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This Week's Citation Classic®

Feizi T. Demonstration by monoclonal antibodies that carbohydrate structures of glycoproteins and glycolipids are onco-developmental antigens. *Nature* **314**:53-7, 1985. [Applied Immunochemistry Research Group, Division of Communicable Diseases, Clinical Research Centre, Harrow. Middlesex. England]

By 1985 it was clear that many monoclonal antibodies to surface antigens that change during embryogenesis, cellular differentiation, and oncogenesis recognize oligosaccharide sequences of glycoproteins and glycolipids. In this article these findings were discussed, and it was proposed that saccharides, including blood group-related structures, may have important roles as ligands for regulators of cell migration, growth, and differentiation, now being borne out by discoveries of complementary proteins. [The *SCI*® indicates that this paper has been cited in more than 630 publications.]

Roles for Oligosaccharides in Biology and Medicine

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In the mid-1960s I became intrigued by the transient autoimmune hemolytic disorder caused by *Mycoplasma pneumoniae.* I observed that the autoantibodies which bind to / antigen are monoclonal or oligoclonal as are those in chronic hemagglutinin disease. During my 1969-1973 stay at Rockefeller University I collaborated with Elvin Kabat at Columbia Medical Center. We established that / antigen, a marker of erythrocytes of the adult, and / antigen of the fetus are expressed on carbohydrate backbones of the major blood group antigens and identified the epitope for one anti-/ as a trisaccharide branch.[1] Later, following collaborations between my group in Harrow and Sen Hakomori's in Seattle, using glycolipids we established that individual anti-/ recognize specific domains on branched, and anti-i on linear poly-N-acetyllactosamine.[2]

Using anti-/and -/as reagents, with Martin Evans, Cambridge, we found changes in backbone branching in the mouse embryo at onset of differentiation. Soon thereafter we established that the developmentally regulated embryonic antigen, SSEA-1 (recognized by a hybridoma antibody raised by Oavor Solter and Barbara Knowles at the Wistar Institute), consists of the α1-3 fucosyl backbones[3] (earlier termed Le^x). I suggested that such oligosaccharides may serve as "area codes" decoded by lectins that direct cell migrations.[4]

Many other hybridoma antibodies raised to markers of developmental stage or neoplastic state were found to recognize oligosaccharides. However, cancer-associated carbohydrates in one cell type were featuring as normal components in others; notable examples are Le^x and siaiyl-Le^x shared by leukocytes and carcinomas. In the *Citation Classic*® I reviewed that knowledge critically, expressed doubts that the cancer-associated carbohydrates could be targets in cancer therapy, but suggested roles for carbohydrates as ligands for regulators of cell growth and signalling.

Judging from letters and comments of approval, the appeal and continued citation of the article is due to the interest it stimulated in the biology of carbohydrates. Support for roles in cell growth and signalling (discussed in subsequent articles, e.g., reference 5) has been no more than suggestive so far. However, support for the concept of the saccharides as "area codes" has come from leukocyte biology: When lectin-like domains were found on the endothelial-leukocyte adhesion molecules, E- and P-selectin, international research focused on Le^x and sialyl-Le^x as potential ligands. Roles are now established for these oligosaccharides,[6] and their sulfated analogues,[7] as ligands for the selectins which mediate interactions crucial for initiating leukocyte recruitment to sites of inflammation. These developments have not only dispelled some of the scepticism prevailing among biologists about the importance of oligosaccharides, but have opened new avenues for design of carbohydrate-based inhibitors for treating diseases of inflammation.

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2. **Feizi T, Childs R A, Watanabe K & Hakomori** S. Three types of blood group I specificity among monoclonal anti-/ autoantibodies revealed by analogues of a branched erythrocyte glycolipid. *J. Exp. Med.* 149:975-80. 1979. (Cited 120 times.)
3. **Gooi H** C, **Feizi T, Kapadia A, Knowles B B, Solter D** *&* **Evans M J.** Stage-specific embryonic antigen SSEA-1 involves <xl-3 fucosylatcd type 2 blood group chains. *Nature* 292:155-8, 1981. (Cited 385 times.)
4. **Feizi T.** Carbohydrate differentiation antigens. *Trends Siochem. Sci.* 6:333-5, 1981.
5. **Feizi T** & **Childs R** A. Carbohydrates as antigenic determinants of glycoproleins. *Biochem. J.* 245:1-11. 1987. (Cited 130 times.)
6. **Bevilacqua M P** *&* **Nelson R M.** Selectins. *J. Clin. Invest.* 91:379-87. 1993.
7. **Yuen C-T, Lawson A M, Chai W, Larkin M, Stoll M S, Stuart A** C, **Sullivan F X, Ahem T J** & **Feizi T.** Novel sulfated ligands for cell adhesion molecule E-selectin revealed by the neoglycolipid technology among O-linked oligosaccharides on an ovarian cystadenoma glycoprotein. *Biochemistry* 31:9126-31, 1992. Received May 10. 1993