesis of sLe^X -bearing ligands [281-283]. These studies underscore several promising modes of novel intervention in the modulation of selectin or selectin ligand activity in inflammation and cancer.

11. Expert opinion

The diverse repertoire of competitive, glycometabolic or glycomimetic inhibitors that target selectins and selectin ligands represent the ensemble of potential regimens for treating inflammation and tumor metastasis. Traditional therapies have consisted of immunosuppressive or immuno-modulatory agents that may have undesirable side effects. Cyclosporin, systemic glucocorticoids or antiproliferative agents (methotrexate and 5-fluoro-uracil), although effective in dampening the immunologic machinery responsible for elicitation of the disease, may cause renal, gastrointestinal, neurologic, hematologic or immunologic toxicities. Agents that inhibit cellular proliferation of tumor cells may cause unwanted toxicity and genetic mutations in several tissues that rapidly divide, elevating the risk of secondary

neoplasia. As such, the authors believe that glyco-mimetics or glycosylation modifiers that target selectin-selectin ligand interactions could offer a novel paradigm in the treatment of inflammatory diseases and of tumor progression and metastasis. These small molecules provide the capacity to subtly modulate structural carbohydrate features, resulting in potent suppression of pathologic phenotypes with less toxicity than existing treatment modalities. In essence, pharmacologic strategies that exploit the selective nature of selectin-binding determinants on effector leukocytes and tumor cells may improve treatment of skin, lung or gut-associated inflammation or tumor metastasis without significantly altering leukocyte trafficking patterns to non-inflamed tissues or causing significant toxicity to other tissues.

It is becoming increasingly clear that effective therapeutics targeting selectin-selectin ligand interactions must take advantage of their functional overlap in lectin-binding activity and structural similarities of carbohydrate ligand determinants. Inhibition of E-selectin alone often results in little or no effect on leukocyte recruitment in animal models of inflammation, involving treatment with TNF-α or IL-1 [284], but may show efficacy in other such models [285]. The differences in therapeutic outcome could result from divergent expression of selectins in different species. Indeed, whereas P- and E-selectin transcripts are elevated in the mouse in response to stimulation with TNF-α or oncostatin M, expression of the corresponding genes in the primate is much more specialized, in as much as TNF-α does not induce P-selectin expression in baboons [286]. Such differences necessitate careful interpretation of models of inflammation and cancer, and should caution extrapolating the role of selectins from mice to humans. With regard to the initiation of circulating leukocyte/tumor cell attachment to the vascular wall, E-selectin functionally overlaps with P-selectin [287]. In other words, E- and P-selectin are coexpressed in most inflamed tissues. P-selectin may be transported to the plasma membrane within minutes from Weibel-Palade bodies of endothelial cells or α-granules of platelets following inflammatory stimuli, suggesting that P-selectin may function even earlier and overlap with E-selectin function in the inflammatory response [288,289]. Second, E-and P-selectin both recognize PSGL-1, suggesting at least some redundancy in ligand recognition [30]. In fact, E-selectin-deficient mice show no defect in leukocyte recruitment to peritoneum unless P-selectin is blocked simultaneously [287]. The consequence of selectin redundancy and functional overlap should be considered when interpreting clinical studies that have found little efficacy with neutralizing antibodies targeting E-selectin [141] or when devising treatment regimens where E-selectin has a clear role, including airway inflammation [290], lung injury [291] or sites of chronic inflammation [84,86,292-294]. Metastasis of colon tumor cells is inhibited in mice deficient in L- or P-selectin compared with wild type, supporting a role for all three selectin family members in disease [295]. To this end, therapies that simultaneously block activities of E-, P- and/or L-selectin or their shared ligand, PSGL-1, may prove more efficacious than blocking either selectin alone in controlling inflammatory conditions or the metastasis of circulating tumor cells. Such therapies could be combined and/or complemented with anti-integrin approaches, especially in diseases where cellular recruitment is independent of selectins [296].

Bibliography

1. TOSI MF. Innate immune responses to infection. J. Allergy Clin. Immunol 2005;116(2):241–249. [PubMed: 16083775]
2. SCHON MP, LUDWIG RJ. Lymphocyte trafficking to inflamed skin - molecular mechanisms and implications for therapeutic target molecules. Expert Opin. Ther. Targets 2005;9(2):225–243. [PubMed: 15934912]
3. SPRINGER TA. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. Cell 1994;76(2):301–314. [PubMed: 7507411]
4. KELLY M, HWANG JM, KUBES P. Modulating leukocyte recruitment in inflammation. J. Allergy Clin. Immunol. 2007InPress

5. SIMON SI, GREEN CE. Molecular mechanics and dynamics of leukocyte recruitment during inflammation. Annu. Rev. Biomed. Eng 2005;7:151–185. [PubMed: 16004569]
6. SACKSTEIN R. The lymphocyte homing receptors: gatekeepers of the multistep paradigm. Curr. Opin. Hematol 2005;12(6):444–450. [PubMed: 16217160]
7. WEBER C, FRAEMOHS L, DEJANA E. The role of junctional adhesion molecules in vascular inflammation. Nat. Rev. Immunol 2007;7(6):467–477. [PubMed: 17525755]
8. FUSTE B, MAZZARA R, ESCOLAR G, et al. Granulocyte colony-stimulating factor increases expression of adhesion receptors on endothelial cells through activation of p38 MAPK. Haematologica 2004;89(5):578–585. [PubMed: 15136221]
9. LEY K. The role of selectins in inflammation and disease. Trends Mol. Med 2003;9(6):263–268. [PubMed: 12829015]
10. LUDWIG RJ, SCHON MP, BOEHNCKE WH. P-selectin: a common therapeutic target for cardiovascular disorders, inflammation and tumour metastasis. Expert Opin. Ther. Targets 2007;11 (8):1103–1117. [PubMed: 17665981]
11. ROMANO SJ. Selectin antagonists: therapeutic potential in asthma and COPD. Treat. Respir. Med 2005;4(2):85–94. [PubMed: 15813660]
12. ROMANO SJ, SLEE DH. Targeting selectins for the treatment of respiratory diseases. Curr. Opin. Investig. Drugs 2001;2(7):907–913.
13. SCHON MP, DREWNIOK C, BOEHNCKE WH. Targeting selectin functions in the therapy of psoriasis. Curr. Drug Targets Infl amm. Allergy 2004;3(2):163–168.
14. BOCK D, PHILIPP S, WOLFF G. Therapeutic potential of selectin antagonists in psoriasis. Expert Opin. Investig. Drugs 2006;15(8):963–979.
15. SFIKAKIS PP, MAVRIKAKIS M. Adhesion and lymphocyte costimulatory molecules in systemic rheumatic diseases. Clin. Rheumatol 1999;18(4):317–327. [PubMed: 10468173]
16. WITZ IP. Tumor-microenvironment interactions: the selectin-selectin ligand axis in tumor-endothelium cross talk. Cancer Treat. Res 2006;130:125–140. [PubMed: 16610706]
17. LAFERRIERE J, HOULE F, HUOT J. Regulation of the metastatic process by E-selectin and stress-activated protein kinase-2/p38. Ann. NY Acad. Sci 2002;973:562–572. [PubMed: 12485930]
18. WITZ IP. The involvement of selectins and their ligands in tumor-progression. Immunol. Lett 2006;104(12):89–93. [PubMed: 16368149]
19. BUTCHER EC, PICKER LJ. Lymphocyte homing and homeostasis. Science 1996;272(5258):60–66. [PubMed: 8600538]
20. KANSAS GS. Selectins and their ligands: current concepts and controversies. Blood 1996;88(9): 3259–3287. [PubMed: 8896391]
21. PATEL KD, NOLLERT MU, MCEVER RP. P-selectin must extend a sufficient length from the plasma membrane to mediate rolling of neutrophils. J. Cell Biol 1995;131(6 Part 2):1893–1902. [PubMed: 8557755]
22. WENZEL K, FELIX S, KLEBER FX, et al. E-selectin polymorphism and atherosclerosis: an association study. Hum. Mol. Genet 1994;3(11):1935–1937. [PubMed: 7533025]
23. WENZEL K, HANKE R, SPEER A. Polymorphism in the human E-selectin gene detected by PCR-SSCP. Hum. Genet 1994;94(4):452–453. [PubMed: 7523276]
24. KANSAS GS, SAUNDERS KB, LEY K, et al. A role for the epidermal growth factor-like domain of P-selectin in ligand recognition and cell adhesion. J. Cell Biol 1994;124(4):609–618. [PubMed: 7508943]
25. GIBSON RM, KANSAS GS, TEDDER TF, FURIE B, FURIE BC. Lectin and epidermal growth factor domains of P-selectin at physiologic density are the recognition unit for leukocyte binding. Blood 1995;85(1):151–158. [PubMed: 7528563]
26. LI SH, BURNS DK, RUMBERGER JM, et al. Consensus repeat domains of E-selectin enhance ligand binding. J. Biol. Chem 1994;269(6):4431–4437. [PubMed: 7508442]
27. GOUVERNEUR M, BERG B, NIEUWDORP M, STROES E, VINK H. Vasculoprotective properties of the endothelial glycocalyx: effects of fluid shear stress. J. Intern. Med 2006;259(4):393–400. [PubMed: 16594907]

