

Selectins

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Introduction

Once in a great while, scientists have the opportunity to witness a dramatic convergence of fields. Such has been the recent experience of researchers in the areas of cell adhesion and carbohydrate biochemistry. In March of 1989, published articles revealed the primary sequences of three independently studied cell surface glycoproteins found on endothelium, platelets, and leukocytes (1–4). At that time, these molecules were commonly known as the murine lymph node homing receptor or MEL-14 antigen, granule membrane protein 140 or platelet activation-dependent granule external membrane protein, and endothelial-leukocyte adhesion molecule 1 (Table I; see [5] for nomenclature summary). Each molecule was found to contain an NH₂ terminal lectin-like domain, an epidermal growth factor (EGF)¹ repeat, and a discrete number of modules (~ 60 amino acids each) similar to those found in certain complement binding proteins (Fig. 1). This collection of domains became the hallmark of a new family of molecules now known as the selectins (5). The presence of an amino terminal region related to the carbohydrate recognition domains of previously described calcium-dependent (C-type) animal lectins (6) sparked an intensive search for carbohydrate ligands. Important successes came quickly, due in large part to a solid foundation laid by biochemists who had previously defined the molecular structures of a wide variety of cell surface carbohydrates (for examples, see [7–11]). By early 1991, six publications identified fucosylated lactosamine structures, including Lewis x (Le^x; Galβ1-4(Fucα1-3)GlcNAc) (12) and sialyl-Lewis x (sLe^x; Neu5Acα2-3Galβ1-4(Fucα1-3)GlcNAc) (13–17) as ligands of two of the selectins. Since that time, fruitful research has been published at a remarkable pace.

The term selectin was originally proposed (18) to highlight the presence of the lectin domain, as well as to emphasize the selective nature of the expression and function of these molecules. A standard nomenclature has been agreed upon (5) which designates each family member according to the cell type on which it was originally identified: E-selectin (endothelium), P-selectin (platelets), and L-selectin (lymphocytes) (Ta-

ble I). In this Perspectives article, we discuss the selectins and their carbohydrate ligands: what they are, where they are found, and why they are important. We attempt to present the major discoveries and developments in sufficient detail for clarity, and to provide insights that may be of help in managing the abundant information in this area. We apologize for any oversights that we have made. Other recent reviews may also be of interest (19–24).

Discovery

Before 1989, L-, P-, and E-selectin were on different experimental pathways, although certain similarities can be seen in retrospect. All three selectins were identified using antibodies. L-selectin, the first of the selectins to be studied, was recognized as an adhesion molecule by using a monoclonal antibody (MEL-14) raised against a murine lymphoma (25). This antibody blocked lymphocyte adhesion to high endothelial venules of lymph nodes in vitro and blocked lymphocyte homing to lymph nodes in vivo. Subsequent studies demonstrated the presence of the MEL-14 antigen on murine neutrophils and monocytes and suggested its role in leukocyte adhesion to endothelium at sites of inflammation (26). Independently, L-selectin was identified as a leukocyte cell surface marker (Leu-8, TQ-1), found on most circulating human lymphocytes, neutrophils, and monocytes (27–30). The connection was made relatively recently (31, 32).

P-selectin (CD62) was discovered by investigators interested in the biochemical events associated with platelet activation. Antibodies were generated that bound to the surface of activated platelets but not resting platelets (33, 34). Immunochemical characterization of the antigen revealed a transmembrane glycoprotein of ~ 140 kD that is associated with α-granules in resting platelets and is rapidly redistributed to the cell surface upon activation. Later, P-selectin was also shown to be present in storage granules of endothelial cells, known as Weibel-Palade bodies (35, 36). As in the case of platelets, endothelial P-selectin is rapidly moved to the surface following stimulation by thrombin and other mediators (35, 36). The function of P-selectin as an adhesion molecule (37, 38) was appreciated after its structure was known and its investigative pathway had intersected with those of L- and E-selectin.

