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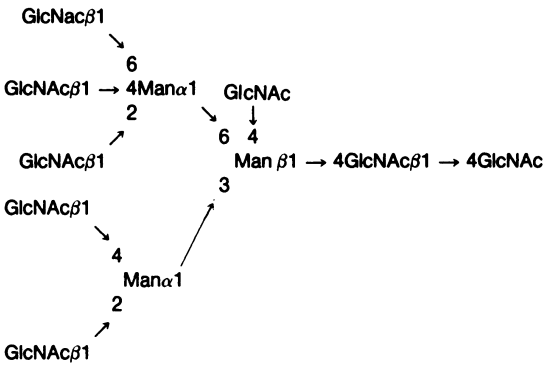
Meeting Report

Sapporo Cancer Seminar: Membrane-associated Alterations in Cancer—Biochemical Strategies against Cancer[1, 2]

One of the major focuses of interest at the Second Symposium of the Sapporo Cancer Seminar was a discussion of the changes in complex carbohydrates associated with oncogenic transformation. A new concept discussed at this conference is that the general glycoconjugate pattern can vary extensively depending on a number of factors (drugs, mutations, vitamin deficiency, and environmental conditions). The changes in bound carbohydrate observed in transformation and malignancy could be the result of a response to genetically controlled changes in the internal environment of the cell. The numerous structural alterations could be responsible for a scramble of small functional changes, none being lethal, from which the malignant cell arises (loss of growth control and capacity to colonize and invade). Although the changes of bound carbohydrate polymers could be epigenetic in nature because they are not template determined, the carbohydrate polymers are, ultimately, defined genetically (L. Warren, Philadelphia, Pa.). Also discussed at this conference is the presence of unique carbohydrate chains in tumors which may be useful in the diagnosis and therapy of cancer. The unique carbohydrate chains could be related to oncofetal expression and a frozen pattern of differentiation (S-I. Hakomori, Seattle, Wash.).

The appearance of relatively high-molecular-weight glycopeptides replacing smaller ones in a large variety of tumor cells is the most frequent chemical phenotype expressed at the cell surface. The structural basis of this phenomenon was demonstrated by A. Kobata (Kobe, Japan) as the presence of an unusual core with a higher degree of branching such as the penta- to hexaantennary structure proposed below.



Other changes of tumor cell carbohydrates were described as follows. (*a*) A high-molecular-weight, mucin-type, highly sialylated glycoprotein is shed by human melanoma and breast cancer cells (E. M. Davidson, Hershey, Pa.). (*b*) An anomalous high-molecular-weight carbohydrate consisting of repeated *N*-acetyllactosamine units found originally in murine teratocarcinoma cells is now reported by T. Muramatsu (Kagoshima, Japan) to be present in human colon cancer cells. (*c*) Several types of abnormalities of glycoprotein side chains have been found presumably due to "incomplete synthesis" first described in glycolipids. (*d*) Incomplete synthesis of side chain carbohydrate of thyroglobulin in transformed thyroid cells (T. Osawa, Tokyo, Japan) and in γ-glutamyltranspeptidase from ascites hepatoma cells has been demonstrated by A. Kobata and N. Taniguchi (Sapporo, Japan). (*e*) A. Kobata has described an outer chain containing GlcNAcβ1–4Man which has never been found in normal glycoprotein. (*f*) T. Muramatsu has described an unusual Fucα1–3Gal (FG3) antigen in human colonic tumors detected by an antibody directed to this oligosaccharide. (*g*) The presence of a glycoconjugate containing *N*-glycolylneuraminic acid has been described in various human cancers which may elicit H-D heterophile antibody production in patients bearing these tumors (M. Naiki, Sapporo, Japan). (*h*) An unusual *O*-glycosidic carbohydrate chain was found in colonic cancer glycoprotein which had the structure GalNAcα1 → 3GalNAcα1 → 0–Ser/or Thr (I. Yamashina, Kyoto, Japan).