28. EHRHARDT C, KNEUER C, BAKOWSKY U. Selectins - an emerging target for drug delivery. Adv. Drug Deliv. Rev 2004;56(4):527–549. [PubMed: 14969757]
29. MOORE KL, EATON SF, LYONS DE, et al. The P-selectin glycoprotein ligand from human neutrophils displays sialylated, fucosylated, O-linked poly-*N*-acetyllactosamine. J. Biol. Chem 1994;269(37):23318–23327. [PubMed: 7521878]
30. MOORE KL. Structure and function of P-selectin glycoprotein ligand-1. Leuk. Lymphoma 1998;29 (12):1–15. [PubMed: 9638971]
31. FUHLBRIGGE RC, KIEFFER JD, ARMERDING D, KUPPER TS. Cutaneous lymphocyte antigen is a specialized form of PSGL-1 expressed on skin-homing T cells. Nature 1997;389(6654):978–981. [PubMed: 9353122]
32. PICKER LJ, WARNOCK RA, BURNS AR, et al. The neutrophil selectin LECAM-1 presents carbohydrate ligands to the vascular selectins ELAM-1 and GMP-140. Cell 1991;66(5):921–933. [PubMed: 1716182]
33. ZOLLNER O, LENTER MC, BLANKS JE, et al. L-selectin from human, but not from mouse neutrophils binds directly to E-selectin. J. Cell Biol 1997;136(3):707–716. [PubMed: 9024699]
34. STEEGMAIER M, LEVINOVITZ A, ISENMANN S, et al. The E-selectin-ligand (ESL-1) is a variant of a receptor for fibroblast growth factor. Nature 1995;373(6515):615–620. [PubMed: 7531823]
35. MATSUMOTO M, ATARASHI K, UMEMOTO E, et al. CD43 functions as a ligand for E-selectin on activated T cells. J. Immunol 2005;175(12):8042–8050. [PubMed: 16339541]
36. FUHLBRIGGE RC, KING SL, SACKSTEIN R, KUPPER TS. CD43 is a ligand for E-selectin on CLA^+ human T cells. Blood 2006;107(4):1421–1426. [PubMed: 16269612]
37. DIMITROFF CJ, LEE JY, RAFII S, FUHLBRIGGE RC, SACKSTEIN R. CD44 is a major E-selectin ligand on human hematopoietic progenitor cells. J. Cell Biol 2001;153(6):1277–1286. [PubMed: 11402070]
38. KOTOVUORI P, TONTTI E, PIGOTT R, et al. The vascular E-selectin binds to the leukocyte integrins CD11/CD18. Glycobiology 1993;3(2):131–136. [PubMed: 7683936]
39. ALON R, FEIZI T, YUEN CT, FUHLBRIGGE RC, SPRINGER TA. Glycolipid ligands for selectins support leukocyte tethering and rolling under physiologic flow conditions. J. Immunol 1995;154(10): 5356–5366. [PubMed: 7537307]
40. GOUT S, MORIN C, HOULE F, HUOT J. Death receptor-3, a new E-selectin counter-receptor that confers migration and survival advantages to colon carcinoma cells by triggering p38 and ERK MAPK activation. Cancer Res 2006;66(18):9117–9124. [PubMed: 16982754]
41. JONES WM, WATTS GM, ROBINSON MK, VESTWEBER D, JUTILA MA. Comparison of E-selectin-binding glycoprotein ligands on human lymphocytes, neutrophils, and bovine γδ T cells. J. Immunol 1997;159(7):3574–3583. [PubMed: 9317157]
42. MONTOYA MC, HOLTMANN K, SNAPP KR, et al. Memory B lymphocytes from secondary lymphoid organs interact with E-selectin through a novel glycoprotein ligand. J. Clin. Invest 1999;103 (9):1317–1327. [PubMed: 10225975]
43. SNAPP KR, DING H, ATKINS K, et al. A novel P-selectin glycoprotein ligand-1 monoclonal antibody recognizes an epitope within the tyrosine sulfate motif of human PSGL-1 and blocks recognition of both P- and L-selectin. Blood 1998;91(1):154–164. [PubMed: 9414280]
44. KANAMORI A, KOJIMA N, UCHIMURA K, et al. Distinct sulfation requirements of selectins disclosed using cells that support rolling mediated by all three selectins under shear flow. L-selectin prefers carbohydrate 6-sulfation totyrosine sulfation, whereas P-selectin does not. J. Biol. Chem 2002;277(36):32578–32586. [PubMed: 12068018]
45. RODGERS SD, CAMPHAUSEN RT, HAMMER DA. Tyrosine sulfation enhances but is not required for PSGL-1 rolling adhesion on P-selectin. Biophys. J 2001;81(4):2001–2009. [PubMed: 11566773]
46. LI F, ERICKSON HP, JAMES JA, et al. Visualization of P-selectin glycoprotein ligand-1 as a highly extended molecule and mapping of protein epitopes for monoclonal antibodies. J. Biol. Chem 1996;271(11):6342–6348. [PubMed: 8626430]
47. MOORE KL, PATEL KD, BRUEHL RE, et al. P-selectin glycoprotein ligand-1 mediates rolling of human neutrophils on P-selectin. J. Cell Biol 1995;128(4):661–671. [PubMed: 7532174]

48. PATEL KD, MOORE KL, NOLLERT MU, MCEVER RP. Neutrophils use both shared and distinct mechanisms to adhere to selectins under static and flow conditions. J. Clin. Invest 1995;96(4):1887–1896. [PubMed: 7560080]
49. WALCHECK B, MOORE KL, MCEVER RP, KISHIMOTO TK. Neutrophil-neutrophil interactions under hydrodynamic shear stress involve L-selectin and PSGL-1. A mechanism that amplifies initial leukocyte accumulation of P-selectin *in vitro*. J. Clin. Invest 1996;98(5):1081–1087. [PubMed: 8787668]
50. LIM YC, SNAPP K, KANSAS GS, et al. Important contributions of P-selectin glycoprotein ligand-1-mediated secondary capture to human monocyte adhesion to P-selectin, E-selectin, and TNF-α-activated endothelium under flow *in vitro*. J. Immunol 1998;161(5):2501–2508. [PubMed: 9725249]
51. BORGES E, EYTNER R, MOLL T, et al. The P-selectin glycoprotein ligand-1 is important for recruitment of neutrophils into inflamed mouse peritoneum. Blood 1997;90(5):1934–1942. [PubMed: 9292527]
52. THATTE A, FICARRO S, SNAPP KR, et al. Binding of function-blocking mAbs to mouse and human P-selectin glycoprotein ligand-1 peptides with and without tyrosine sulfation. J. Leuk. Biol 2002;72(3):470–477.
53. FRENETTE PS, DENIS CV, WEISS L, et al. P-Selectin glycoprotein ligand 1 (PSGL-1) is expressed on platelets and can mediate platelet-endothelial interactions *in vivo*. J. Exp. Med 2000;191(8):1413–1422. [PubMed: 10770806]
54. NELSON RM, DOLICH S, ARUFFO A, CECCONI O, BEVILACQUA MP. Higher-affinity oligosaccharide ligands for E-selectin. J. Clin. Invest 1993;91(3):1157–1166. [PubMed: 7680663]
55. BRANDLEY BK, KISO M, ABBAS S, et al. Structure-function studies on selectin carbohydrate ligands. Modifications to fucose, sialic acid and sulphate as a sialic acid replacement. Glycobiology 1993;3(6):633–641. [PubMed: 7510548]
56. KOENIG A, JAIN R, VIG R, et al. Selectin inhibition: synthesis and evaluation of novel sialylated, sulfated and fucosylated oligosaccharides, including the major capping group of GlyCAM-1. Glycobiology 1997;7(1):79–93. [PubMed: 9061367]
57. DUBE DH, BERTOZZI CR. Glycans in cancer and inflammation - potential for therapeutics and diagnostics. Nat. Rev. Drug Discov 2005;4(6):477–488. [PubMed: 15931257]
58. HENNET T. The galactosyltransferase family. Cell Mol. Life Sci 2002;59(7):1081–1095. [PubMed: 12222957]
59. LEY K, KANSAS GS. Selectins in T-cell recruitment to non-lymphoid tissues and sites of inflammation. Nat. Rev. Immunol 2004;4(5):325–335. [PubMed: 15122198]
60. LOWE JB. Glycan-dependent leukocyte adhesion and recruitment in inflammation. Curr. Opin. Cell Biol 2003;15(5):531–538. [PubMed: 14519387]
61. SCHOTTELIUS AJ, HAMANN A, ASADULLAH K. Role of fucosyltransferases in leukocyte trafficking: major impact for cutaneous immunity. Trends Immunol 2003;24(3):101–104. [PubMed: 12615200]
62. LOWE JB. Glycosylation in the control of selectin counter - receptor structure and function. Immunol. Rev 2002;186:19–36. [PubMed: 12234359]
63. DE VRIES T, KNEGTEL RM, HOLMES EH, MACHER BA. Fucosyltransferases: structure/function studies. Glycobiology 2001;11(10):R119–R128.
64. KUKOWSKA-LATALLO JF, LARSEN RD, NAIR RP, LOWE JB. A cloned human cDNA determines expression of a mouse stage-specific embryonic antigen and the Lewis blood group α (1,3/1,4)fucosyltransferase. Genes Dev 1990;4(8):1288–1303. [PubMed: 1977660]
65. GOELZ SE, HESSION C, GOFF D, et al. ELFT: a gene that directs the expression of an ELAM-1 ligand. Cell 1990;63(6):1349–1356. [PubMed: 1702034]
66. GOELZ S, KUMAR R, POTVIN B, et al. Differential expression of an E-selectin ligand (SLex) by two Chinese hamster ovary cell lines transfected with the same α(1,3)-fucosyltransferase gene (ELFT). J. Biol. Chem 1994;269(2):1033–1040. [PubMed: 7507103]
67. KUMAR R, POTVIN B, MULLER WA, STANLEY P. Cloning of a human α(1,3)-fucosyltransferase gene that encodes ELFT but does not confer ELAM-1 recognition on Chinese hamster ovary cell transfectants. J. Biol. Chem 1991;266(32):21777–21783. [PubMed: 1718983]