The discovery of E-selectin involved a monoclonal antibody-based strategy that combined identification of a cellular activation antigen and adhesion blocking. In search of endothelial molecules that supported the increased leukocyte adhesion observed on cytokine-activated endothelial cells (39), a monoclonal antibody was raised that recognized a cytokine-inducible glycoprotein in vitro (40) and endothelial cells at sites of inflammation in vivo (41). A second monoclonal antibody recognized the same endothelial molecule and blocked neutrophil adhesion, allowing the proposal of a new adhesion molecule (42).

Since their discovery, each of the three selectins has become

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1. Abbreviations used in this paper: EGF, epidermal growth factor; PPME, phosphomannan monoester core polysaccharide; sLe^a, sialyl Lewis a; sLe^x, sialyl Lewis x; TNF, tumor necrosis factor.

Table I. Selectins: Nomenclature and Expression

Old names	Cell type	Surface expression
L-selectin		
mLHR, Leu8	Lymphocytes	Constitutive surface expression
TQ-1, gp90 ^{MEL}	Monocytes	Conformational change(?)
Lam-1, Lecam-1, Leccam-1	Neutrophils	Shed after cellular activation
P-selectin		
PADGEM	Platelets	Thrombin, histamine, others
GMP-140	Endothelium	From storage granules (minutes) Cytokine inducible (hours) RNA, protein synthesis
E-selectin		
ELAM-1	Endothelium	Cytokine inducible (hours) RNA, protein synthesis

ELAM-1, endothelial-leukocyte adhesion molecule 1; GMP-140, granule membrane protein 140; PADGEM, platelet activation-dependent granule external membrane protein.

the subject of substantial investigative efforts. The intensity of these efforts increased dramatically after cloning and sequencing of selectin cDNAs demonstrated their relatedness. Although it remains possible that many new family members will be found, as in the integrin and immunoglobulin superfamilies, no other selectin has yet been reported.

Structure, function, and expression

Structural identity of a selectin resides in its unique domain composition (Fig. 1). E-, P-, and L-selectin are > 60% identical in their NH₂ terminal 120 amino acid residues, the lectin domain (1–4, 31, 43). The EGF repeats have comparable sequence similarity. Each complement regulatory-like module is ~ 60 amino acids in length and contains six cysteinyl residues capable of disulfide bond formation. This feature distinguishes the selectin modules from those found in complement binding proteins, such as complement receptors 1 and 2, which contain four cysteines (44, 45).

Cloning and structural analysis of genes for the selectins

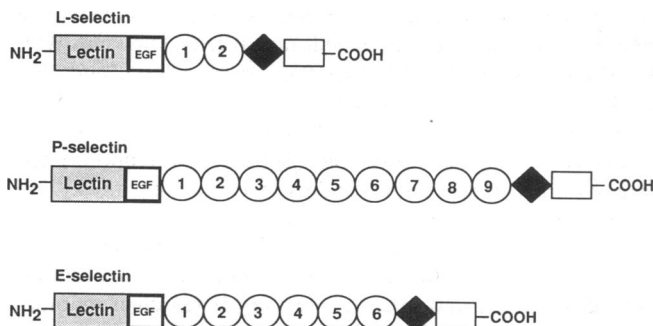


Figure 1. Domain composition of the three known human selectins. The extracellular portion of each selectin contains an amino terminal domain homologous to C-type lectins and an adjacent epidermal growth factor-like domain. These are followed by a variable number of complement regulatory-like modules (numbered circles) and a transmembrane sequence (black diamond). A short cytoplasmic sequence (open rectangle) is at the carboxyl terminus of each selectin. The number of amino acids present in the mature proteins as deduced from the cDNA sequences are: L, 385; P, 789; and E, 589.

