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Lectin Cell Adhesion Molecules (LEC-CAMs): A New Family of Cell Adhesion Proteins Involved With Inflammation

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Abstract The means by which leukocytes, including lymphocytes, monocytes, and neutrophils, migrate from the circulation to sites of acute and chronic inflammation is an area of intense research interest. Although a number of soluble mediators of these important cellular interactions have been identified, a major site of great importance to the inflammatory response is the physical interface between the white cell and the endothelium. This critical association is mediated by an array of cell surface adhesion molecules. Previous data have demonstrated that the integrin subfamily of heterotypic adhesion molecules was a major component of these adhesive interactions, although it was clear that other, non-integrin-like molecules of unknown identity also seemed to be involved during the inflammatory process. A number of these other cell-surface glycoproteins which may be involved with inflammation have recently been characterized by molecular cloning. These glycoproteins, including the peripheral lymph node homing receptor (pln HR), the endothelial cell adhesion molecule (ELAM), and PADGEM/gmp140, are all members of a family of proteins which are unified by the inclusion of three characteristic protein motifs: a lectin or carbohydrate recognition domain, an epidermal growth factor (egf) domain, and a variable number of short concensus repeats (scr) which are also found in members of the complement regulatory proteins. The appearance of lectin domains in all of these adhesion molecules is consistent with the possibility that these glycoproteins function by binding to carbohydrates which are expressed in a cell and/or region specific manner, and the members of this adhesion family have been given the generic name LEC-CAM (lectin cell adhesion molecules). The discovery of adhesive proteins which appear to utilize the recognition of carbohydrate moieties for restricted cell adhesion may present new opportunities for the development of carbohydrate-based anti-inflammatory drugs.

Key words: cell adhesion, leukocytes, endothelium, lectins, epidermal growth factor, complement regulatory motifs

INTRODUCTION

The inflammatory process consists of a number of important cellular phenomena, not the least of which are the adhesive interactions between the circulating leukocyte populations and the vascular endothelium adjoining the inflammatory site. The ability of specific leukocytic populations to adhere to the endothelium at the appropriate time and place is an extremely critical aspect of the inflammatory process since it allows for the pertinent influx of white cells to the inflammatory site and prevents the inappropriate migration of these powerful immune cells to normal tissue locations. These adhesive interactions work in concert with soluble mediators of inflammation which are released from inflammatory sites so that a remarkably coordinated cellular cascade of activation, adhesion, migration, and resultant inflammatory response can occur. While this highly evolved inflammatory system is critical for the defense of the organism, there are various situations, such as autoimmune disease, reperfusion injury, and organ rejection, where the inflammatory response can have deleterious effects. The development of pharmaceutical reagents which inhibit these adverse inflammatory reactions is of major interest in both the academic and industrial sectors, and the blockade of the cellular adhesion events which mediate inflammation is unquestionably a potentially fruitful avenue of pursuit.

The adhesion molecules which are thought to be involved in inflammation are a highly diverse group. A large body of work exists which implies that some members of the integrin family of adhesion molecules play a critical role during the inflammatory response (for example, [1]). The integrins are an extensive family of mole-

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cules which are involved with leukocyte adhesion to both the endothelium as well as to the extracellular matrix. Integrins of diverse function are constructed from heterotypic alpha and beta subunits, with adhesive specificity being generated from a large number of distinct alpha chains and a smaller number of different beta chains. These heterodimeric adhesion molecules either recognize extracellular matrix components, such as fibronection, vitronectin, and collagen, or, perhaps more importantly for the inflammatory process, glycoprotein ligands found on the surface of the endothelium. The leukocyte integrins have been clearly shown to be involved with inflammatory processes in both in vitro (for example, [2]) (i.e., cell binding assays) as well as in vivo (for example, [3]) (i.e., inhibition of neutrophil-mediated inflammation by anti-integrin subunit antibodies) situations. These protein-protein interactions can thus result in specific adhesion between leukocytic cells expressing certain integrin subsets and various adhesive ligands found, for example, at endothelial sites responding to inflammatory stimuli.