68. NATSUKA S, GERSTEN KM, ZENITA K, KANNAGI R, LOWE JB. Molecular cloning of a cDNA encoding a novel human leukocyte α-1,3-fucosyltransferase capable of synthesizing the sialyl Lewis X determinant. J. Biol. Chem 1994;269(32):20806. [PubMed: 8051184]
69. DAGIA NM, GADHOUM SZ, KNOBLAUCH CA, et al. G-CSF induces E-selectin ligand expression on human myeloid cells. Nat. Med 2006;12(10):1185–1190. [PubMed: 16980970]
70. BROCKHAUSEN I. The role of galactosyltransferases in cell surface functions and in the immune system. Drug News Perspect 2006;19(7):401–409. [PubMed: 17080203]
71. WAGERS AJ, WATERS CM, STOOLMAN LM, KANSAS GS. Interleukin 12 and interleukin 4 control T cell adhesion to endothelial selectins through opposite effects on α1,3-fucosyltransferase VII gene expression. J. Exp. Med 1998;188(12):2225–2231. [PubMed: 9858509]
72. JAIN RK, PISKORZ CF, HUANG BG, et al. Inhibition of L- and P-selectin by a rationally synthesized novel core 2-like branched structure containing GalNAc-Lewisx and Neu5Acα2 - 3Galβ1 - 3GalNAc sequences. Glycobiology 1998;8(7):707–717. [PubMed: 9621111]
73. KUMAR R, CAMPHAUSEN RT, SULLIVAN FX, CUMMING DA. Core2 β-1,6-*N*-acetylglucosaminyltransferase enzyme activity is critical for P-selectin glycoprotein ligand-1 binding to P-selectin. Blood 1996;88(10):3872–3879. [PubMed: 8916952]
74. BURDICK MM, BOCHNER BS, COLLINS BE, SCHNAAR RL, KONSTANTOPOULOS K. Glycolipids support E-selectin-specific strong cell tethering under flow. Biochem. Biophys. Res. Commun 2001;284(1):42–49. [PubMed: 11374868]
75. SPERANDIO M, THATTE A, FOY D, et al. Severe impairment of leukocyte rolling in venules of core 2 glucosaminyltransferase-deficient mice. Blood 2001;97(12):3812–3819. [PubMed: 11389021]
76. ELLIES LG, SPERANDIO M, UNDERHILL GH, et al. Sialyltransferase specificity in selectin ligand formation. Blood 2002;100(10):3618–3625. [PubMed: 12393657]
77. KNIBBS RN, CRAIG RA, NATSUKA S, et al. The fucosyltransferase FucT-VII regulates E-selectin ligand synthesis in human T cells. J. Cell Biol 1996;133(4):911–920. [PubMed: 8666674]
78. WAGERS AJ, LOWE JB, KANSAS GS. An important role for the α1,3 fucosyltransferase, FucT-VII, in leukocyte adhesion to E-selectin. Blood 1996;88(6):2125–2132. [PubMed: 8822932]
79. KNIBBS RN, CRAIG RA, MALY P, et al. α(1,3)-fucosyltransferase VII-dependent synthesis of P- and E-selectin ligands on cultured T lymphoblasts. J. Immunol 1998;161(11):6305–6315. [PubMed: 9834120]
80. HUANG MC, LASKOWSKA A, VESTWEBER D, WILD MK. The α(1,3)-fucosyltransferase FucT-IV, but not FucT-VII, generates sialyl Lewis X-like epitopes preferentially on glycolipids. J. Biol. Chem 2002;277(49):47786–47795. [PubMed: 12359718]
81. KEELAN ET, LICENCE ST, PETERS AM, BINNS RM, HASKARD DO. Characterization of E-selectin expression *in vivo* with use of a radiolabeled monoclonal antibody. Am. J. Physiol 1994;266 (1 Part 2):H278–H290. [PubMed: 7508207]
82. SCHWEITZER KM, DRAGER AM, VAN DER VALK P, et al. Constitutive expression of E-selectin and vascular cell adhesion molecule-1 on endothelial cells of hematopoietic tissues. Am. J. Pathol 1996;148(1):165–175. [PubMed: 8546203]
83. ROCHE WR, MONTEFORT S, BAKER J, HOLGATE ST. Cell adhesion molecules and the bronchial epithelium. Am. Rev. Respir. Dis 1993;148(6 Part 2):S79–S82. [PubMed: 8256927]
84. COTRAN RS, GIMBRONE MA Jr, BEVILACQUA MP, MENDRICK DL, POBER JS. Induction and detection of a human endothelial activation antigen *in vivo*. J. Exp. Med 1986;164(2):661–666. [PubMed: 3723080]
85. MUNRO JM, POBER JS, COTRAN RS. TNF and interferon-γ induce distinct patterns of endothelial activation and associated leukocyte accumulation in skin of *Papio anubis*. Am. J. Pathol 1989;135 (1):121–133. [PubMed: 2505619]
86. PICKER LJ, KISHIMOTO TK, SMITH CW, WARNOCK RA, BUTCHER EC. ELAM-1 is an adhesion molecule for skin-homing T cells. Nature 1991;349(6312):796–799. [PubMed: 1705666]
87. BEVILACQUA MP, POBER JS, MENDRICK DL, COTRAN RS, GIMBRONE MA Jr. Identification of an inducible endothelial-leukocyte adhesion molecule. Proc. Natl. Acad. Sci. USA 1987;84(24):9238–9242. [PubMed: 2827173]

88. HARALDSEN G, KVALE D, LIEN B, FARSTAD IN, BRANDTZAEG P. Cytokine-regulated expression of E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) in human microvascular endothelial cells. J. Immunol 1996;156(7):2558–2565. [PubMed: 8786319]

89. GHERSA P, HOOFT VAN HUIJSDUIJNEN R, WHELAN J, DELAMARTER JF. Labile proteins play a dual role in the control of endothelial leukocyte adhesion molecule-1 (ELAM-1) gene regulation. J. Biol. Chem 1992;267(27):19226–19232. [PubMed: 1382069]

90. SUBRAMANIAM M, KOEDAM JA, WAGNER DD. Divergent fates of P- and E-selectins after their expression on the plasma membrane. Mol. Biol. Cell 1993;4(8):791–801. [PubMed: 7694691]

91. JENSEN LE, WHITEHEAD AS. ELAM-1/E-selectin promoter contains an inducible AP-1/CREB site and is not NF-κB-specific. Biotechniques 2003;35(1):54–56. 58. [PubMed: 12866405]

92. ISHII H, TAKADA K. Bleomycin induces E-selectin expression in cultured umbilical vein endothelial cells by increasing its mRNA levels through activation of NF-κB/Rel. Toxicol. Appl. Pharmacol 2002;184(2):88–97. [PubMed: 12408953]

93. LOEWE R, PILLINGER M, DE MARTIN R, et al. Dimethylfumarate inhibits TNF-induced CD62E expression in an NF-κB-dependent manner. J. Invest. Dermatol 2001;117(6):1363–1368. [PubMed: 11886496]

94. BEVILACQUA MP, STENGELIN S, GIMBRONE MA JR, SEED B. Endothelial leukocyte adhesion molecule 1: an inducible receptor for neutrophils related to complement regulatory proteins and lectins. Science 1989;243(4895):1160–1165. [PubMed: 2466335]

95. GAMBLE JR, KHEW-GOODALL Y, VADAS MA. Transforming growth factor-β inhibits E-selectin expression on human endothelial cells. J. Immunol 1993;150(10):4494–4503. [PubMed: 7683321]

96. LANGE PH, VESSELLA RL. Mechanisms, hypotheses and questions regarding prostate cancer micrometastases to bone. Cancer Metast. Rev 1998;17(4):331–336.

97. YIN JJ, POLLOCK CB, KELLY K. Mechanisms of cancer metastasis to the bone. Cell Res 2005;15(1):57–62. [PubMed: 15686629]

98. SACKSTEIN R. The bone marrow is akin to skin: HCELL and the biology of hematopoietic stem cell homing. J. Investig. Dermatol. Symp. Proc 2004;9(3):215–223.

99. GRAVES BJ, CROWTHER RL, CHANDRAN C, et al. Insight into E-selectin/ligand interaction from the crystal structure and mutagenesis of the lec/EGF domains. Nature 1994;367(6463):532–538. [PubMed: 7509040]

100. ETZIONI A, FRYDMAN M, POLLACK S, et al. Brief report: recurrent severe infections caused by a novel leukocyte adhesion deficiency. N. Engl. J. Med 1992;327(25):1789–1792. [PubMed: 1279426]

101. VON ANDRIAN UH, BERGER EM, RAMEZANI L, et al. *In vivo* behavior of neutrophils from two patients with distinct inherited leukocyte adhesion deficiency syndromes. J. Clin. Invest 1993;91(6):2893–2897. [PubMed: 7685776]

102. HELLBUSCH CC, SPERANDIO M, FROMMHOLD D, et al. Golgi GDP-fucose transporter-deficient mice mimic congenital disorder of glycosylation IIc/leukocyte adhesion deficiency II. J. Biol. Chem 2007;282(14):10762–10772. [PubMed: 17276979]

103. SMITH PL, MYERS JT, ROGERS CE, et al. Conditional control of selectin ligand expression and global fucosylation events in mice with a targeted mutation at the FX locus. J. Cell Biol 2002;158(4):801–815. [PubMed: 12186857]

104. MARQUARDT T, LUHN K, SRIKRISHNA G, et al. Correction of leukocyte adhesion deficiency type II with oral fucose. Blood 1999;94(12):3976–3985. [PubMed: 10590041]

105. BECKER DJ, LOWE JB. Fucose: biosynthesis and biological function in mammals. Glycobiology 2003;13(7):R41–R53.

106. YAKUBENIA S, WILD MK. Leukocyte adhesion deficiency II. Advances and open questions. FEBS J 2006;273(19):4390–4398. [PubMed: 16956371]

107. BECKER DJ, LOWE JB. Leukocyte adhesion deficiency type II. Biochim. Biophys. Acta 1999;1455(23):193–204. [PubMed: 10571012]

108. WENINGER W, ULFMAN LH, CHENG G, et al. Specialized contributions by α(1,3)-fucosyltransferase-IV and FucT-VII during leukocyte rolling in dermal microvessels. Immunity 2000;12(6):665–676. [PubMed: 10894166]

109. SMITHSON G, ROGERS CE, SMITH PL, et al. FucT-VII is required for T helper 1 and T cytotoxic 1 lymphocyte selectin ligand expression and recruitment in inflammation, and together with FucT-IV regulates naive T cell trafficking to lymph nodes. J. Exp. Med 2001;194(5):601–614. [PubMed: 11535629]

110. HOMEISTER JW, THALL AD, PETRYNIAK B, et al. The α(1,3) fucosyltransferases FucT-IV and FucT-VII exert collaborative control over selectin-dependent leukocyte recruitment and lymphocyte homing. Immunity 2001;15(1):115–126. [PubMed: 11485743]

111. YOSHIDA M, SZENTE BE, KIELY JM, ROSENZWEIG A, GIMBRONE MA Jr. Phosphorylation of the cytoplasmic domain of E-selectin is regulated during leukocyte-endothelial adhesion. J. Immunol 1998;161(2):933–941. [PubMed: 9670972]

112. HU Y, KIELY JM, SZENTE BE, ROSENZWEIG A, GIMBRONE MA Jr. E-selectin-dependent signaling via the mitogen-activated protein kinase pathway in vascular endothelial cells. J. Immunol 2000;165(4):2142–2148. [PubMed: 10925300]

113. HU Y, SZENTE B, KIELY JM, GIMBRONE MA Jr. Molecular events in transmembrane signaling via E-selectin. SHP2 association, adaptor protein complex formation and ERK1/2 activation. J. Biol. Chem 2001;276(51):48549–48553. [PubMed: 11602579]

114. YOSHIDA M, WESTLIN WF, WANG N, et al. Leukocyte adhesion to vascular endothelium induces E-selectin linkage to the actin cytoskeleton. J. Cell Biol 1996;133(2):445–455. [PubMed: 8609175]

115. KAPLANSKI G, FARNARIER C, BENOLIEL AM, et al. A novel role for E- and P-selectins: shape control of endothelial cell monolayers. J. Cell Sci 1994;107(Part 9):2449–2457. [PubMed: 7531200]

116. TREMBLAY PL, AUGER FA, HUOT J. Regulation of transendothelial migration of colon cancer cells by E-selectin-mediated activation of p38 and ERK MAP kinases. Oncogene 2006;25(50): 6563–6573. [PubMed: 16715142]