revealed that each extracellular domain is encoded by a single exon (46–48). The genes encoding all three selectins have been localized to a cluster on the long arm of human and murine chromosome 1, closely linked to the gene for coagulation Factor V, and in proximity to genes for complement binding proteins (43, 47, 49, 50). The cloning of human L-selectin revealed a close structural similarity to its murine counterpart (31, 43, 51, 52). Recent analysis of cDNAs encoding murine E- and P-selectins, rabbit E-selectin, and canine P-selectin further revealed interspecies conservation of structure and function (53–56). Human E-, P-, and L-selectin contain 11, 12, and 7 potential sites of N-linked glycosylation, respectively; migration on polyacrylamide gels and quantitative analysis indicate that glycosylation of the selectins accounts for ≥ 30% of their mass (3, 4, 31, 43, 57). The precise composition and function of carbohydrates on the selectins are not yet known.

The three selectins act in concert with other cell adhesion molecules (e.g., intracellular adhesion molecule [ICAM-1], vascular cell adhesion molecule-1, and leukocyte integrins; reviewed in [58–63]) to effect adhesive interactions of leukocytes, platelets, and endothelial cells. E-selectin was first shown to support the adhesion of neutrophils to cytokine-activated endothelium (4, 42). Subsequent studies in vitro have suggested that E-selectin also supports the binding of monocytes, a subpopulation of memory T lymphocytes, eosinophils, and basophils (64–74). Similarly, P-selectin expressed on activated platelets mediates binding to multiple leukocyte types (37, 75–78). Endothelial P-selectin also supports leukocyte adhesion (38, 79, 80). In addition to its role in lymphocyte homing (reviewed in [81, 82]), L-selectin appears to participate in the adhesion of neutrophils, monocytes, and lymphocytes to activated endothelium (83–86). This function is best observed when the binding interaction occurs under the influence of fluid shear stress. Experiments in vitro and in vivo have suggested that selectins may be especially important in leukocyte rolling on the vessel wall, a process that can precede firm attachment and extravasation during inflammation (87–89).

Elucidation of structure–function relationships of selectins has established the importance of the lectin and EGF domains. Most adhesion-blocking monoclonal antibodies recognize epitopes located within these regions (15, 49, 90–92). Results of adhesion experiments using recombinant fusion proteins lacking one or more domains, and with chimeras having mixed selectin domains, further support the importance of the two amino terminal domains in mediating cell adhesion (91–93). Short peptides based on amino acid sequences from three separate regions of the lectin domain have been shown to block leukocyte adhesion to P-selectin (94, 95). When conjugated to albumin, these peptides support leukocyte adhesion. Peptides from two of these regions appear to bind calcium, and are also effective in blocking adhesion to E-selectin. It has been suggested the calcium binding peptides correspond to regions in the native molecule that coordinate calcium and possibly bind ligands (95). Studies using site-specific mutagenesis have suggested a functional contribution of several specific amino acids within the lectin domain of E-selectin (96) and P-selectin (Hollenbaugh, D., and A. Aruffo, personal communication). Interestingly, these amino acids fall outside the regions corresponding to the adhesion blocking peptides described above. Ultimate identification of the amino acids directly involved in ligand binding will require additional methods of structural analysis (e.g., x-ray crystallography). The function of the com-

plement regulatory-like modules is less well defined. It is noteworthy, however, that one monoclonal antibody that binds to these modules in L-selectin also recognizes E-selectin, and inhibits adhesive function of both molecules (97). In addition, L-selectin-immunoglobulin fusion proteins that lack the complement regulatory-like modules exhibit diminished activity (93). To date, no published studies have demonstrated the binding of complement proteins to selectins.