While the importance of the leukocyte integrins cannot be overestimated, a number of findings have suggested that other adhesion molecules may also be at work during the process of white cell inflammation. Experiments investigating the ability of monoclonal antibodies directed against the common beta subunit of the leukocyte integrins showed residual neutrophil binding to endothelial cells activated by various inflammatory stimuli, implying that other, non-integrin adhesion systems might contribute to the adhesion of neutrophils to activated endothelial cells (for example, [4]). Patients with deficiencies in the expression of the leukocyte integrins, the so-called leukocyte adhesion deficiency or LAD patients [5], showed normal lymphocyte-mediated inflammation, suggesting that these cells may utilize non beta 2 integrin-mediated adhesion to migrate to inflammatory sites. Finally, a monoclonal antibody directed against a receptor which will be described below (the homing receptor) showed a high degree of inhibition of neutrophil inflammation in vivo, consistent with the possibility that this non-integrin adhesion molecule is involved with acute inflammatory responses [6,7]. These results, among others, strongly suggested that the leukocyte integrins may act in concert with other adhesion molecules.

Over the past year, cDNAs encoding three related adhesion molecules have been characterized. These molecules appear to be members of a family of proteins which may utilize protein-carbohydrate interactions for specific cell adhesion during various types of inflammation. The purpose of this review is to contrast these three molecules at both the molecular and biological levels (see Table 1).

THE LEUKOCYTE HOMING RECEPTOR: A PARADIGM FOR LECTIN CELL ADHESION MOLECULES

The trafficking of lymphocytes from the circulation to the various lymphoid tissues is accomplished by the efficient adhesion of these cells to the post capillary venule endothelium within these organs [8]. A glycoprotein, termed the homing receptor, was initially characterized as the adhesion molecule on the lymphocyte cell surface which accomplished the efficient binding of B and T cells to the peripheral lymph node (pln) endothelium [9]. This glycoprotein has been found to be expressed on all leukocytic cells, and a monoclonal antibody, termed Mel 14, directed against the murine form of this protein was found to efficiently block the binding of all leukocytes to the lymphoid endothelium [9]. Immunoprecipitation analysis of the antigen recognized by Mel 14 revealed that it was a monomeric glycoprotein of approximately 90,000–110,000 daltons molecular mass (depending upon the cell type analyzed), implying that it was not a

TABLE I. Functional Aspects of the LEC-CAMs

LEC-CAM	Location	Expression	Function
PLN homing receptor	Leukocytes	On until activation	PLN migration, chronic and acute inflammation (?)
ELAM 1	Endothelium	Transient after inflammation stimulus (~ h)	Acute neutrophil and monocyte inflammation
PADGEM/GMP140	Platelet and endothelial storage granules	Granule release after thrombin stimulus (~ s)	Acute neutrophil and monocyte inflammation (thrombosis?)

member of the heterodimeric integrin adhesion family. Interestingly, this adhesion system seemed to be specific for pln and mesenteric lymph node endothelium, since the Mel 14 monoclonal antibody was unable to block the binding of lymphocytes to the gut-associated Peyer's patch endothelial tissue. This latter result suggested a lymphoid organ specific presentation of the endothelial ligand recognized by the homing receptor [9,10].

Shortly after the initial characterization of this glycoprotein, work from the laboratory of Rosen revealed that this cell adhesion molecule had carbohydrate binding activities. Initial work from this laboratory demonstrated that lymphocyte-pin endothelial interactions could be blocked by relatively high concentrations of certain charged monomeric sugars, such as mannose-6-phosphate, and lower levels of polymers of charged sugars, such as polyphosphomannan ester (ppme) or fucoidin [11,12]. In addition, treatment of endothelial cell sections with sialidase abolished lymphocyte binding, implying that sialic acid may be involved with the adhesion event [13]. These results suggested that a carbohydrate binding protein may have been involved with lymphocyte-pin endothelial adhesion. Subsequent experiments revealed that the Mel 14 monoclonal antibody could inhibit the binding of fluorescent beads coated with the carbohydrate ppme to the lymphocyte surface, consistent with the possibility that the glycoprotein recognized by Mel 14 was a carbohydrate binding protein involved with pln endothelial adhesion [14]. Thus, the fact that the Mel 14 monoclonal antibody and ppme both blocked lymphocyte-endothelial cell binding implied that protein-carbohydrate interactions may have been involved with this type of adhesion.