S-I. Hakomori discussed various carbohydrate structures linked to lipids, such as the A-like antigen (GalNAcβ1–3Galβ1–4Hex) without fucose in tumors of Blood Group O individuals, P-like antigen (GalNAcβ1–3Galβ1–4GlcNAβ1–3Galβ1–4Glcβ) in a tumor of a rare genotype, and polyfucosylated type 2 chain [Galβ1–4(Fucα1–3)GlcNAcβ1–3Galβ1–4(Fucα1–3)GlcNAcβ1–3Galβ1–R] in human colonic cancer. These are new additions to Forssman or Ginsburg-Koprowski's sialyl-Le^a structure defined by tumor-specific monoclonal antibodies. Overall, it appears that, although the predominant change in bound carbohydrates is one of enlargement, they frequently are reduced in size (especially in glycolipids). In some tumors, new groups appear and probably in others some carbohydrate groups cease to be made. Absolute levels of bound carbohydrate may also change in malignancy. Those unique potentially antigenic structures appearing in experimental tumors and in human cancer could be the target of monoclonal antibodies which might eventually be utilized in the diagnosis and therapy of human cancer.

Another major subject extensively discussed was the changes that occur in several enzymes, most of which appear to be membrane-bound glycoproteins. These enzymes include alkaline phosphatase (K. Higashino, Osaka, Japan), arylamidase (M. Niinobe and S. Fujii, Osaka, Japan), arylsulfatase, and γ-glutamyl transglutaminase. An entire session was devoted to the latter enzyme, its changes in malignancy (A. Szewczuk, Wroclaw, Poland; N. Taniguchi), in precancerous tissue (K. Sato, Hirosaki, Japan), and during development (T. Higashi and Y. Sakamoto, Osaka, Japan). The enzyme may be of use as a clinical marker in hepatobiliary disease (N. Sawabu, Kanazawa, Japan). In gen-

[1] Report of the Second Symposium of the Sapporo Cancer Seminar held in Sapporo, Japan, July 14 to 17, 1982. The chairman of the meeting was Professor A. Makita (Sapporo, Japan). The work presented at this meeting will be published as a *Gann Monograph on Cancer Research* (1983).

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eral, changes in enzyme levels and in isozyme patterns were described. γ-Glutamyl transferase as well as most glycoprotein enzymes discussed at this meeting underwent changes in their carbohydrate moiety in the malignant cell.

The functioning of glycosyltransferases involved in complex type carbohydrate chain synthesis was discussed by H. Schacter (Toronto, Canada). Specificity resides in the immediate sugar acceptor and also in distant steric requirements. It is believed both by H. Schacter and A. Kobata that the addition of a residue of *N*-acetylglucosamine to the core carbohydrate structure of glycoproteins early in their synthesis is a key to the changes seen in these structures in the malignant cell.

Glycosyltransferases have been isolated and chemically characterized by several participants (E. G. Berger, Berne, Switzerland; S. Ochiai and A. Makita, Sapporo, Japan; T. Miyagi and S. Tsuiki, Sendai, Japan; Y. Ikehara, Fukuoka, Japan). Notable achievements, for example, are the isolation and immunohistological characterization of galactosyltransferases isolated from human milk (E. Berger) and sialyltransferase isozymes purified from rat liver (S. Tsuiki and T. Miyagi) and the demonstration of diminished sialyltransferase in the Golgi membranes of hepatoma cells (Y. Ikehara). In addition, the enzymology of hydrolases, which may be abnormal in cancer, was extensively discussed. Arylsulfatase (B_1) is a novel variant which appears in human lung cancer as originally found by Makita *et al.* (S. Gasa, Sapporo, Japan). The enzyme is phosphorylated in both the sugar and peptide moieties. Phosphorylation of protein-bound carbohydrate (*P*-mannose), which is also found in thyroglobulin from malignant cells (T. Osawa), is likely to be an exciting subject of future investigations.