Although the selectins are closely related in structure and function, their patterns of expression are quite different. The expression of E-selectin appears to be largely restricted to activated endothelial cells. In vitro, cultured endothelium will express E-selectin following stimulation by endotoxin or the inflammatory cytokines IL-1 or tumor necrosis factor (TNF) (4, 42). This expression peaks in ~ 4–6 h, declines to basal levels by 24–48 h, and requires de novo RNA and protein synthesis. Interferon gamma does not itself induce E-selectin expression but appears to prolong its expression in response to IL-1 and TNF (98, 99). Examination of 5' regulatory regions of the human E-selectin gene have revealed the presence of sequences consistent with NF- κ B and AP-1 binding sites (47, 53, 100, 101). The former appears to be necessary but not sufficient for cytokine-inducible expression of the human gene (100, 101), and two additional upstream elements have also been implicated (101). The murine E-selectin promoter region also supports cytokine-inducible gene expression, but does not contain a sequence corresponding to the consensus NF- κ B site (53). It is anticipated that reagents capable of blocking E-selectin expression will diminish inflammatory responses in vivo. Interestingly, a recent study suggests that the antiinflammatory effects of corticosteroids may, at least in part, involve such a mechanism: dexamethasone can inhibit endothelial cell expression of E-selectin stimulated by LPS and IL-1 (102).

Unlike E-selectin, P-selectin is synthesized constitutively and stored intracellularly in both platelets and endothelial cells. After synthesis, it appears to be targeted to storage/secretory granules by virtue of a sorting signal present in its cytoplasmic domain (103, 104). From these intracellular pools, P-selectin can be rapidly mobilized to the cell surface, where it binds leukocytes. A variety of mediators, including thrombin, histamine, terminal complement components, and H₂O₂ have been shown to induce rapid surface expression of P-selectin (35, 36, 105–107). Sphingosine derivatives and certain inhibitors of protein kinase C appear to block the mobilization of P-selectin (108). The expression of P-selectin at the cell surface is short lived, declining substantially within minutes. Recent studies suggest that new P-selectin synthesis may be induced by cytokines such as IL-1 and TNF in a manner similar to that of E-selectin (54, 56, 109). In a separate field, it has been suggested that viral infection of endothelial monolayers can result in the expression of E- and P-selectin, apparently through cytokine release and thrombin generation, respectively (79, 110). Of the three selectins, only L-selectin is constitutively expressed at the cell surface. Interestingly, leukocytes rapidly shed this selectin following activation (111–113). Thus, the activity of the selectins appears to be controlled in large part by regulation of their appearance and disappearance from the cell surface. Conformational changes may also help regulate selectin function. It has been reported that activation of neutrophils and lymphocytes by lineage-specific stimuli results in a rapid and transient increase in L-selectin activity before its being shed (114).

Carbohydrate ligands

The realization that selectins contain domains homologous to C-type lectins has led to an intensive search for carbohydrate ligands. Individual selectins have been shown to bind to a variety of natural and synthetic carbohydrate structures. The structures identified to date fall into three general categories: (a) oligosaccharides related to sialyl-Lewis x (sLe^x) and sialyl-Lewis a (sLe^a) (Fig. 2); (b) phosphorylated mono- and polysaccharides; and (c) sulfated polysaccharides. As described below, certain data point to an important contribution of specific cell-surface proteins in the presentation of selectin ligands. It should be noted that the molecular details of selectin–ligand interactions (e.g., binding sites and bond formation) have not yet been determined. A corollary to this statement is that the binding of individual selectins to different carbohydrate types may or may not be by the same mechanism.

Many recent studies on selectin–carbohydrate interactions have focused on oligosaccharides. An early success was the observation that P-selectin–dependent rosetting of activated platelets to leukocytes is blocked by LNF-III, a pentasaccharide containing the Lewis x determinant (Le^x; Gal β 1-4(Fuc α 1-3)GlcNAc) (12). Other studies identified the sialylated form of this oligosaccharide, sLe^x (Neu5Ac α 2-3Gal β 1-4(Fuc α 1-3)-