The cloning and nucleotide sequence of the cDNA encoding the murine form of the homing receptor revealed that this adhesion molecule was, in fact, a carbohydrate binding protein [15,16]. The cDNA encoded a transmembrane glycoprotein of 372 amino acids which contained a number of protein motifs which were homologous to previously described domains. Perhaps the most interesting domain was at the N-terminus of the protein, where a motif homologous to lectins, or carbohydrate binding proteins, in the type C or calcium-dependent family was found [17]. This was consistent with both the carbohydrate blocking experiments described above as well as experiments which demonstrated that the binding of leukocytes to the pin endothelium was strictly calcium dependent. As will be described below, these results were consistent with the direct involvement of the lectin domain in cell adhesion to the pin endothelium. Following the lectin domain was an epidermal growth factor (egf) domain, and then two exact copies of a short concensus repeat (scr) domain which is also found on members of the complement regulatory family of proteins, thus completing the extracellular portion of the molecule (Fig. 1). A highly homologous protein was also found in the human [18,19], implying (and confirming) the conservation of adhesion mechanisms in lymphocyte-pin endothelium binding. In addition, two groups demonstrated that the human version of the homing receptor was identical to the antigen recognized by the Leu 8 and TQ-1 monoclonal antibodies [21,22]. The mosaic structure of this protein was reflected in the structure of the genomic locus encoding the homing receptors in both the mouse and human, where it was found that each protein motif was encoded by a separate exon ([20], T. Tedder, personal communication). Interestingly, the gene encoding the homing receptor was found to map to chromosome 1 in both the murine and human cases, adjacent to the region encoding a number of complement binding proteins that all contain variable numbers of the scr repeats found in the homing receptor.

Subsequent work on the role of carbohydrate binding in pln homing receptor function has confirmed the hypothesis that the lectin domain plays a major role in the cell adhesion mediated by this glycoprotein. The ability of the Mel 14 antibody to block the binding of leukocytes to pln endothelium suggested that localization of the epitope recognized by this antibody would allow for a prediction of potentially important functional domains of the homing receptor [23]. This mapping demonstrated that the Mel 14 antibody recognized a determinant within the first 53 amino acids of the lectin domain, consistent with the possibility that the lectin domain was directly involved with endothelial recognition. Interestingly, the ability of this antibody to react with this determinant was dependent upon the inclusion of the adjacent egf-like domain, implying that the conformation of the lectin domain may require the egf-like region. A similar result was found in the case of the human homing receptor as well (Bowen and Lasky, unpublished observations). The indirect and di-