117. HIDALGO A, PEIRED AJ, WILD MK, VESTWEBER D, FRENETTE PS. Complete identification of E-selectin ligands on neutrophils reveals distinct functions of PSGL-1, ESL-1, and CD44. Immunity 2007;26(4):477–489. [PubMed: 17442598]

118. LO SK, LEE S, RAMOS RA, et al. Endothelial-leukocyte adhesion molecule 1 stimulates the adhesive activity of leukocyte integrin CR3 (CD11b/CD18, Mac-1, αm β2) on human neutrophils. J. Exp. Med 1991;173(6):1493–1500. [PubMed: 1709677]

119. GREEN CE, PEARSON DN, CAMPHAUSEN RT, STAUNTON DE, SIMON SI. Shear-dependent capping of L-selectin and P-selectin glycoprotein ligand 1 by E-selectin signals activation of high-avidity β_2-integrin on neutrophils. J. Immunol 2004;172(12):7780–7790. [PubMed: 15187162]

120. HENTZEN E, MCDONOUGH D, MCINTIRE L, et al. Hydrodynamic shear and tethering through E-selectin signals phosphorylation of p38 MAP kinase and adhesion of human neutrophils. Ann. Biomed. Eng 2002;30(8):987–1001. [PubMed: 12449760]

121. SIMON SI, HU Y, VESTWEBER D, SMITH CW. Neutrophil tethering on E-selectin activates β_2 integrin binding to ICAM-1 through a mitogen-activated protein kinase signal transduction pathway. J. Immunol 2000;164(8):4348–4358. [PubMed: 10754335]

122. PICADO C. Early and late-phase asthmatic reactions: a hypothesis. Allergy 1992;47(4 Part 1):331–333. [PubMed: 1443455]

123. PAWANKAR R, YAMAGISHI S, TAKIZAWA R, YAGI T. Mast cell-IgE- and mast cell-structural cell interactions in allergic airway disease. Curr. Drug Targets Infl amm. Allergy 2003;2(4):303–312.

124. KUPPER TS, FUHLBRIGGE RC. Immune surveillance in the skin: mechanisms and clinical consequences. Nat. Rev. Immunol 2004;4(3):211–222. [PubMed: 15039758]

125. PIGOTT R, DILLON LP, HEMINGWAY IH, GEARING AJ. Soluble forms of E-selectin, ICAM-1 and VCAM-1 are present in the supernatants of cytokine activated cultured endothelial cells. Biochem. Biophys. Res. Commun 1992;187(2):584–589. [PubMed: 1382417]

126. KOBAYASHI T, HASHIMOTO S, IMAI K, et al. Elevation of serum soluble intercellular adhesion molecule-1 (sICAM-1) and sE-selectin levels in bronchial asthma. Clin. Exp. Immunol 1994;96(1): 110–115. [PubMed: 7512004]

127. JANSON C, LUDVIKSDOTTIR D, GUNNBJORNSDOTTIR M, et al. Circulating adhesion molecules in allergic and non-allergic asthma. Respir. Med 2005;99(1):45–51. [PubMed: 15672848]

128. KOWALZICK L, KLEINHEINZ A, NEUBER K, et al. Elevated serum levels of soluble adhesion molecules ICAM-1 and ELAM-1 in patients with severe atopic eczema and influence of UVA1 treatment. Dermatology 1995;190(1):14–18. [PubMed: 7534511]

129. KRASOWSKA D, PIETRZAK A, LECEWICZ-TORUN B. Serum level of sELAM-1 in psoriatic patients correlates with disease activity. J. Eur. Acad. Dermatol. Venereol 1999;12(2):140–142. [PubMed: 10343943]

130. SZEPIETOWSKI J, WASIK F, BIELICKA E, NOCKOWSKI P, NOWOROLSKA A. Soluble E-selectin serum levels correlate with disease activity in psoriatic patients. Clin. Exp. Dermatol 1999;24(1):33–36. [PubMed: 10233646]

131. CZECH W, SCHOPF E, KAPP A. Soluble E-selectin in sera of patients with atopic dermatitis and psoriasis - correlation with disease activity. Br. J. Dermatol 1996;134(1):17–21. [PubMed: 8745880]

132. BALLMER-WEBER BK, BRAATHEN LR, BRAND CU. sICAM-1, sE-selectin and sVCAM-1 are constitutively present in human skin lymph and increased in allergic contact dermatitis. Arch. Dermatol. Res 1997;289(5):251–255. [PubMed: 9164633]

133. KOIDE M, FURUKAWA F, TOKURA Y, SHIRAHAMA S, TAKIGAWA M. Evaluation of soluble cell adhesion molecules in atopic dermatitis. J. Dermatol 1997;24(2):88–93. [PubMed: 9065702]

134. WOLKERSTORFER A, SAVELKOUL HF, DE WAARD VAN DER SPEK FB, et al. Soluble E-selectin and soluble ICAM-1 levels as markers of the activity of atopic dermatitis in children. Pediatr. Allergy Immunol 2003;14(4):302–306. [PubMed: 12911509]

135. WOLKERSTORFER A, LAAN MP, SAVELKOUL HF, et al. Soluble E-selectin, other markers of inflammation and disease severity in children with atopic dermatitis. Br. J. Dermatol 1998;138(3): 431–435. [PubMed: 9580795]

136. KIM DS, LEE KY. Serum soluble E-selectin levels in Kawasaki disease. Scand. J. Rheumatol 1994;23(5):283–286. [PubMed: 7526448]

137. OKA N, AKIGUCHI I, KAWASAKI T, OHNISHI K, KIMURA J. Elevated serum levels of endothelial leukocyte adhesion molecules in Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy. Ann. Neurol 1994;35(5):621–624. [PubMed: 7513983]

138. WENISCH C, MYSKIW D, PARSCHALK B, et al. Soluble endothelium-associated adhesion molecules in patients with Graves' disease. Clin. Exp. Immunol 1994;98(2):240–244. [PubMed: 7525128]

139. BODARY PF, HOMEISTER JW, VARGAS FB, et al. Generation of soluble P- and E-selectins *in vivo* is dependent on expression of P-selectin glycoprotein ligand-1. J. Thromb. Haemost 2007;5 (3):599–603. [PubMed: 17229053]

140. RUCHAUD-SPARAGANO MH, DROST EM, DONNELLY SC, et al. Potential pro-inflammatory effects of soluble E-selectin upon neutrophil function. Eur. J. Immunol 1998;28(1):80–89. [PubMed: 9485188]

141. BHUSHAN M, BLEIKER TO, BALLSDON AE, et al. Anti-E-selectin is ineffective in the treatment of psoriasis: a randomized trial. Br. J. Dermatol 2002;146(5):824–831. [PubMed: 12000379]

142. JUNG K, LINSE F, PALS ST, et al. Adhesion molecules in atopic dermatitis: patch tests elicited by house dust mite. Contact Dermatitis 1997;37(4):163–172. [PubMed: 9385511]

143. SILBER A, NEWMAN W, REIMANN KA, et al. Kinetic expression of endothelial adhesion molecules and relationship to leukocyte recruitment in two cutaneous models of inflammation. Lab. Invest 1994;70(2):163–175. [PubMed: 8139258]

144. GOSSET P, TILLIE-LEBLOND I, JANIN A, et al. Expression of E-selectin, ICAM-1 and VCAM-1 on bronchial biopsies from allergic and non-allergic asthmatic patients. Int. Arch. Allergy Immunol 1995;106(1):69–77. [PubMed: 7529075]

145. BENTLEY AM, DURHAM SR, ROBINSON DS, et al. Expression of endothelial and leukocyte adhesion molecules interacellular adhesion molecule-1, E-selectin, and vascular cell adhesion molecule-1 in the bronchial mucosa in steady-state and allergen-induced asthma. J. Allergy Clin. Immunol 1993;92(6):857–868. [PubMed: 7505008]

146. MILSTONE DS, FUKUMURA D, PADGETT RC, et al. Mice lacking E-selectin show normal numbers of rolling leukocytes but reduced leukocyte stable arrest on cytokine-activated microvascular endothelium. Microcirculation 1998;5(23):153–171. [PubMed: 9789256]

147. RAMOS CL, KUNKEL EJ, LAWRENCE MB, et al. Differential effect of E-selectin antibodies on neutrophil rolling and recruitment to inflammatory sites. Blood 1997;89(8):3009–3018. [PubMed: 9108422]

148. KUNKEL EJ, DUNNE JL, LEY K. Leukocyte arrest during cytokine-dependent inflammation *in vivo*. J. Immunol 2000;164(6):3301–3308. [PubMed: 10706723]

149. LEY K, ALLIETTA M, BULLARD DC, MORGAN S. Importance of E-selectin for firm leukocyte adhesion *in vivo*. Circ. Res 1998;83(3):287–294. [PubMed: 9710121]

150. SUBRAMANIAM M, SAFFARIPOUR S, VAN DE WATER L, et al. Role of endothelial selectins in wound repair. Am. J. Pathol 1997;150(5):1701–1709. [PubMed: 9137094]

151. SANTAMARIA BABI LF, PICKER LJ, PEREZ SOLER MT, et al. Circulating allergen-reactive T cells from patients with atopic dermatitis and allergic contact dermatitis express the skin-selective homing receptor, the cutaneous lymphocyte-associated antigen. J. Exp. Med 1995;181(5):1935–1940. [PubMed: 7722470]

152. STAITE ND, JUSTEN JM, SLY LM, BEAUDET AL, BULLARD DC. Inhibition of delayed-type contact hypersensitivity in mice deficient in both E-selectin and P-selectin. Blood 1996;88(8):2973–2979. [PubMed: 8874194]

153. AUSTRUP F, VESTWEBER D, BORGES E, et al. P- and E-selectin mediate recruitment of T-helper-1 but not T-helper-2 cells into inflammed tissues. Nature 1997;385(6611):81–83. [PubMed: 8985251]

154. CATALINA MD, ESTESS P, SIEGELMAN MH. Selective requirements for leukocyte adhesion molecules in models of acute and chronic cutaneous inflammation: participation of E- and P- but not L-selectin. Blood 1999;93(2):580–589. [PubMed: 9885219]

155. MCMURRAY RW. Adhesion molecules in autoimmune disease. Semin. Arthritis Rheum 1996;25(4):215–233. [PubMed: 8834012]

156. ROSEN SD, SINGER MS, YEDNOCK TA, STOOLMAN LM. Involvement of sialic acid on endothelial cells in organ-specific lymphocyte recirculation. Science 1985;228(4702):1005–1007. [PubMed: 4001928]

157. WALZ G, ARUFFO A, KOLANUS W, BEVILACQUA M, SEED B. Recognition by ELAM-1 of the sialyl-Lex determinant on myeloid and tumor cells. Science 1990;250(4984):1132–1135. [PubMed: 1701275]