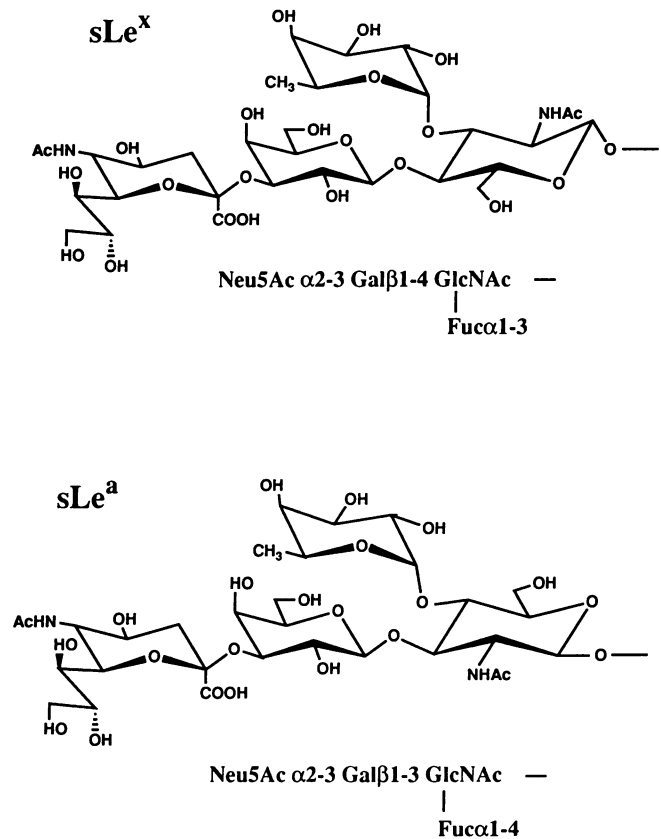


Figure 2. Oligosaccharide ligands of the selectins: structural representations of the isomers sLe^x and sLe^a. They contain a terminal sialic acid (Neu5Ac) linked α -2-3 to galactose (Gal), in turn linked to an N-acetylglucosamine (GlcNAc). Both structures contain a fucose coupled to the GlcNAc. sLe^x and sLe^a differ in the linkages of galactose and fucose to the GlcNAc. The indicated structures are typically found as terminal residues of larger oligosaccharides on glycoproteins and glycolipids.

GlcNAc) and/or closely related structures as ligands of E-selectin (13–17). sLe^x and other fucosylated lactosamines are found in abundance on circulating neutrophils and monocytes (115–120) and on a small percentage of blood lymphocytes (120–122). Separate studies have demonstrated that sialic acid is a component of some P-selectin ligands (123, 124), and that oligosaccharides containing sLe^x are recognized by this molecule (125, 126). Most recently, murine L-selectin was also shown to interact with sLe^x-containing structures (127, 128). In addition, human E- and P-selectin and murine L-selectin have been shown to interact with molecules containing sLe^a (Neu5Ac α 2-3Gal β 1-3(Fuc α 1-4)GlcNAc), a structural isomer of sLe^x (121, 128–130). sLe^a is not typically expressed by blood leukocytes but is expressed by certain cancer cells, suggesting a possible role in metastasis (see below).

Lectin–carbohydrate interactions are characteristically less restricted and of lower affinity than most well described protein–protein binding interactions (e.g., antibody–antigen, hormone–receptor). Therefore, it is essential to characterize lectins according to their binding specificities and to establish their ligand binding affinities. This effort is now under way for the selectins, facilitated by the use of purified and synthetic oligosaccharides. Several reports have suggested that E-selectin recognition of sLe^x and sLe^a requires both sialic acid and fucose in specific position and linkage (121, 129, 131). However, one recent study describes adhesion of cells expressing recombinant E-selectin at high density to fucose-containing oligosaccharides that lack sialic acid (132). In addition, structures related to sLe^x and sLe^a in which the sialic acid is replaced by a sulfate group support adhesion of E-selectin–transfected cells (133). Although P-selectin also binds to sLe^x and sLe^a, it appears to recognize a wider array of oligosaccharides than E-selectin. For example, P-selectin binds the nonsialylated trisaccharides Le^x and Le^a (37, 125, 131, 134) and may bind tetrasaccharides related to sLe^x and sLe^a having sialic acid linked α 2–6 instead of α 2–3 (134, 135), although this point is controversial (127).