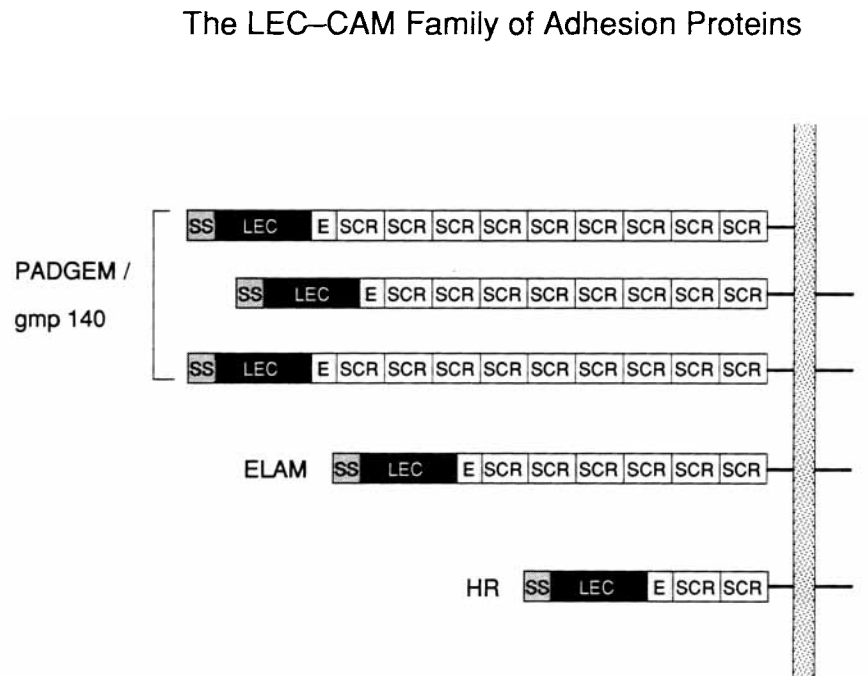

Fig. 1. Structures of the known LEC-CAM adhesion molecules. Illustrated are the structures of the homing receptor (HR), endothelial-leukocyte adhesion molecule (ELAM), and full-length, scr-deleted, and soluble forms of PADGEM/gmp140. The proteins contain a signal sequence (SS), lectin (LEC), epidermal growth factor like (E), short consensus repeats (SCR), membrane anchor (with the exception of soluble PADGEM/gmp140), and cytoplasmic domains.

rect demonstrations of binding of the isolated homing receptor glycoprotein to the pln endothelium [24], together with the Mel 14 mapping studies, calcium dependence, and carbohydrate blocking experiments, strongly implied that this adhesion molecule bound to a carbohydrate-containing ligand on the endothelial surface. Along these lines, it has recently been shown that the binding to the pln endothelium of a recombinant form of the homing receptor is abolished when the endothelial cells are treated with sialidases [25,26], in agreement with cell binding studies mentioned above and suggesting that some potentially unique form of sialic acid is a major component of the ligand recognized by this adhesion molecule. Finally, a ~90,000 dalton, glycosylated protein recognized by the monoclonal antibody MECA 79 and specific for pln endothelium may be a component of the homing receptor ligand [27]. Together, these results provide strong evidence for the contention that the ligand recognized by the homing receptor is carbohydrate in nature, although the exact form of the carbohydrate (i.e., glycoprotein, glycolipid, etc.) remains to be elucidated.

Recently, Siegelman et al. presented evidence for the identity between the homing receptor and the allotypic murine antigen Ly-22 [28]. These data also suggested that the Ly-22 monoclonal antibody recognized an allotypic determinant contained within the egf-like domain of the homing receptor. Perhaps most interestingly, these investigators also showed that this antibody was capable of effectively inhibiting pln endothelium binding by lymphocytes. In addition, the antibody did not appear to inhibit the binding of ppme to the lectin domain of the receptor, as opposed to the Mel 14 monoclonal antibody, implying that it was not acting upon the ability of the homing receptor to recognize carbohydrates. These results have been interpreted to suggest that the egf-like domain may also be involved in binding of the homing receptor to the pln endothelium, perhaps by interaction with a protein specifically expressed on these endothelial cells.

While the role of the homing receptor in the trafficking of lymphocytes to pln is clear, its possible role(s) in inflammation is less well established. The fact that both neutrophils and monocytes express high levels of this receptor, yet do

not appear to efficiently traffic to pln, implies that this adhesion molecule may have another potential role in these inflammatory cells. The finding that the activation of monocytes and neutrophils results in the immediate loss of the homing receptor and concomitant upregulation of the integrin Mac 1 may be interpreted to suggest that the homing receptor functions to localize the neutrophil to inflammatory sites and, once localized, is lost, while, simultaneously, the association between the neutrophil and endothelium is strengthened by the increased expression of the Mac 1 adhesion molecule [29]. In addition, work from the laboratory of Butcher has clearly shown a role for the neutrophil homing receptor in acute inflammatory responses in vivo [6,7]. Work from this same laboratory has shown that the binding of neutrophils to activated endothelium can be blocked in vitro by antibodies against the homing receptor, suggesting that a component of this adhesive interaction involves this receptor [6,7]. While these results are consistent with the involvement of the homing receptor in neutrophil-mediated inflammation, further work must be done on the potential contributions of this adhesion system to both acute and chronic inflammatory responses.