158. PICKER LJ, MICHIE SA, ROTT LS, BUTCHER EC. A unique phenotype of skin-associated lymphocytes in humans. Preferential expression of the HECA-452 epitope by benign and malignant T cells at cutaneous sites. Am. J. Pathol 1990;136(5):1053–1068. [PubMed: 1693467]

159. BERG EL, YOSHINO T, ROTT LS, et al. The cutaneous lymphocyte antigen is a skin lymphocyte homing receptor for the vascular lectin endothelial cell-leukocyte adhesion molecule 1. J. Exp. Med 1991;174(6):1461–1466. [PubMed: 1720810]

160. BERG EL, ROBINSON MK, MANSSON O, BUTCHER EC, MAGNANI JL. A carbohydrate domain common to both sialyl Le(a) and sialyl Le(X) is recognized by the endothelial cell leukocyte adhesion molecule ELAM-1. J. Biol. Chem 1991;266(23):14869–14872. [PubMed: 1714447]

161. ALON R, ROSSITER H, WANG X, SPRINGER TA, KUPPER TS. Distinct cell surface ligands mediate T lymphocyte attachment and rolling on P and E selectin under physiological flow. J. Cell Biol 1994;127(5):1485–1495. [PubMed: 7525609]

162. SUEYOSHI S, TSUBOI S, SAWADA-HIRAI R, et al. Expression of distinct fucosylated oligosaccharides and carbohydrate-mediated adhesion efficiency directed by two different α-1,3-fucosyltransferases. Comparison of E- and L-selectin-mediated adhesion. J. Biol. Chem 1994;269(51):32342–32350. [PubMed: 7528213]

163. BERG EL, MULLOWNEY AT, ANDREW DP, GOLDBERG JE, BUTCHER EC. Complexity and differential expression of carbohydrate epitopes associated with L-selectin recognition of high endothelial venules. Am. J. Pathol 1998;152(2):469–477. [PubMed: 9466573]

164. SACKSTEIN R, DIMITROFF CJ. A hematopoietic cell L-selectin ligand that is distinct from PSGL-1 and displays N-glycan-dependent binding activity. Blood 2000;96(8):2765–2774. [PubMed: 11023510]

165. DIMITROFF CJ, LEE JY, FUHLBRIGGE RC, SACKSTEIN R. A distinct glycoform of CD44 is an L-selectin ligand on human hematopoietic cells. Proc. Natl. Acad. Sci. USA 2000;97(25):13841–13846. [PubMed: 11095749]

166. DIMITROFF CJ, LEE JY, SCHOR KS, SANDMAIER BM, SACKSTEIN R. differential L-selectin binding activities of human hematopoietic cell L-selectin ligands, HCELL and PSGL-1. J. Biol. Chem 2001;276(50):47623–47631. [PubMed: 11591704]

167. DAVIS RE, SMOLLER BR. T lymphocytes expressing HECA-452 epitope are present in cutaneous acute graft-versus-host disease and erythema multiforme, but not in acute graft-versus-host disease in gut organs. Am. J. Pathol 1992;141(3):691–698. [PubMed: 1381561]

168. ROSSITER H, VAN REIJSEN F, MUDDE GC, et al. Skin disease-related T cells bind to endothelial selectins: expression of cutaneous lymphocyte antigen (CLA) predicts E-selectin but not P-selectin binding. Eur. J. Immunol 1994;24(1):205–210. [PubMed: 7517361]

169. ROOK AH, HEALD P. The immunopathogenesis of cutaneous T-cell lymphoma. Hematol. Oncol. Clin. North Am 1995;9(5):997–1010. [PubMed: 8522492]

170. FUHLBRIGGE RC, KING SL, DIMITROFF CJ, KUPPER TS, SACKSTEIN R. Direct real-time observation of E- and P-selectin-mediated rolling on cutaneous lymphocyte-associated antigen immobilized on Western blots. J. Immunol 2002;168(11):5645–5651. [PubMed: 12023362]

171. BOROWITZ MJ, WEIDNER A, OLSEN EA, PICKER LJ. Abnormalities of circulating T-cell subpopulations in patients with cutaneous T-cell lymphoma: cutaneous lymphocyte-associated antigen expression on T cells correlates with extent of disease. Leukemia 1993;7(6):859–863. [PubMed: 7684799]

172. FERENCZI K, FUHLBRIGGE RC, PINKUS J, PINKUS GS, KUPPER TS. Increased CCR4 expression in cutaneous T cell lymphoma. J. Invest. Dermatol 2002;119(6):1405–1410. [PubMed: 12485447]

173. YAMAGUCHI T, OHSHIMA K, TSUCHIYA T, et al. Thecomparison of expression of cutaneous lymphocyte-associated antigen (CLA), and Th1- and Th2-associated antigens in mycosis fungoides and cutaneous lesions of adult T-cell leukemia/lymphoma. Eur. J. Dermatol 2003;13(6):553–559. [PubMed: 14721775]

174. DUIJVESTIJN AM, HORST E, PALS ST, et al. High endothelial differentiation in human lymphoid and inflammatory tissues defined by monoclonal antibody HECA-452. Am. J. Pathol 1988;130(1): 147–155. [PubMed: 3276207]

175. HUNGER RE, YAWALKAR N, BRAATHEN LR, BRAND CU. The HECA-452 epitope is highly expressed on lymph cells derived from human skin. Br. J. Dermatol 1999;141(3):565–569. [PubMed: 10583071]

176. DIMITROFF CJ, BERNACKI RJ, SACKSTEIN R. Glycosylation-dependent inhibition of cutaneous lymphocyte-associated antigen expression: implications in modulating lymphocyte migration to skin. Blood 2003;101(2):602–610. [PubMed: 12393521]

177. BLANDER JM, VISINTIN I, JANEWAY CA Jr, MEDZHITOV R. α(1,3)-Fucosyltransferase VII and α(2,3)-sialyltransferase IV are up-regulated in activated CD4 T cells and maintained after their differentiation into Th1 and migration into inflammatory sites. J. Immunol 1999;163(7):3746–3752. [PubMed: 10490970]

178. WAGERS AJ, KANSAS GS. Potent induction of α(1,3)-fucosyltransferase VII in activated $CD4^+$ T cells by TGF-β1 through a p38 mitogen-activated protein kinase-dependent pathway. J. Immunol 2000;165(9):5011–5016. [PubMed: 11046029]

179. LOWE JB, STOOLMAN LM, NAIR RP, et al. ELAM-1-dependent cell adhesion to vascular endothelium determined by a transfected human fucosyltransferase cDNA. Cell 1990;63(3):475–484. [PubMed: 1699667]

180. MALY P, THALL A, PETRYNIAK B, et al. The α(1,3)fucosyltransferase Fuc-TVII controls leukocyte trafficking through an essential role in L-, E-, and P-selectin ligand biosynthesis. Cell 1996;86(4):643–653. [PubMed: 8752218]
181. ELLIES LG, TSUBOI S, PETRYNIAK B, et al. Core 2 oligosaccharide biosynthesis distinguishes between selectin ligands essential for leukocyte homing and inflammation. Immunity 1998;9(6): 881–890. [PubMed: 9881978]
182. ASANO M, NAKAE S, KOTANI N, et al. Impaired selectin-ligand biosynthesis and reduced inflammatory responses in β-1,4-galactosyltransferase-I-deficient mice. Blood 2003;102(5):1678–1685. [PubMed: 12714507]
183. AINSLIE MP, MCNULTY CA, HUYNH T, SYMON FA, WARDLAW AJ. Characterisation of adhesion receptors mediating lymphocyte adhesion to bronchial endothelium provides evidence for a distinct lung homing pathway. Thorax 2002;57(12):1054–1059. [PubMed: 12454301]
184. WOLBER FM, CURTIS JL, MALY P, et al. Endothelial selectins and α_4 integrins regulate independent pathways of T lymphocyte recruitment in the pulmonary immune response. J. Immunol 1998;161(8):4396–4403. [PubMed: 9780218]
185. CURTIS JL, SONSTEIN J, CRAIG RA, et al. Subset-specific reductions in lung lymphocyte accumulation following intratracheal antigen challenge in endothelial selectin-deficient mice. J. Immunol 2002;169(5):2570–2579. [PubMed: 12193727]
186. LUKACS NW, JOHN A, BERLIN A, et al. E- and P-selectins are essential for the development of cockroach allergen-induced airway responses. J. Immunol 2002;169(4):2120–2125. [PubMed: 12165540]
187. DONG ZM, BROWN AA, WAGNER DD. Prominent role of P-selectin in the development of advanced atherosclerosis in ApoE-deficient mice. Circulation 2000;101(19):2290–2295. [PubMed: 10811597]
188. MANKA D, COLLINS RG, LEY K, BEAUDET AL, SAREMBOCK IJ. Absence of P-selectin, but not intercellular adhesion molecule-1, attenuates neointimal growth after arterial injury in apolipoprotein E-deficient mice. Circulation 2001;103(7):1000–1005. [PubMed: 11181476]
189. CAMERON MD, SCHMIDT EE, KERKVLIET N, et al. Temporal progression of metastasis in lung: cell survival, dormancy, and location dependence of metastatic inefficiency. Cancer Res 2000;60(9):2541–2546. [PubMed: 10811137]
190. KRAUSE T, TURNER GA. Areselectins involved in metastasis? Clin. Exp. Metast 1999;17(3): 183–192.
191. BURDICK MM, CHU JT, GODAR S, SACKSTEIN R. HCELL is the major E- and L-selectin ligand expressed on LS174T colon carcinoma cells. J. Biol. Chem 2006;281(20):13899–13905. [PubMed: 16565092]
192. HANLEY WD, NAPIER SL, BURDICK MM, et al. Variantisoforms of CD44 are P- and L-selectin ligands on colon carcinoma cells. FASEB J 2006;20(2):337–339. [PubMed: 16352650]
193. HANLEY WD, BURDICK MM, KONSTANTOPOULOS K, SACKSTEIN R. CD44 on LS174T colon carcinoma cells possesses E-selectin ligand activity. Cancer Res 2005;65(13):5812–5817. [PubMed: 15994957]
194. BURDICK MM, MCCAFFERY JM, KIM YS, BOCHNER BS, KONSTANTOPOULOS K. Colon carcinoma cell glycolipids, integrins, and other glycoproteins mediate adhesion to HUVECs under flow. Am. J. Physiol. Cell Physiol 2003;284(4):C977–C987. [PubMed: 12477667]
195. LAFERRIERE J, HOULE F, HUOT J. Adhesion of HT-29 colon carcinoma cells to endothelial cells requires sequential events involving E-selectin and integrin β4. Clin. Exp. Metast 2004;21(3): 257–264.
196. LAFERRIERE J, HOULE F, TAHER MM, VALERIE K, HUOT J. Transendothelial migration of colon carcinoma cells requires expression of E-selectin by endothelial cells and activation of stress-activated protein kinase-2 (SAPK2/p38) in the tumor cells. J. Biol. Chem 2001;276(36):33762–33772. [PubMed: 11448946]
197. SOLTESZ SA, POWERS EA, GENG JG, FISHER C. Adhesion of HT-29 colon carcinoma cells to E-selectin results in increased tyrosine phosphorylation and decreased activity of c-src. Int. J. Cancer 1997;71(4):645–653. [PubMed: 9178821]