The relative binding affinities of selectin–carbohydrate interactions are now being defined. Cell adhesion assays have yielded contradictory results on the relative binding activity of E-selectin for sLe^x and sLe^a (121, 129), whereas quantitative inhibition assays using solution-phase oligosaccharides indicate that sLe^a binds E-selectin with a higher affinity than does sLe^x (131). In addition, two modifications of sLe^x and sLe^a that result in substantial increases in apparent binding affinities for E-selectin have been identified (131). These are the addition of an 8-methoxycarbonyloctyl aglycone ($-(\text{CH}_2)_8\text{CO}_2\text{CH}_3$) attached in a β -glycosidic linkage to the reducing sugar, and the substitution of an amino or azido moiety for the N-acetyl group at carbon 2 of GlcNAc. Together these modifications on sLe^a increased inhibitory activity more than 35-fold compared to the reducing tetrasaccharide sLe^x in a competitive E-selectin–binding assay (131). As noted above, human E- and P-selectin and murine L-selectin have all been shown to bind sLe^x and sLe^a. Precise binding parameters (rate constants and equilibrium dissociation constants) of the selectins for these carbohydrates are not yet known, but certain lines of evidence suggest that they may differ. For example, solution phase sLe^x or sLe^a block E-selectin binding interactions better than P- and L-selectin interactions (131, 134, 136). In addition, several cell lines that express sLe^x or sLe^a adhere to E-selectin but not to P-selectin or L-selectin. As a prelude to points made below, it is

interesting to note that protease treatment of neutrophils and HL-60 cells abolishes their adhesion to P-selectin without substantially altering adhesion to E-selectin (135).

Coincident with the studies on oligosaccharide ligands of the selectins were demonstrations that certain proteins may contribute in an important way to cellular ligands of L- and P-selectin (124, 137–139). For example, L-selectin has been used to affinity purify two sulfated, fucosylated, and sialylated glycoproteins of 50 and 90 kD from murine lymph nodes (137). The 50-kD glycoprotein was cloned and found to be a mucin containing two serine/threonine rich domains, consistent with substantial O-linked glycosylation (138). The term vascular addressin has been used to refer to tissue-specific adhesion molecules involved in leukocyte homing (82). The peripheral lymph node addressin is defined by monoclonal antibody MECA-79, an IgM that binds to lymph node high endothelial venules and blocks lymphocyte adhesion (140). This antibody was used to precipitate multiple glycoprotein species, perhaps through recognition of a carbohydrate epitope, including the 50- and 90-kD glycoproteins described above (137). It has also been appreciated that L-selectin functions in the adhesion of neutrophils, monocytes, and lymphocytes to cytokine-activated endothelial monolayers, apparently through an inducible ligand (85). The nature of the carbohydrate and/or protein components of this L-selectin ligand on cytokine-activated endothelial cells is not yet established.

P-selectin has been shown to bind specifically to protease-sensitive sites on neutrophils and HL60 cells (124, 135, 139, 141). Further, it has been used to affinity purify from leukocyte extracts a glycoprotein displaying an apparent molecular weight on polyacrylamide gels of \sim 120,000 under reducing conditions (139). Thus, both P- and L-selectin appear to bind with high affinity to a relatively small number of cell surface glycoproteins. The nature of the participation of protein and carbohydrate in these selectin ligands remains to be determined. Moreover, the relative contributions of high and low affinity binding sites to cell adhesion *in vitro* and *in vivo* are not yet known. In conjunction with these observations, it is notable that antibodies that bind to the EGF repeat of L-selectin have been shown to block cellular adhesion without hindering the binding of certain phosphorylated carbohydrate ligands (49, 91, 136). A separate line of investigation has suggested that L-selectin may present carbohydrate ligands to E- and P-selectin (142). It is important to note, however, that cell types with little or no surface L-selectin, such as phorbol ester–stimulated neutrophils, the promyelocytic cell line HL60, and certain human colon cancers, can adhere to E- and P-selectin (15, 124, 143).