THE ENDOTHELIAL LEUKOCYTE ADHESION MOLECULE: AN INDUCIBLE ADHESION MOLECULE LOCALIZED TO THE ENDOTHELIUM

The adhesive interactions between neutrophils and activated endothelial cells are of critical importance to acute inflammatory reactions. The ability to induce such endothelial adhesion molecules with inflammatory mediators such as Interleukin 1 (IL-1) and tumor necrosis factor (TNF) led to the production, by Bevilacqua et al., of monoclonal antibodies against such inducible proteins which were capable of blocking the binding of neutrophils to human umbilical vein endothelium activated by these mediators of inflammation [30]. Characterization of the cell surface glycoprotein recognized by one of these blocking monoclonal antibodies revealed that it recognized a ~110,000 dalton molecule which was induced within hours of the inflammatory stimulus and which appeared to be responsible for predominantly neutrophil adhesion, although it may also be involved in monocyte-endothelial interactions as well. Because of this apparent interaction, the molecule recognized by this monoclonal antibody was termed the endothelial leukocyte adhesion molecule, or ELAM. The binding of neutrophils to ELAM appeared to be completely calcium dependent, a finding which, together with the characterization of the size and non-hetrodimeric nature of the protein, suggested that this was not a member of the integrin family of molecules, but was a potentially new type of adhesive protein. Other studies demonstrated that ELAM was found on activated endothelium in vivo [31] and that its expression could be activated not only by inflammatory mediators such as IL 1 or TNF but also by, for example, mast cell degranulation [32]. The results together suggested that ELAM represented a potentially new type of endothelial adhesion molecule which was activated during inflammation and which appeared to serve as a mediator of relatively rapid (i.e., ~ hours post-stimulation) influx of neutrophils.

The cDNA clone encoding the ELAM antigen was isolated by the panning technique of Bevilacqua et al. [33]. The DNA sequence of this clone revealed that its structure bore a striking resemblance to that found for the homing receptor. The mature N-terminus of this transmembrane glycoprotein encoded a lectin-like domain which was also a member of the type C or calcium-dependent carbohydrate binding family. This domain was followed by an egf-like domain, after which six copies (as opposed to two in the homing receptor) of the short concensus repeat of the complement binding proteins were seen (Fig. 1). Interestingly, both the lectin and egf-like domains of ELAM showed a 65–70% homology with those motifs found in the homing receptor as compared to only 25–30% overall homology when these domains are compared to lectin or egf-like domains in other, apparently non-related proteins (Fig. 2) [15]. In addition, as can be seen in this figure, the N-terminus of the lectin domains of these two adhesion molecules showed relatively less homology than did the rest of these motifs, consistent with the possibility that these lectins may recognize different types of carbohydrates. The scr repeats show a much lower degree of homology (~40%) and contained six cysteine residues, as opposed to the four residues found in the complement binding proteins such as factor H and DAF [15,33]. Analysis of the messenger RNAs encoding this receptor revealed that the increased

