Sticky sugars for selectins

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CELL-adhesion research has suddenly become sweeter. Only a year after three members of a family of cell-adhesion molecules were found to have lectin-like N-terminal domains^{1,2}, a spate of reports has appeared identifying the sticky sugar structures that are their putative ligands (see figure). That a good portion of these papers come from biotechnology companies reflects the fact that carbohydrate cell-adhesion ligands are relatively small, simple structures; thus the synthesis of drug analogues that will be tested for anti-inflammatory and anti-thrombogenic properties cannot be far off.

The role of carbohydrates in cell interactions started to receive close attention with the recognition that proteoglycans and glycosaminoglycans are important components of the extracellular matrix. Heparan, chondroitin sulphate and hyaluronic acid bind to many proteins in the matrix. In theory, carbohydrates are well suited for specific recognition — monosaccharides have many hydroxyls that can be linked *O*-glycosidically in both branched and linear arrays, so far more carbohydrate than protein structures can be created from the same number of monomers. Protein-protein recognition has received most of the limelight in studies of cell-cell adhesion, because this is the dominant and perhaps exclusive form of recognition by adhesion receptors of the integrin and immunoglobulin superfamilies¹. But work on carbohydrates has advanced rapidly with the determination of many complex structures by fast-atom-bombardment mass spectrometry, and of cell type-specific carbohydrate structures and linkages that are regulated during cell differentiation by selective expression of glycosyl transferases. Recent examples of the identification of carbohydrate receptors on cell surfaces include one on sperm which recognizes an *O*-linked carbohydrate in the zona pellucida³; and CD44, a widely distributed surface receptor for hyaluronic acid^{4,5}.

Now a family of adhesion-receptor glycoproteins critical to interactions of circulating cells within the vasculature must be added to the list. This family has been designated the selectins (ref. 6) or LEC-CAMS (ref. 2). The name selectin capitalizes on the derivation of 'lectin' and 'select' from the same Latin root, meaning to separate by picking out, and is in keeping with those of the immunoglobulin, integrin and cadherin adhesion-receptor families. The homing receptor selectin, also called gp90^{nc1}, LAM-1, LEC-CAM-1 or LECAM-1, is expressed on leukocytes and facilitates their binding to endothelium during lymphocyte recirculation

through peripheral lymph nodes and neutrophil emigration at inflammatory sites. The PADGEM, GMP-140 or CD62 molecule is a granule-associated glycoprotein of platelets and endothelial cells that is brought to the cell surface after stimulation by thrombogenic agents, allowing these cells to bind neutrophils and monocytes at the site of tissue injury. The ELAM-1 glycoprotein is synthesized by endothelial cells in response to inflammatory agents and promotes adhesion of neutrophils, monocytes and a subpopulation of lymphocytes. These proteins thus mediate adhesion of leukocytes to endothelium and platelets during inflammation and clotting^{1,2,7}.

Clues that the selectins are carbohydrate-specific came from two directions. Early studies had shown that the homing receptor selectin could bind to algal or yeast polysaccharides rich in fucose sulphate or mannose phosphate; that these and related monosaccharides could competitively inhibit binding to lymph-node endothelial cells; that binding is Ca^{2+} -dependent; and that binding is abrogated by neuraminidase treatment of the endothelial cells⁸. Subsequent cloning of complementary DNAs revealed that the homing receptor, ELAM-1, and CD62

are members of a structurally related adhesion-receptor family that has an N-terminal domain homologous to Ca^{2+} -dependent (C-type) animal lectins (see figure). Some animal lectins are found at cell surfaces, and include hepatic receptors that are specific for terminal galactose and fucose⁹. Although the homing receptor was the first selectin thought to have a carbohydrate ligand⁷, the identity of the biological ligand remains unclear; the recent results concern the ligands of the other two selectins, CD62 and ELAM-1.

The CD62 ligand, known to be present on neutrophils and monocytes, was putatively identified by screening for monoclonal antibodies that would block binding of these cells to CD62. CD15, also known as Lewis x (see figure), was thus identified as a component of the ligand, and this was supported by the ability of a purified Lewis x adduct of lactose found in human milk to partially inhibit adhesion at relatively high concentrations⁹.

No less than five independent papers have appeared within the past three months on the structure of the ELAM-1 ligand and the enzymes that synthesize it. Neutrophils are rich in Lewis x and sialylated Lewis x (refs 10 and 11; see figure). These are $\alpha(1\rightarrow3)$ fucosylated derivatives of polylactosamine that are found at the nonreducing termini of glycolipids, *O*-linked carbohydrates and *N*-linked oligosaccharides. Expression of sialylated Lewis x in neutrophils and a variety of cell

When beauty is only skin deep

THE appeal of this tempting punnet of fruits from the tropical tree *Elaeocarpus angustifolius* lies in iridescence, a property more usually associated with birds and butterflies than higher plants. Ripe *Elaeocarpus* fruits are iridescent owing to remarkable structures called iridosomes in their skins, described by D.W. Lee on page 260 of this issue. Thin-film interference in stacks of polysaccharide fibrils — the right thickness (78 nm) to reflect blue light with a wavelength of 439 nm — allows the fruits to be brightly coloured and yet still admit the yellow-green light needed for photosynthesis. So not only do the fruits stand out in the forest gloom, they allow the trees to soak up every drop of available light right up to the final stages of fruit maturation. Henry Gee