198. HILLER KM, MAYBEN JP, BENDT KM, et al. Transfectionof α(1,3)fucosyltransferase antisense sequences impairs the proliferative and tumorigenic ability of human colon carcinoma cells. Mol. Carcinog 2000;27(4):280–288. [PubMed: 10747292]

199. WESTON BW, HILLER KM, MAYBEN JP, et al. Expression of human α(1,3)fucosyltransferase antisense sequences inhibits selectin-mediated adhesion and liver metastasis of colon carcinoma cells. Cancer Res 1999;59(9):2127–2135. [PubMed: 10232599]

200. FLUGY AM, D'AMATO M, RUSSO D, et al. E-selectin modulates the malignant properties of T84 colon carcinoma cells. Biochem. Biophys. Res. Commun 2002;293(3):1099–1106. [PubMed: 12051773]

201. DI BELLA MA, FLUGY AM, RUSSO D, et al. Different phenotypes of colon carcinoma cells interacting with endothelial cells: role of E-selectin and ultrastructural data. Cell Tissue Res 2003;312(1):55–64. [PubMed: 12684869]

202. SAWADA R, TSUBOI S, FUKUDA M. Differential E-selectin-dependent adhesion efficiency in sublines of a human colon cancer exhibiting distinct metastatic potentials. J. Biol. Chem 1994;269 (2):1425–1431. [PubMed: 7507108]

203. SRINIVAS U, PAHLSSON P, LUNDBLAD A. E-selectin: sialyl Lewis, a dependent adhesion of colon cancer cells, is inhibited differently by antibodies against E-selectin ligands. Scand. J. Immunol 1996;44(3):197–203. [PubMed: 8795712]

204. KIM YJ, BORSIG L, HAN HL, VARKI NM, VARKI A. Distinct selectin ligands on colon carcinoma mucins can mediate pathological interactions among platelets, leukocytes, and endothelium. Am. J. Pathol 1999;155(2):461–472. [PubMed: 10433939]

205. MANNORI G, CROTTET P, CECCONI O, et al. Differential colon cancer cell adhesion to E-, P-, and L-selectin: role of mucin-type glycoproteins. Cancer Res 1995;55(19):4425–4431. [PubMed: 7545541]

206. DEJANA E, MARTIN-PADURA I, LAURI D, et al. Endothelial leukocyte adhesion molecule-1-dependent adhesion of colon carcinoma cells to vascular endothelium is inhibited by an antibody to Lewis fucosylated type I carbohydrate chain. Lab. Invest 1992;66(3):324–330. [PubMed: 1371572]

207. YAMADA N, CHUNG YS, SAWADA T, OKUNO M, SOWA M. Role of SPan-1 antigen in adhesion of human colon cancer cells to vascular endothelium. Dig. Dis. Sci 1995;40(5):1005–1012. [PubMed: 7537192]

208. CHO M, DAHIYA R, CHOI SR, et al. Mucins secreted by cell lines derived from colorectal mucinous carcinoma and adenocarcinoma. Eur. J. Cancer 1997;33(6):931–941. [PubMed: 9291818]

209. NAKAMORI S, KAMEYAMA M, IMAOKA S, et al. Involvement of carbohydrate antigen sialyl Lewis(x) in colorectal cancer metastasis. Dis. Colon Rectum 1997;40(4):420–431. [PubMed: 9106690]

210. BRODT P, FALLAVOLLITA L, BRESALIER RS, et al. Liver endothelial E-selectin mediates carcinoma cell adhesion and promotes liver metastasis. Int. J. Cancer 1997;71(4):612–619. [PubMed: 9178816]

211. BRESALIER RS, BYRD JC, BRODT P, et al. Liver metastasis and adhesion to the sinusoidal endothelium by human colon cancer cells is related to mucin carbohydrate chain length. Int. J. Cancer 1998;76(4):556–562. [PubMed: 9590134]

212. DIMITROFF CJ, LECHPAMMER M, LONG-WOODWARD D, KUTOK JL. Rolling of human bone-metastatic prostate tumor cells on human bone marrow endothelium under shear flow is mediated by E-selectin. Cancer Res 2004;64(15):5261–5269. [PubMed: 15289332]

213. TOZEREN A, KLEINMAN HK, GRANT DS, et al. E-selectin-mediated dynamic interactions of breast- and colon-cancer cells with endothelial-cell monolayers. Int. J. Cancer 1995;60(3):426–431. [PubMed: 7530236]

214. NARITA T, KAWASAKI-KIMURA N, MATSUURA N, FUNAHASHI H, KANNAGI R. Adhesion of human breast cancer cells to vascular endothelium mediated by sialyl Lewis &supx/ E-selectin. Breast Cancer 1996;3(1):19–23. [PubMed: 11091549]

215. MOSS MA, ZIMMER S, ANDERSON KW. Role of metastatic potential in the adhesion of human breast cancer cells to endothelial monolayers. Anticancer Res 2000;20(3A):1425–1433. [PubMed: 10928052]

216. LAFRENIE RM, GALLO S, PODOR TJ, BUCHANAN MR, ORR FW. The relative roles of vitronectin receptor, E-selectin and $\alpha_4\beta_1$ in cancer cell adhesion to interleukin-1-treated endothelial cells. Eur. J. Cancer 1994;30A(14):2151–2158. [PubMed: 7531992]

217. IWAI K, ISHIKURA H, KAJI M, et al. Importance of E-selectin (ELAM-1) and sialyl Lewis(a) in the adhesion of pancreatic carcinoma cells to activated endothelium. Int. J. Cancer 1993;54(6):972–977. [PubMed: 7687590]

218. MARTIN-SATUE M, MARRUGAT R, CANCELAS JA, BLANCO J. Enhanced expression of α (1,3)-fucosyltransferase genes correlates with E-selectin-mediated adhesion and metastatic potential of human lung adenocarcinoma cells. Cancer Res 1998;58(7):1544–1550. [PubMed: 9537262]

219. MARTIN-SATUE M, DE CASTELLARNAU C, BLANCO J. Overexpression of α(1,3)-fucosyltransferase VII is sufficient for the acquisition of lung colonization phenotype in human lung adenocarcinoma HAL-24Luc cells. Br. J. Cancer 1999;80(8):1169–1174. [PubMed: 10376968]

220. REDDI AH, ROODMAN D, FREEMAN C, MOHLA S. Mechanisms of tumor metastasis to the bone: challenges and opportunities. J. Bone Miner. Res 2003;18(2):190–194. [PubMed: 12568395]

221. LEHR JE, PIENTA KJ. Preferential adhesion of prostate cancer cells to a human bone marrow endothelial cell line. J. Natl. Cancer Inst 1998;90(2):118–123. [PubMed: 9450571]

222. SCOTT LJ, CLARKE NW, GEORGE NJ, et al. Interactions of human prostatic epithelial cells with bone marrow endothelium: binding and invasion. Br. J. Cancer 2001;84(10):1417–1423. [PubMed: 11355957]

223. SIMPSON MA, REILAND J, BURGER SR, et al. Hyaluronan synthase elevation in metastatic prostate carcinoma cells correlates with hyaluronan surface retention, a prerequisite for rapid adhesion to bone marrow endothelial cells. J. Biol. Chem 2001;276(21):17949–17957. [PubMed: 11278609]

224. COOPER CR, MCLEAN L, WALSH M, et al. Preferential adhesion of prostate cancer cells to bone is mediated by binding to bone marrow endothelial cells as compared to extracellular matrix components *in vitro*. Clin. Cancer Res 2000;6(12):4839–4847. [PubMed: 11156243]

225. ZIPIN A, ISRAELI-AMIT M, MESHEL T, et al. Tumor-microenvironment interactions: the fucose-generating FX enzyme controls adhesive properties of colorectal cancer cells. Cancer Res 2004;64 (18):6571–6578. [PubMed: 15374970]

226. BIANCONE L, ARAKI M, ARAKI K, VASSALLI P, STAMENKOVIC I. Redirection of tumor metastasis by expression of E-selectin *in vivo*. J. Exp. Med 1996;183(2):581–587. [PubMed: 8627169]

227. RENKONEN J, PAAVONEN T, RENKONEN R. Endothelial and epithelial expression of sialyl Lewis(x) and sialyl Lewis(a) in lesions of breast carcinoma. Int. J. Cancer 1997;74(3):296–300. [PubMed: 9221808]

228. HOFF SD, MATSUSHITA Y, OTA DM, et al. Increased expression of sialyl-dimeric LeX antigen in liver metastases of human colorectal carcinoma. Cancer Res 1989;49(24 Part 1):6883–6888. [PubMed: 2573422]

229. NAKAMORI S, FURUKAWA H, HIRATSUKA M, et al. Expression of carbohydrate antigen sialyl Le(a): a new functional prognostic factor in gastric cancer. J. Clin. Oncol 1997;15(2):816–825. [PubMed: 9053509]

230. KISHIMOTO T, ISHIKURA H, KIMURA C, et al. Phenotypes correlating to metastatic properties of pancreas adenocarcinoma *in vivo*: the importance of surface sialyl Lewis(a) antigen. Int. J. Cancer 1996;69(4):290–294. [PubMed: 8797870]

231. DIMITROFF CJ, DESCHENY L, TRUJILLO N, et al. Identification of leukocyte E-selectin ligands, P-selectin glycoprotein ligand-1 and E-selectin ligand-1, on human metastatic prostate tumor cells. Cancer Res 2005;65(13):5750–5760. [PubMed: 15994950]

232. JORGENSEN T, BERNER A, KAALHUS O, et al. Up-regulation of the oligosaccharide sialyl LewisX: a new prognostic parameter in metastatic prostate cancer. Cancer Res 1995;55(9):1817–1819. [PubMed: 7728744]

233. MATSUURA N, NARITA T, MITSUOKA C, et al. Increased concentration of soluble E-selectin in the sera of breast cancer patients. Anticancer Res 1997;17(2B):1367–1372. [PubMed: 9137500]

234. FOX SB, TURNER GD, LEEK RD, et al. The prognostic value of quantitative angiogenesis in breast cancer and role of adhesion molecule expression in tumor endothelium. Breast Cancer Res. Treat 1995;36(2):219–226. [PubMed: 8534869]