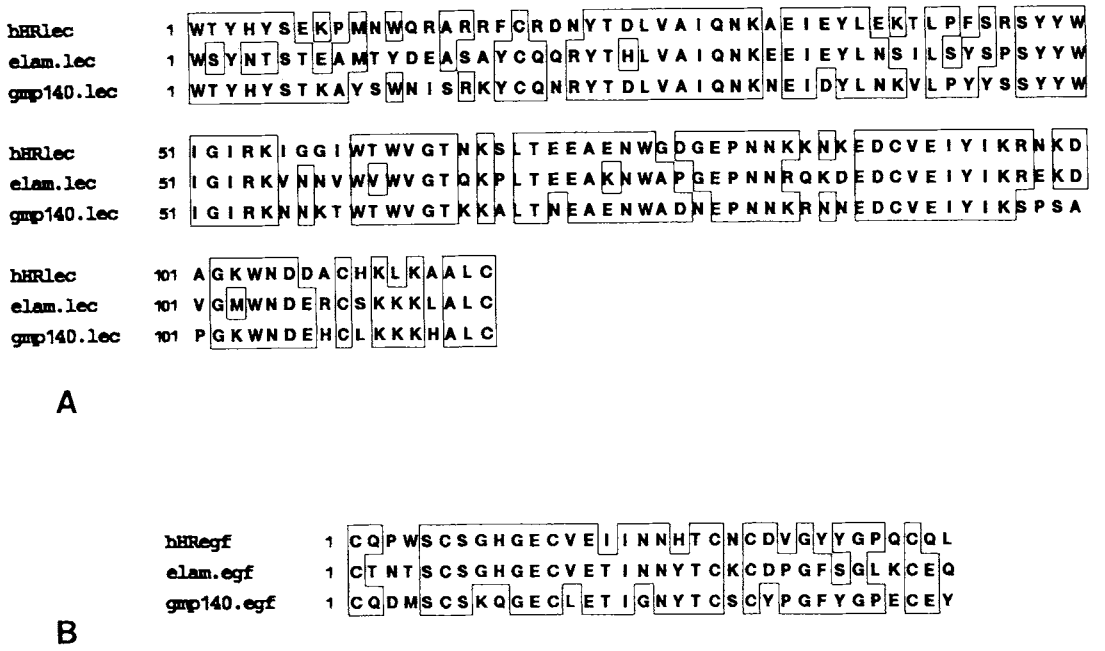

Fig. 2. Relative sequence homologies of the lectin and EGF domains of the homing receptor (hHR), ELAM, and PADGEM/gmp140 adhesion molecules. The lectin (lec) and egf motifs of these glycoproteins were compared using the align homology program. Boxed regions show amino acid homologies in the lectin (A) and egf (B) motifs of these three adhesion proteins.

expression of ELAM after IL 1 or TNF stimulation was due to increased levels of ELAM RNA. As was found with the homing receptor, the gene encoding ELAM is broken up into exons which correspond to the functional domains found within the protein (M. Bevilacqua, personnal communication). Interestingly, the ELAM gene has been found to map adjacent to the homing receptor gene on chromosome 1, suggesting that these genes may have evolved by duplication from an original ancestral gene [20].

Does ELAM bind to a carbohydrate ligand as it appears that the homing receptor does? As is the case for the homing receptor, the calcium dependence of the neutrophil endothelial adhesive interaction [34] suggests that the calcium-dependent lectin domain plays an important role in adhesion. In addition, analysis of the epitope recognized by a monoclonal antibody able to block neutrophil-endothelial adhesion has shown that it maps within the lectin domain and, as was the case for the homing receptor, its recognition required the adjacent egf-like domain (M. Bevilacqua, personnal communication). While one group failed at blocking the ELAM-dependent adhesion of neutrophils with carbohydrates [34], their analysis was far from exhaustive. However, it is interesting that carbohydrates, such as fucoidin, which are known to inhibit the homing receptor endothelial interaction, were ineffective at blocking ELAM adhesion, consistent with the possibility that ELAM may recognize a different carbohydrate ligand than the homing receptor [34].

PADGEM/GMP140: A GRANULE-SPECIFIC ADHESION MOLECULE

PADGEM (platelet activation dependent granule-external membrane protein) is a 140,000 dalton (gmp140) component of the alpha granules of platelets and Weible-Palade bodies of endothelial cells [35,36]. The granule-associated glycoprotein is an integral membrane protein whose cell surface expression is established within seconds after thrombin stimulation. PADGEM/gmp140 is an adhesion molecule that binds neutrophils and monocytes to activated platelets or endothelium in an EDTA-sensitive, predominantly calcium-dependent manner [37,38]. Its apparent calcium dependence and homomeric form suggested that it was not a member of the integrin family. Its rapid mobilization by thrombin implies that it may be involved with neutrophil and/or monocyte adhesion during thrombotic events.

The cloning and sequencing of the cDNA encoding the PADGEM/gmp140 glycoprotein demonstrated that it was also a member of the family of adhesion proteins which may utilize protein-carbohydrate interactions to accomplish specific cell binding [39]. The glycoprotein has a type C, calcium-dependent lectin domain at its N-terminus, as found for the homing receptor and ELAM. This lectin domain is followed by an egf-like motif and either eight or nine copies of the scr complement binding repeat (Fig. 1). The variability in scr numbers is probably a reflection of differential splicing events, as is the presence or absence of a transmembrane binding domain which serves to bind the protein to the cell surface. The absence of this transmembrane anchor in some cDNA clones suggests that a soluble, secreted form of this receptor is also made. The overall homology of the PADGEM/gmp140 lectin and egf-like domains as compared to those found in either the homing receptor or ELAM is approximately 65–70%, a remarkably high degree of conservation (as compared to the 25–30% sequence homology when comparing these lectin domains to other type C lectins [15]), which implies that they may have evolved to recognize similar types of carbohydrate structures and that these three molecules were created by amplification of an original progenitor gene (Fig. 2) [20]. In agreement with this possibility, the overall genomic structure of the PADGEM/gmp140 gene is identical to that described for the other members of this adhesion family, with all of the functional domains of the protein encoded by separate exons (R. McEver, personal communication). Perhaps more interesting is the finding that not only is the PADGEM/gmp140 gene localized on chromosome 1, but also that pulse-field gel electrophoretic analysis of the linkage of the homing receptor, ELAM, and PADGEM/gmp140 genes in the human genome shows that they are all within ~200 kilobases of each other (R. McEver, personal communication). The fact that these genes are all within a relatively small region of the genome, in addition to the finding that they are also adjacent to the regulation of complement locus (encoding a number of genes with various scr repeat numbers), implies that these genes evolved by duplication of the scr repeats, insertion of lectin and egf-like exons, and amplification of a progenitor lectin-egf-scr-containing gene [20].

