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Observations and Thoughts on Oligosaccharide Involvement in Malignancy

by Ten Feizi*

This brief communication highlights some observations that have raised the possibility that the oligosaccharides of glycoproteins may have roles as ligands or recognition structures in cell growth regulation. The initial experience with a new technology designed for investigating roles of glycoprotein oligosaccharides as recognition structures is also discussed.

Among the long awaited developments in modern cell biology is an understanding of the roles of the diverse oligosaccharide structures of glycoproteins, proteoglycans, and glycolipids and the significance of the pronounced changes that occur in their structures, proportions and patterning in embryogenesis, cell differentiation, and malignancy (*1,2*). Evidence is accumulating for the occurrence of numerous carbohydrate-recognizing proteins (lectins) among secreted, membrane-associated, cytosolic and nuclear proteins (*3*). A role for lectin-oligosaccharide interactions in cell growth regulation is suggested, for example, by the observations (*4*) that the epidermal growth-factor receptor of A431 cells can be stimulated to autophosphorylate (a phenomenon associated with receptor activation) by perturbing its oligosaccharide chains with anti-carbohydrate antibodies. The role of lectin-oligosaccharide interactions in cell growth regulation is also suggested by the fact that the human and bovine receptor for insulinlike growth factor II is also a lectin with specificity for oligosaccharides containing 6-phosphorylated mannose (*5,6*). These observations, together with the knowledge that exogenously added plant lectins (e.g., phytohemagglutinin) are mitogenic for animal cells, have led us to suggest (*4,7*), as depicted in Figure 1, that receptors for growth factors may be part of a network of glycoproteins and glycolipids interconnected by oligosaccharide-protein interactions that tune the state of cell responsiveness to growth-factors and mediate growth control signals in and across cell membranes. Such a mechanism would be a versatile and adjustable means of communication between growth-factor receptors in the same cells (*7*) and could explain many cooperative effects that have been observed among growth-factor receptors. Moreover, such growth-control networks would be disrupted when there is inappropriate glycosylation as seen regularly in malignant cells.

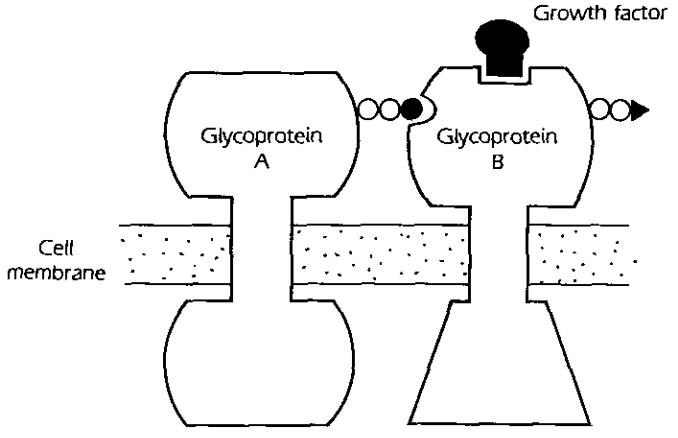

FIGURE 1. Diagram depicting part of a hypothetical growth-regulating network involving oligosaccharide recognition. The growth-factor receptor is shown here as a bifunctional glycoprotein (*B*) with a combining site for the growth factor and a lectinlike site for an oligosaccharide structure that occurs on a second growth-regulatory glycoprotein (*A*). Reproduced with permission (*2*).

Studies of the involvement of glycoprotein oligosaccharides as recognition structures using the intact macromolecules are difficult to interpret for several reasons. First, a contribution of the protein moiety cannot always be excluded. Second, the multiplicity of oligosaccharide structures typically associated with a single glycoprotein means that it may not be feasible to define precisely the oligosaccharide species recognized. With these questions in mind, procedures are being developed (*8,9*) that involve the release of oligosaccharides from glycoproteins and their conjugation to lipid to form mixtures of neoglycolipids for use as probes in ligand-binding assays. The initial experience (*10–12*) with several mammalian carbohydrate-binding proteins indicates that the neoglycolipid technology has considerable

*MRC Clinical Research Centre, Harrow, Middlesex HA1 3UJ, UK

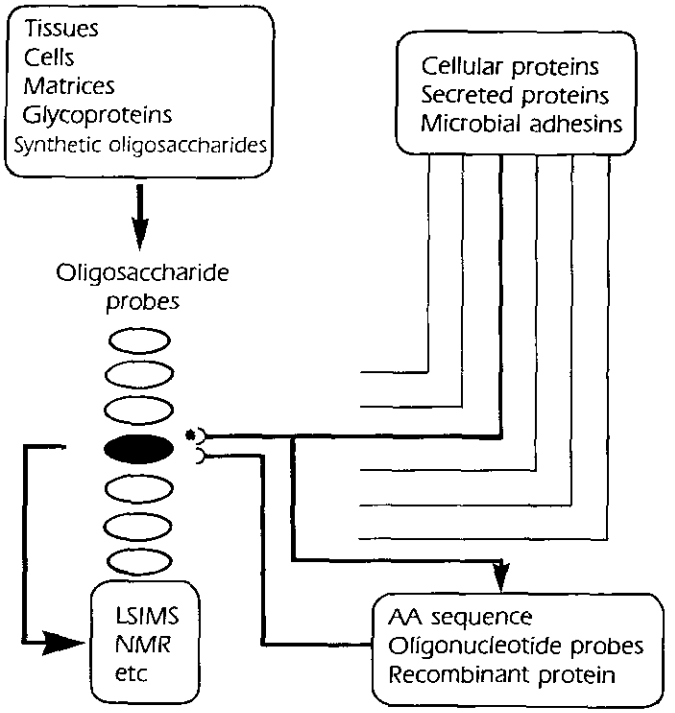

FIGURE 2. *A general strategy for elucidating oligosaccharide recognition systems.* Whole tissues, isolated cells, extracellular matrices, or individual glycoproteins, in addition to desired synthetic oligosaccharides, are used to prepare neoglycolipids that are used in overlay experiments with radiolabeled proteins. In this way individual cellular or secreted proteins or microbial adhesins (*) with carbohydrate recognition properties are singled out and characterized at the level of protein and gene structure. In parallel, the oligosaccharides recognized are characterized by state-of-the-art methods of structural analysis. LSIMS, liquid secondary ion mass spectrometry; AA, amino acid; NMR, nuclear magnetic resonance. Reproduced with permission (*13*).

potential in studies of oligosaccharide recognition coupled with structural assignment. For example, by this approach it has been established that conglutinin, which binds to one of the glycoprotein products (iC3b) generated in the complement cascade, recognizes certain *N*-linked oligosaccharides of high-mannose type as well as complex type oligosaccharides with nonreducing terminal *N*-acetylglucosamine residues.

A general strategy (*13*) for elucidating novel oligosaccharide recognition systems in a diversity of settings is presented in Figure 2. The information thus gained could form the basis of novel drug designs variously targeted at tumor cell growth inhibition or the prevention of the initial stages of microbial infection. I have also proposed (*13*) that the neoglycolipid approach may be ideal for the quality control of the sugar chains of recombinant glycoproteins produced by molecular engineering for administration to man.

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