235. YE C, KIRIYAMA K, MISTUOKA C, et al. Expression of E-selectin on endothelial cells of small veins in human colorectal cancer. Int. J. Cancer 1995;61(4):455–460. [PubMed: 7538975]

236. SCHADENDORF D, HEIDEL J, GAWLIK C, SUTER L, CZARNETZKI BM. Association with clinical outcome of expression of VLA-4 in primary cutaneous malignant melanoma as well as P-selectin and E-selectin on intratumoral vessels. J. Natl. Cancer Inst 1995;87(5):366–371. [PubMed: 7531774]

237. ALLEN MH, ROBINSON MK, STEPHENS PE, MACDONALD DM, BARKER JN. E-selectin binds to squamous cell carcinoma and keratinocyte cell lines. J. Invest. Dermatol 1996;106(4):611–615. [PubMed: 8617993]

238. NARITA T, KAWAKAMI-KIMURA N, MATSUURA N, HOSONO J, KANNAGI R. Corticosteroids and medroxyprogesterone acetate inhibit the induction of E-selectin on the vascular endothelium by MDA-MB-231 breast cancer cells. Anticancer Res 1995;15(6B):2523–2527. [PubMed: 8669817]

239. BALKWILL F, MANTOVANI A. Inflammation and cancer: back to Virchow? Lancet 2001;357 (9255):539–545. [PubMed: 11229684]

240. NIESWANDT B, HAFNER M, ECHTENACHER B, MANNEL DN. Lysis of tumor cells by natural killer cells in mice is impeded by platelets. Cancer Res 1999;59(6):1295–1300. [PubMed: 10096562]

241. BORSIG L, WONG R, FERAMISCO J, et al. Heparin and cancer revisited: mechanistic connections involving platelets, P-selectin, carcinoma mucins, and tumor metastasis. Proc. Natl. Acad. Sci. USA 2001;98(6):3352–3357. [PubMed: 11248082]

242. WITTIG BM, KAULEN H, THEES R, et al. Elevated serum E-selectin in patients with liver metastases of colorectal cancer. Eur. J. Cancer 1996;32A(7):1215–1218. [PubMed: 8758256]

243. ALEXIOU D, KARAYIANNAKIS AJ, SYRIGOS KN, et al. Serum levels of E-selectin, ICAM-1 and VCAM-1 in colorectal cancer patients: correlations with clinicopathological features, patient survival and tumour surgery. Eur. J. Cancer 2001;37(18):2392–2397. [PubMed: 11720833]

244. ALEXIOU D, KARAYIANNAKIS AJ, SYRIGOS KN, et al. Clinical significance of serum levels of E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 in gastric cancer patients. Am. J. Gastroenterol 2003;98(2):478–485. [PubMed: 12591072]

245. ZHANG GJ, ADACHI I. Serumlevels of soluble intercellular adhesion molecule-1 and E-selectin in metastatic breast carcinoma: correlations with clinicopathological features and prognosis. Int. J. Oncol 1999;14(1):71–77. [PubMed: 9863011]

246. HEBBAR M, PEYRAT JP. Significance of soluble endothelial molecule E-selectin in patients with breast cancer. Int. J. Biol. Markers 2000;15(1):15–21. [PubMed: 10763135]

247. ITO K, YE CL, HIBI K, et al. Paired tumor marker of soluble E-selectin and its ligand sialyl Lewis A in colorectal cancer. J. Gastroenterol 2001;36(12):823–829. [PubMed: 11777210]

248. UNER A, AKCALI Z, UNSAL D. Serum levels of soluble E-selectin in colorectal cancer. Neoplasma 2004;51(4):269–274. [PubMed: 15254658]

249. VELIKOVA G, BANKS RE, GEARING A, et al. Serum concentrations of soluble adhesion molecules in patients with colorectal cancer. Br. J. Cancer 1998;77(11):1857–1863. [PubMed: 9667659]

250. HEBBAR M, REVILLION F, LOUCHEZ MM, et al. Therelationship between concentrations of circulating soluble E-selectin and clinical, pathological, and biological features in patients with breast cancer. Clin. Cancer Res 1998;4(2):373–380. [PubMed: 9516925]

251. CERVELLO M, VIRRUSO L, LIPANI G, et al. Serum concentration of E-selectin in patients with chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. J. Cancer Res. Clin. Oncol 2000;126 (6):345–351. [PubMed: 10870645]

252. FUHLBRIGGE RC, WEISHAUPT C. Adhesion molecules in cutaneous immunity. Semin. Immunopathol 2007;29(1):45–57. [PubMed: 17621953]

253. EPPIHIMER MJ, SCHAUB RG. Soluble P-selectin antagonist mediates rolling velocity and adhesion of leukocytes in acutely inflamed venules. Microcirculation 2001;8(1):15–24. [PubMed: 11296849]

254. SAKO D, COMESS KM, BARONE KM, et al. A sulfated peptide segment at the amino terminus of PSGL-1 is critical for P-selectin binding. Cell 1995;83(2):323–331. [PubMed: 7585949]

255. HICKS AE, NOLAN SL, RIDGER VC, HELLEWELL PG, NORMAN KE. Recombinant P-selectin glycoprotein ligand-1 directly inhibits leukocyte rolling by all 3 selectins *in vivo*: complete inhibition of rolling is not required for anti-inflammatory effect. Blood 2003;101(8):3249–3256. [PubMed: 12480716]

256. SCALIA R, HAYWARD R, ARMSTEAD VE, MINCHENKO AG, LEFER AM. Effect of recombinant soluble P-selectin glycoprotein ligand-1 on leukocyte-endothelium interaction *in vivo*. Role in rat traumatic shock. Circ. Res 1999;84(1):93–102. [PubMed: 9915778]

257. SCALIA R, ARMSTEAD VE, MINCHENKO AG, LEFER AM. Essential role of P-selectin in the initiation of the inflammatory response induced by hemorrhage and reinfusion. J. Exp. Med 1999;189(6):931–938. [PubMed: 10075976]

258. HAYWARD R, LEFER AM. Acute mesenteric ischemia and reperfusion: protective effects of recombinant soluble P-selectin glycoprotein ligand-1. Shock 1999;12(3):201–207. [PubMed: 10485598]

259. HAYWARD R, CAMPBELL B, SHIN YK, SCALIA R, LEFER AM. Recombinant soluble P-selectin glycoprotein ligand-1 protects against myocardial ischemic reperfusion injury in cats. Cardiovasc. Res 1999;41(1):65–76. [PubMed: 10325954]

260. KYRIAKIDES C, AUSTEN W Jr, WANG Y, et al. Endothelial selectin blockade attenuates lung permeability of experimental acid aspiration. Surgery 2000;128(2):327–331. [PubMed: 10923012]

261. BANNERT N, CRAIG S, FARZAN M, et al. Sialylated O-glycans and sulfated tyrosines in the NH_2-terminal domain of CC chemokine receptor 5 contribute to high affinity binding of chemokines. J. Exp. Med 2001;194(11):1661–1673. [PubMed: 11733580]

262. VEERMAN KM, WILLIAMS MJ, UCHIMURA K, et al. Interaction of the selectin ligand PSGL-1 with chemokines CCL21 and CCL19 facilitates efficient homing of T cells to secondary lymphoid organs. Nat. Immunol 2007;8(5):532–539. [PubMed: 17401367]

263. COMPAIN P, MARTIN OR. Carbohydrate mimetics-based glycosyltransferase inhibitors. Bioorg. Med. Chem 2001;9(12):3077–3092. [PubMed: 11711283]

264. MITCHELL ML, TIAN F, LEE LV, WONG CH. Synthesis and evaluation of transition-state analogue inhibitors of α-1,3-fucosyltransferase. Angew. Chem. Int. Ed. Engl 2002;41(16):3041–3044. [PubMed: 12203452]

265. MURRAY BW, TAKAYAMA S, SCHULTZ J, WONG CH. Mechanism and specificity of human α-1,3-fucosyltransferase V. Biochemistry 1996;35(34):11183–11195. [PubMed: 8780523]

266. MIURA Y, KIM S, ETCHISON JR, et al. Aglycone structure influences α-fucosyltransferase III activity using *N*-acetyllactosamine glycoside acceptors. Glycoconj. J 1999;16(11):725–730. [PubMed: 11003557]

267. DE VRIES T, PALCIC MP, SCHOENMAKERS PS, VAN DEN EIJNDEN DH, JOZIASSE DH. Acceptor specificity of GDP-Fuc:Gal β1->4GlcNAc-R α3-fucosyltransferase VI(FucT-VI) expressed in insect cells as soluble, secreted enzyme. Glycobiology 1997;7(7):921–927. [PubMed: 9363434]

268. LEE LV, MITCHELL ML, HUANG SJ, et al. A potent and highly selective inhibitor of human α-1,3-fucosyltransferase via click chemistry. J. Am. Chem. Soc 2003;125(32):9588–9589. [PubMed: 12904015]

269. BRYAN MC, LEE LV, WONG CH. High-throughput identification of fucosyltransferase inhibitors using carbohydrate microarrays. Bioorg. Med. Chem. Lett 2004;14(12):3185–3188. [PubMed: 15149672]

270. BENGTSON P, LUNDBLAD A, LARSON G, PAHLSSON P. Polymorphonuclear leukocytes from individuals carrying the G329A mutation in the α1,3-fucosyltransferase VII gene (FUT7) roll on E- and P-selectins. J. Immunol 2002;169(7):3940–3946. [PubMed: 12244194]

271. DESCHENY L, GAINERS ME, WALCHECK B, DIMITROFF CJ. Ameliorating skin-homing receptors on malignant T cells with a fluorosugar analog of *N*-acetylglucosamine: P-selectin ligand is a more sensitive target than E-selectin ligand. J. Invest. Dermatol 2006;126(9):2065–2073. [PubMed: 16691194]

272. DIMITROFF CJ, KUPPER TS, SACKSTEIN R. Prevention of leukocyte migration to inflamed skin with a novel fluorosugar modifier of cutaneous lymphocyte-associated antigen. J. Clin. Invest 2003;112(7):1008–1018. [PubMed: 14523038]

273. SPEVA KW, FOXALL C, CHARYCH DH, DASGUPTA F, NAGY JO. Carbohydrates in an acidic multivalent assembly: nanomolar P-selectin inhibitors. J. Med. Chem 1996;39(5):1018–1020. [PubMed: 8676335]

274. CAPPI MW, MOREE WJ, QIAO L, et al. Synthesis of novel 6-amido-6-deoxy-L-galactose derivatives as sialyl Lewis X mimetics. Bioorg. Med. Chem 1997;5(2):283–296. [PubMed: 9061193]

