14 *ABSTRACT*

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Structure and Biosynthesis of Selectin Ligands and O-Glycans

profile

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Richard D. Cummings received his B.S. from the University of Montevallo in 1974 and his Ph.D. from The Johns Hopkins University in 1980, and subsequently conducted his post-doctoral studies at Washington University School of Medicine, in St. Louis. He is currently the George Lynn Cross Distinguished Research Professor and Ed Miller Endowed Chair in Molecular Biology at the University of Oklahoma Health Sciences Center, College of Medicine in Oklahoma City, OK. In addition, Dr. Cummings is Director of the Oklahoma Center for Medical Glycobiology. He is Past-President of the Society for Glycobiology (2001) and is Chair of the Gordon Research Conference on Glycobiology (2003). Dr. Cummings is a Regular Member of the NIH Physiological Chemistry Study Section and his research has been continuously funded by the NIH since 1980. He is a Co-Editor of the textbook *Essentials of Glycobiology* and is the author or co-author of more than 150 scientific publications and reviews. His research focuses on the functions and biosynthesis of glycoconjugates, including carbohydrate-binding proteins (selectins and galectins) and glycosyltransferases.

Key words Selectins, mucin, glycoprotein, O-glycan, galactosyltransferases, chaperones

The leukocyte ligands for selectins include a number of mucins that express sialic acid- and fucose-containing O-glycans, in addition to sulfated components. The predominant ligand for P-selectin is PSGL-1, a membrane-bound dimeric mucin containing multiple O-glycans and a very small number of N-glycans. The important determinants for selectin recognition of PSGL-1 reside at the extreme N-terminus of the mucin. We have now defined the molecular determinants required for P-selectin recognition, using recombinant glycosyltransferases and synthetic glycosulfopeptides to generate a large number of derivatives. The results demonstrate that and P-selectin recognizes a specific tripartite arrangement of a sialyl Lewis x-containing core-2 based O-glycan, peptide, and three tyrosine sulfate determinants, all of which dictate the high affinity interactions (1,2,3). Surprisingly, L-selectin also binds with high affinity to glycosulfopeptides containing sulfated tyrosine, and the affinity is higher than that demonstrated for sulfated carbohydrate-containing glycoconjugates (4).

Thus, the glycosulfopeptide domain at the N-terminus of PSGL-1 is specifically recognized by both P- and L-selectin, and similar determinants are bound by both selectins. Interestingly, in mice, PSGL-1 may also be one of the ligands recognized by E-selectin (5). In related studies, we discovered that expression of the PSGL-1 ligand requires a key regulatory enzyme for O-glycan biosynthesis, the core 1 β 3 galactosyltransferase. This unique activity is encoded by a single gene located at human chromosome 7p14-p13 (6,7). Genetic changes resulting in altered expression of the core 1 β3 galactosyltransferase activity dramatically alter cellular glycosylation. We have now discovered that expression of the core 1 β3 galactosyltransferase is highly dependent on a unique molecular chaperone specific for this enzyme and that alterations in chaperone expression have remarkable consequences for expression of the core 1 β3 galactosyltransferase (8). This presentation will highlight the unique molecular controls of selectin ligand biosynthesis and especially the regulatory factors for O-glycan biosynthesis.

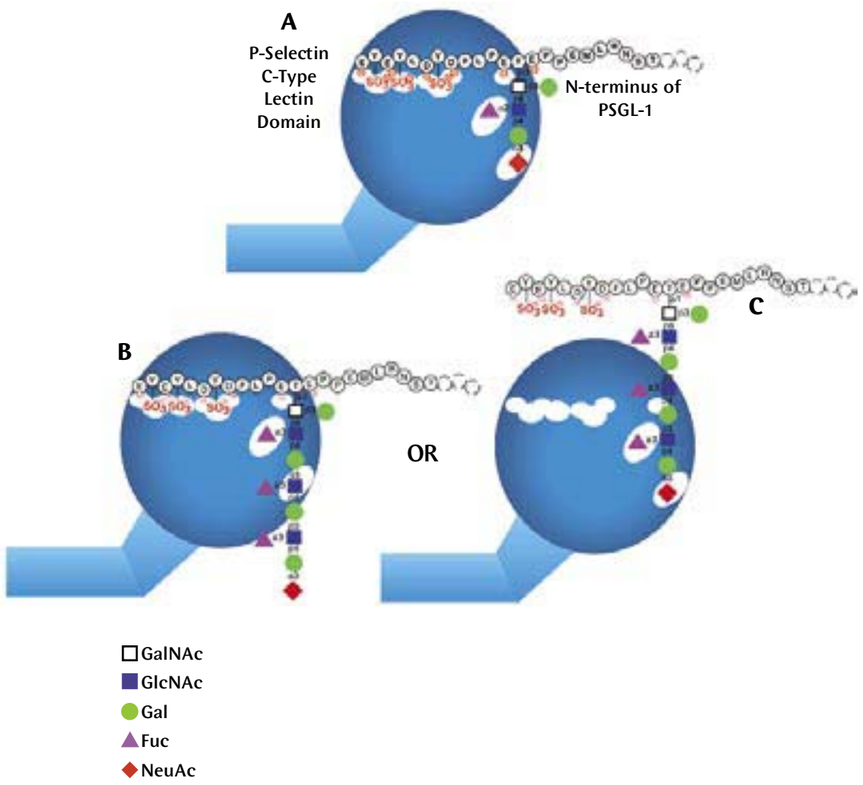

Figure 1. A model depicting the possible interaction between the C-type lectin domain of P-selectin with glycosulfopeptides.
The predicted and defined interactions between GSP-6 and P-selectin are indicated in (A). The predicted reduced interaction with the glycosulfopeptide GSP-6″ containing sLex in sialylated PFPL are shown in B and C. In one hypothetical model of binding, the peptide moiety and fucose, but not sialic acid, residues are involved in the interaction of GSP-6″ with P-selectin (B), whereas in the other model, fucose and sialic acid residues, but not the peptide moiety, are involved in the interaction (C).

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