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Targeting selectins and selectin ligands in inflammation and cancer

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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

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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 $\alpha 4 \beta 1$ (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], β 2 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 similarity 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 α 1,3 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 α 1,4-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, glycosyltransferases 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, β 1,6-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] and may 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- κ B 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 α 1,3 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 supplies ~ 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 $\alpha M\beta 2$ (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 $\beta 2$ 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-1 β [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-1 β 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 α 2,3 sialyl- and α 1,3fucosyltransferases. 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 stimulate 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 $\alpha M\beta 2$ 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-immunoglobulin (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 $\alpha 1,3$ - and $\alpha 1,4$ -FTs that generate 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 (Gal β 1,4GlcNAc) 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 Gal β 1,3GlcNAc or Gal β 1,4GlcNAc 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-fluorouracil), 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].

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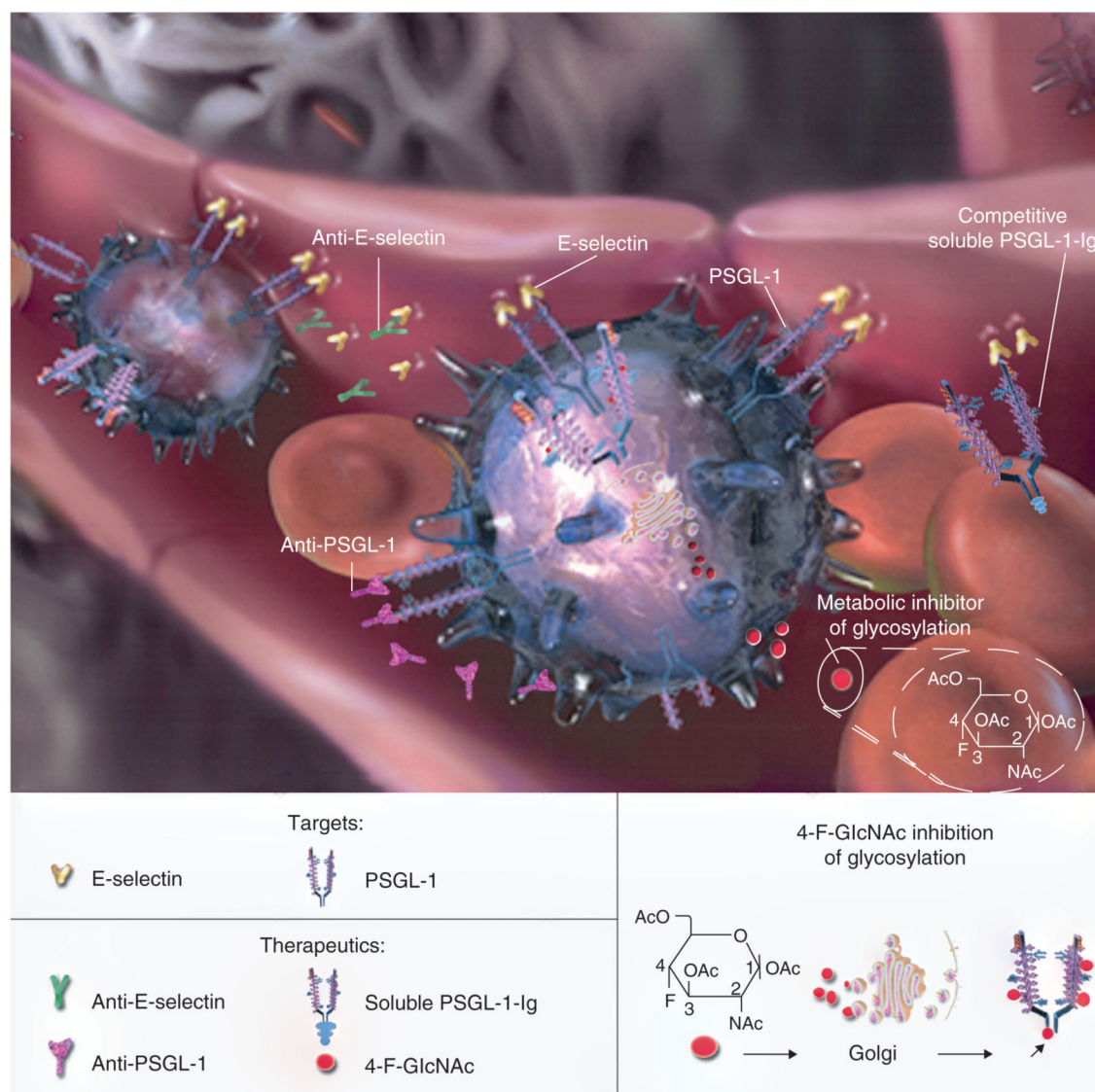


Figure 1. Therapeutic modalities targeting E-selectin and ligands of E-selectin in inflammation and cancer

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.

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