The earliest studies on interactions of selectins with carbohydrates predated the elucidation of selectin structure. It was demonstrated that lymphocyte adhesion to high endothelial venules of lymph nodes could be blocked by relatively high concentrations (5–10 mM) of certain phosphorylated monosaccharides, such as mannose-6-phosphate, and by yeast-derived phosphomannan (PPME), a high molecular weight core polysaccharide containing mannose-6-phosphate (144). Moreover, PPME-coated beads were shown to bind to lymphocytes, a process that could be blocked by the MEL-14 anti-L-selectin antibody (145). Recent studies using recombinant proteins have confirmed that L-selectin binds to PPME (91, 93, 136). In contrast, P- and E-selectin do not appear to bind to this polysaccharide ([91, 124], and unpublished observation). In

separate investigations, L- and P-selectin, but not E-selectin, have been shown to interact with sulfated polysaccharides such as fucoidan and heparin (131, 145–149). Although the determinants of binding have not been defined, these polysaccharides are perhaps most similar in being sulfated polyanions. Whether or not interaction of these molecules with P- and L-selectin involves binding in the lectin domain is unclear, and it must be pointed out that many proteins (e.g., growth factors, fibronectin) can bind to these same polyanionic macromolecules. P- and L-selectin also bind to 3-*O*-sulfate-galactosyl ceramide (sulfatides) coated on surfaces or incorporated in micelles (147, 148). In these physical forms, sulfatides may also present a sulfated polyanionic binding surface. In summary, E-selectin binds to the tetrasaccharides sLe^x, sLe^a, and related structures, while P-selectin binds to some of these molecules as well as to certain sulfated polyanionic polysaccharides, such as fucoidan. L-selectin appears to bind sLe^x and sLe^a (although less well than E-selectin), sulfated polysaccharides, and the mannose-6-phosphate-containing polysaccharide PPME. A fuller understanding of these interactions will require analysis of selectin-ligand complexes by x-ray crystallography and nuclear magnetic resonance spectroscopy. Definitive determination of binding affinities and rate constants will provide important additional information.

Selectins and disease

From the perspective of an invading microorganism, the human host presents a formidable array of defenses. If successful in penetrating the perimeter shields (e.g., skin and mucous membranes), it must face the onslaught of attacking leukocytes. Central to this process is the host's ability to recruit leukocytes to specific sites in the body where they are most needed. Leukocyte recruitment involves an orchestration of soluble mediators (e.g., cytokines) and cell-surface molecules that results in focal leukocyte attachment to the vessel wall and extravasation. The importance of the selectins in this process is now widely accepted. The function of selectins *in vitro*, as well as their patterns of expression *in vivo*, points to their involvement in a wide variety of human diseases, from acute appendicitis to asthma to myocardial infarction.

Selectin expression *in situ* has been described using animal and human tissues. The earliest study on E-selectin expression (41) predated its demonstration as an adhesion molecule. This work revealed the presence of an endothelial activation antigen at a site of a delayed-type hypersensitivity reaction in human skin. The expression of this antigen was temporally and spatially associated with inflammatory infiltrates. Activated endothelium expressing this marker was also found in inflamed lymph nodes, tonsil, thyroid, and appendix. Subsequent reports from numerous laboratories have confirmed and extended these observations (reviewed in 58, 150–153). A unifying theme that has emerged is the expression of E-selectin on endothelial cells at sites of active inflammation. Typically, it is most easily detected on endothelium of postcapillary venules, the site of prominent vascular leak and leukocyte extravasation during inflammation. In certain animal disease models, such as septic shock, E-selectin is also found on capillary endothelium (154). Although frequently associated with neutrophil infiltrates (150, 155, 156), E-selectin can be found at inflammatory sites where the cellular infiltrate is predominantly mononuclear (41, 157, 158).