A few papers were presented on membrane changes associated with differentiation: (*a*) extensive work in various colonic carcinoma cells on enzyme changes associated with differentiation caused by various inducers (Y. S. Kim, San Francisco, Calif.); (*b*) induced synthesis of globotriosylceramide and lactotriosylceramide in murine leukemia cells M1 (T. Taki and M. Matsumoto *et al.*, Shizuoka, Japan); and (*c*) impressive new phospholipid analogues claimed by M. Hozumi (Saitama, Japan) to be differentiation inducers. Membrane protein profiles during hematopoiesis and stem cell differentiation in the erythrocytes of patients with polycythemia vera were discussed by D. F. H. Wallach (Boston, Mass.). A protein marker for stem cells was described. Application of inducers of differentiation in "phenotype therapy" of cancer may be an important theme in the near future.

Relatively few discussions were heard on the role of pericellular glycoconjugate in oncogenesis such as glycosaminoglycan, fibronectin, laminin, and collagen. Many transformed cells *in vivo* have significant alterations in the structure and organization of these pericellular components. G. Nicolson (Houston, Texas) described a model for metastases utilizing cultured vascular endothelial cells which synthesize a basolateral extracellular matrix. He has shown that metastatic cells bind to the endothelial cell monolayer, cause breakage of endothelial junctions, retraction of the endothelial cells, and adhesion to and destruction of the underlying matrix. The most malignant cells cause the most solubilization of the matrix.

Alterations of membrane turnover and dynamics were discussed by W. Reutter, Berlin, Federal Republic of Germany. He analyzed the turnover of 5 well-defined glycoconjugates from hepatoma membranes. Interestingly, the turnover of peripheral sugars was significantly higher than core structures at least in some glycoproteins. A marked alteration in catabolism of glycoproteins was found in hepatoma plasma membranes. Shedding of macromolecules from the cancer cell membrane was discussed by P. Black (Boston, Mass.). Shedding is normally important in turnover of certain membrane (glyco)proteins. However, in cancer cells, shedding occurs continuously in a disregulated way. The importance of this phenomenon in causing the cancer cell phenotype as well as certain pathophysiological events (*e.g.*, loss of adhesion, thrombosis, invasion and metastasis, the immunosuppression of cancer) that occur in cancer patients was described.

Another subject discussed at the conference concerned tumor promoters and cell activation. T. Sugimura (Tokyo, Japan) described three new tumor promoters: teleocidin, lyngbyatoxin A (both indole alkaloids), and aplysiatoxin (a polyacetate compound). These compounds have hydrophilic and hydrophobic portions in their structure as does phorbol myristate acetate, a well-known tumor promoter. Lymphocyte activation and the signals regulating this event were discussed by A. Novogrodsky (Petah-Tikva, Israel). The importance of cell surface saccharide moieties in T-cell proliferation, particularly an oxidized aldehyde of galactose, was stressed. Thus, one can now begin to understand the molecular events in the cell membrane that lead to cell activation.

The wealth of comparative biochemical data presented at the symposium made apparent the complexity of the malignant process. However, certain patterns of change in membrane components and in the bound carbohydrates have been discerned and, with new information available, efforts are being made to define the possible common ground of growth, differentiation, and malignancy. Some exciting new specific findings were also reported. As deficient as our present understanding of cancer may be, some of the information and ideas presented at this symposium will surely help in the formulation of therapy in the near future.

P. H. Black
Hubert H. Humphrey Cancer Research Center
Boston University School of Medicine
80 East Concord St.
Boston, Massachusetts 02118

Sen-itoroh Hakomori
Department of Pathobiology, Microbiology and Immunology
University of Washington
Biochemical Oncology, Fred Hutchinson Cancer Research Center 1124
Seattle, Washington 98104

L. Warren[3]
The Wistar Institute
36th and Spruce Sts.
Philadelphia, Pennsylvania 19104

[3] To whom requests for reprints should be addressed.