What is the nature of the adhesive ligand recognized by PADGEM/gmp140? By analogy to the other members of this adhesion family, it seems plausible to assume that a carbohydrate is an important component. The predominantly calcium dependence of the PADGEM/gmp140-mediated binding of neutrophils to platelets is consistent with mediation of this adhesive event by the calcium-dependent lectin domain [38]. Preliminary carbohydrate blocking studies have shown that chondroitin sulfate effectively inhibits platelet-neutrophil adhesion, suggesting that this carbohydrate may be competing with ligand binding in a manner analogous to that found for the homing receptor (D. Wagner, personal communication). Interestingly, chondroitin sulfate does not inhibit the adhesion dependent upon the homing receptor, implying that these LEC-CAMs may have different carbohydrate specificities.

SUMMARY AND FUTURE PROSPECTS

The discovery of three adhesion molecules with highly conserved overall structures containing lectin, egf-like, and scr (complement binding) motifs suggests that these glycoproteins be placed in a new family of cell adhesion molecules. While the name "selectin" has been proposed for this family [38], we favor the more descriptive term LEC-CAM (Lectin-Egf-Complement-cell adhesion molecules) as coined by Stoolman [40]. The findings reviewed here bring to four the number of families of widely accepted cell adhesion molecules: the integrin family (i.e., LFA, VLA, etc.), the immunoglobulin superfamily molecules (i.e., NCAM, ICAMS, fasciclin II, neuroglian, etc.), the cadherins (i.e., P and E cadherin), and the LEC-CAMs. While at least one other potential adhesion molecule, the fibroblast proteoglycan versican [41], appears to have some components of the LEC-CAMs, the question of whether there are other members in the LEC-CAM adhesion family remains to be answered. The discovery of LEC-CAMs provides compelling evidence for the potential role of carbohydrate-protein interactions in cell-to-cell adhesion in the immune system.

A number of questions remain to be answered with respect to the LEC-CAMs. The nature of the ligands recognized by these adhesion molecules will certainly be of great interest. Assuming that carbohydrate ligands are integral to the adhesive activity of these glycoproteins, will these molecules recognize carbohydrates in the con-

text of glycoproteins, glycolipids, or glycosaminoglycans or in some other form? Does the adhesive interaction involve the binding to protein as well as potential carbohydrate ligands? What will the structure(s) of the carbohydrates recognized by these lectin domains be? In addition to questions about the ligands for these receptors, the relative role(s) of these molecules in inflammation remains to be elucidated. For example, what is the function of the homing receptor on neutrophils and monocytes, since it seems clear that it is not involved with pln trafficking in these cells? Is there a temporal relationship between these molecules in neutrophil-mediated inflammation such that the homing receptor represents a constitutive adhesion molecule, perhaps involved with neutrophil margination or "rolling," while PADGEM/gmp140 is involved with rapid neutrophil binding during thrombolytic or inflammatory events and ELAM is involved with slower neutrophil influx? Is the homing receptor involved with the trafficking of lymphocytes to sites of chronic inflammation? Can carbohydrate antagonists of defined structure be developed which effectively inhibit the adhesive activity of these molecules and, if so, will they prove effective in in vivo models of inflammation? The answers to these and other questions may allow for a more well-defined approach to the development of compounds potentially effective in the prevention of deleterious inflammatory responses.

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