Several recent studies in animal models have demonstrated

the participation of the selectins in inflammatory processes *in vivo*. A role for E-selectin in acute lung injury has been indicated by antibody blocking of neutrophil extravasation and vascular permeability in rat IgG immune complex-induced damage (159). Interestingly, IgA immune complex-induced damage, which appears to involve primarily mononuclear leukocyte infiltrates (rather than neutrophil infiltrates as in IgG induced damage), was not blocked by anti-E-selectin antibodies (160). In a separate report, anti-P-selectin antibodies were found to protect against neutrophil-dependent acute lung injury that occurs after intravenous activation of complement by cobra venom factor (161). In a primate model of extrinsic asthma, antibody-blocking data have suggested that E-selectin plays a major role in neutrophil influx associated with late phase airway obstruction (162). As noted above, recent animal studies have suggested that P-selectin synthesis and expression can also be induced by cytokines like IL-1 and TNF. This observation emphasizes the need to assess carefully the expression and function of all selectins in a variety of disease processes. New data suggest that both E- and P-selectin may participate in the neutrophil-mediated damage associated with ischemic reperfusion injury in the heart (56, 163). Antibodies to L-selectin and soluble recombinant forms of L-selectin have been used to demonstrate the participation of this molecule in a variety of animal models of homing and inflammation (25, 26, 164, 165). Other recent observations may also lead to increased understanding of selectin function in human disease processes. As noted above, activated leukocytes shed L-selectin. In addition to shed L-selectin, soluble forms of P-selectin, perhaps synthesized from alternatively spliced mRNA, have been proposed (3, 46, 166). Recent reports describe the measurement of soluble forms of P-selectin and L-selectin in normal human plasma, finding ~ 0.1 – $0.3 \mu\text{g/ml}$ (167) and $\sim 1.5 \mu\text{g/ml}$ (168), respectively. It is possible that soluble forms of selectins modulate inflammatory responses.

Selectin-carbohydrate interactions are also being studied in the relationship to hematogenous spread of cancer cells. This effort began with the demonstration that E-selectin can support the adhesion of human colon cancers (143, 169). The mechanism of this interaction became clearer after the demonstration that E-selectin binds to sLe^x and sLe^a, both of which are expressed in abundance on most human colon cancers (15, 170–173). Since platelet interactions with tumor cells can influence metastasis, it is likely that P-selectin also participates in this disease process.

Selectins and other adhesion molecules work in conjunction with a variety of cell-associated and soluble mediators (e.g., platelet activating factor, IL-8) to orchestrate the development of inflammatory reactions (58–60, 62). The extent of cooperation between selectins and other molecules in determining the composition and kinetics of inflammatory infiltrates is a topic of intense research. In this regard, it is noteworthy that two studies have suggested that E-selectin binding to neutrophils activates their CD11/CD18 adhesion molecules, which can in turn bind to endothelial cell adhesion molecules ICAM-1 and ICAM-2 (174, 175). P-selectin has been reported to facilitate the activation of neutrophils by platelet activating factor, a lipid mediator produced by endothelial cells (176), but has been reported to inhibit TNF-induced neutrophil activation (166, 177). P-selectin also appears to modify lymphocyte production of proinflammatory cytokines in response to anti-T cell receptor monoclonal antibodies (178).

Recent evidence supporting the importance of selectin-carbohydrate interactions in inflammation comes from a newly described human disease called leukocyte adhesion deficiency type 2 (179). This rare disorder is characterized by inadequate inflammatory responses to infection, which may result from an inability to add fucose to carbohydrate structures, including the selectin ligands sLe^a and sLe^x. Research efforts now in progress will more precisely define the roles of the selectins in inflammatory and immunological disease processes as well as in cancer. Many laboratories are attempting to identify novel antiinflammatory compounds based on an understanding of selectin-carbohydrate interactions. These efforts involve antibody-, peptide- and carbohydrate-based approaches to block selectin-dependent adhesion directly. Selectin antagonists may prove to be effective therapeutic agents alone or may complement drugs designed to block the expression and function of other adhesion molecules. It is hoped that selectin research will lead to new therapies before the turn of the century.

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