275. MUROHARA T, MARGIOTTA J, PHILLIPS LM, et al. Cardioprotection by liposome-conjugated sialyl LewisX-oligosaccharide in myocardial ischaemia and reperfusion injury. Cardiovasc. Res 1995;30(6):965–974. [PubMed: 8746213]

276. FRIEDRICH M, BOCK D, PHILIPP S, et al. Pan-selectin antagonism improves psoriasis manifestation in mice and man. Arch. Dermatol. Res 2006;297(8):345–351. [PubMed: 16362415]

277. OOSTINGH GJ, LUDWIG RJ, ENDERS S, et al. Diminished lymphocyte adhesion and alleviation of allergic responses by small-molecule- or antibody-mediated inhibition of L-selectin functions. J. Invest. Dermatol 2007;127(1):90–97. [PubMed: 16902419]

278. SCHON MP, KRAHN T, SCHON M, et al. Efomycine M, a new specific inhibitor of selectin, impairs leukocyte adhesion and alleviates cutaneous inflammation. Nat. Med 2002;8(4):366–372. [PubMed: 11927942]

279. LUDWIG RJ, ALBAN S, BISTRIAN R, et al. The ability of different forms of heparins to suppress P-selectin function *in vitro* correlates to their inhibitory capacity on bloodborne metastasis *in vivo*. Thromb. Haemost 2006;95(3):535–540. [PubMed: 16525583]

280. STEVENSON JL, CHOI SH, VARKI A. Differential metastasis inhibition by clinically relevant levels of heparins - correlation with selectin inhibition, not antithrombotic activity. Clin. Cancer Res 2005;11(19 Part 1):7003–7011. [PubMed: 16203794]

281. SARKAR AK, FRITZ TA, TAYLOR WH, ESKO JD. Disaccharide uptake and priming in animal cells: inhibition of sialyl Lewis X by acetylated Galβ1->4GlcNAc β-*O*-naphthalenemethanol. Proc. Natl. Acad. Sci. USA 1995;92(8):3323–3327. [PubMed: 7724561]

282. SARKAR AK, ROSTAND KS, JAIN RK, MATTA KL, ESKO JD. Fucosylation of disaccharide precursors of sialyl LewisX inhibit selectin-mediated cell adhesion. J. Biol. Chem 1997;272(41): 25608–25616. [PubMed: 9325281]

283. SARKAR AK, BROWN JR, ESKO JD. Synthesis and glycan priming activity of acetylated disaccharides. Carbohydr. Res 2000;329(2):287–300. [PubMed: 11117312]

284. LEY K, BULLARD DC, ARBONES ML, et al. Sequential contribution of L- and P-selectin to leukocyte rolling *in vivo*. J. Exp. Med 1995;181(2):669–675. [PubMed: 7530761]

285. OLOFSSON AM, ARFORS KE, RAMEZANI L, et al. E-selectin mediates leukocyte rolling in interleukin-1-treated rabbit mesentery venules. Blood 1994;84(8):2749–2758. [PubMed: 7522640]

286. YAO L, SETIADI H, XIA L, et al. Divergent inducible expression of P-selectin and E-selectin in mice and primates. Blood 1999;94(11):3820–3828. [PubMed: 10572097]

287. LABOW MA, NORTON CR, RUMBERGER JM, et al. Characterization of E-selectin-deficient mice: demonstration of overlapping function of the endothelial selectins. Immunity 1994;1(8):709–720. [PubMed: 7541306]

288. LOWENSTEIN CJ, MORRELL CN, YAMAKUCHI M. Regulation of Weibel-Palade body exocytosis. Trends Cardiovasc. Med 2005;15(8):302–308. [PubMed: 16297768]

289. MERTEN M, THIAGARAJAN P. P-selectin in arterial thrombosis. Z. Kardiol 2004;93(11):855–863. [PubMed: 15568145]

290. GUNDEL RH, WEGNER CD, TORCELLINI CA, et al. Endothelial leukocyte adhesion molecule-1 mediates antigen-induced acute airway inflammation and late-phase airway obstruction in monkeys. J. Clin. Invest 1991;88(4):1407–1411. [PubMed: 1717514]

291. MULLIGAN MS, VARANI J, DAME MK, et al. Role of endothelial-leukocyte adhesion molecule 1 (ELAM-1) in neutrophil-mediated lung injury in rats. J. Clin. Invest 1991;88(4):1396–1406. [PubMed: 1717513]

292. GROBER JS, BOWEN BL, EBLING H, et al. Monocyte-endothelial adhesion in chronic rheumatoid arthritis. *In situ* detection of selectin and integrin-dependent interactions. J. Clin. Invest 1993;91 (6):2609–2619. [PubMed: 7685772]

293. KOCH AE, BURROWS JC, HAINES GK, et al. Immunolocalization of endothelial and leukocyte adhesion molecules in human rheumatoid and osteoarthritic synovial tissues. Lab. Invest 1991;64 (3):313–320. [PubMed: 1706003]

294. ALLEN MD, MCDONALD TO, HIMES VE, et al. E-selectin expression in human cardiac grafts with cellular rejection. Circulation 1993;88(5 Part 2):II243–II247. [PubMed: 7693367]

295. BORSIG L, WONG R, HYNES RO, VARKI NM, VARKI A. Synergistic effects of L- and P-selectin in facilitating tumor metastasis can involve non-mucin ligands and implicate leukocytes as enhancers of metastasis. Proc. Natl. Acad. Sci. USA 2002;99(4):2193–2198. [PubMed: 11854515]

296. BARTHOLDY C, MARKER O, THOMSEN AR. Migration of activated CD8(+) T lymphocytes to sites of viral infection does not require endothelial selectins. Blood 2000;95(4):1362–1369. [PubMed: 10666212]

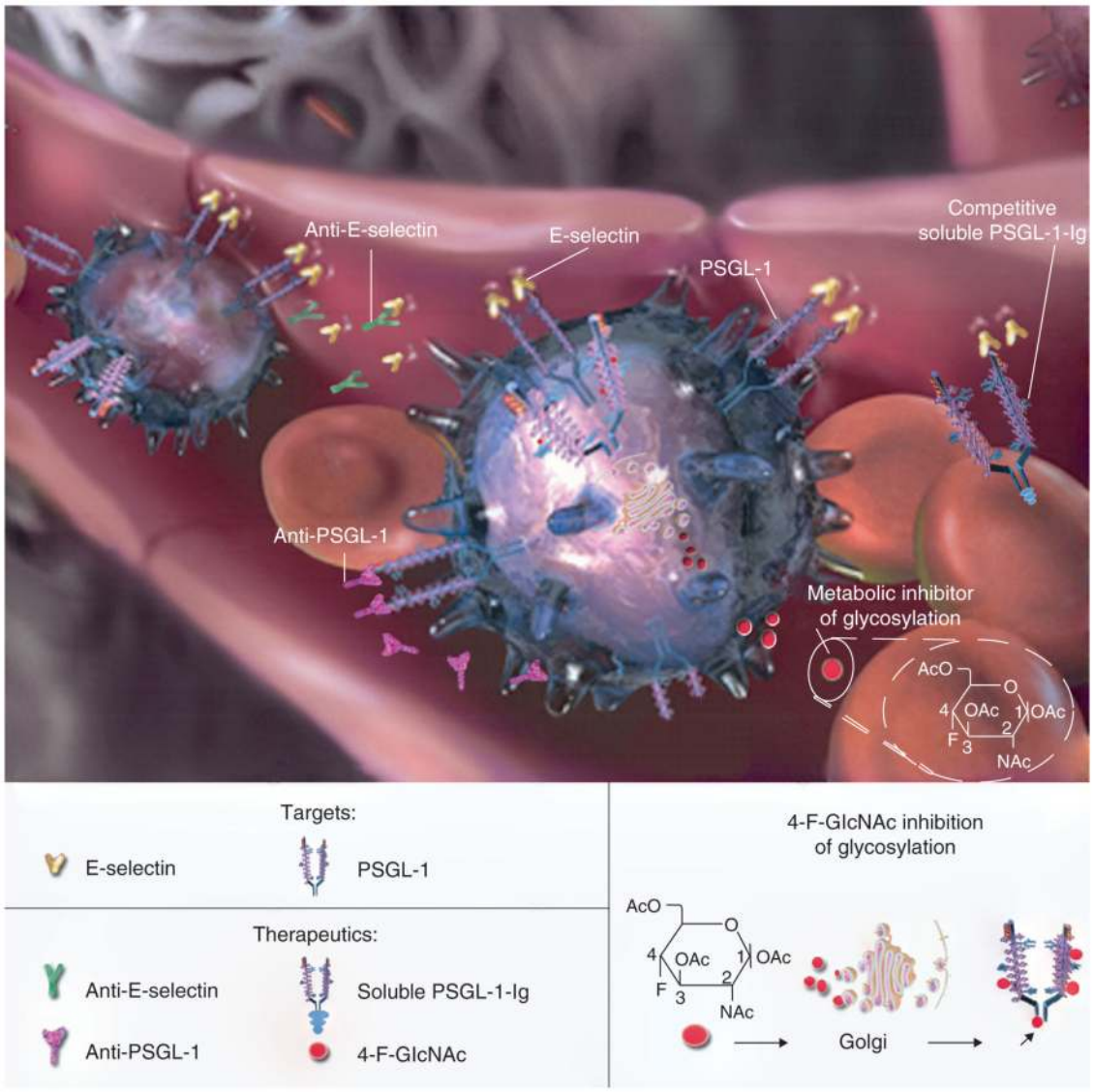

Figure 1. Therapeutic modalities targeting E-selectin and ligands of E-selectin in inflammation and cancer

PSGL-1 expressed on circulating leukocytes or tumor cells may promote cellular extravasation or metastasis by recognizing E-selectin expressed on blood vessel walls. The interaction could be blocked by competitive inhibitors, including antibodies that recognize E-selectin on the vascular wall, antibodies recognizing PSGL-1 on the leukocyte or tumor cell surface, or with soluble PSGL-1-Ig. The interaction may also be antagonized by metabolic inhibitors of glycosylation such as 4-F-GlcNAc. 4-F-GlcNAc can penetrate membranes of the cell and Golgi compartment, where it competes with GlcNAc for incorporation into the lactosamine backbones of PSGL-1. Incorporation of 4-F-GlcNAc truncates branching and elongation of glycans on PSGL-1, thereby, preventing synthesis of sLe^X or sLe^a by fucosyltransferases. Copyright 2007 Cynthia Turner/cynthiaturner.com

4-F-GlcNAc: Peracetylated-4-fluorinated-D-glucosamine; PSGL-1: P-selectin glycoprotein ligand-1.