In conclusion, there are currently 2 ways of improving survival for IF patients. Both have different potential complications that reduce quality of life and survival. The use of HPN as the first therapy is well established and should be continued; it allows the patient to survive while deciding on long-term management. In the longer term, it is clear that progressive liver disease should be an indication for early transplantation. Early transplantation should also be considered for those who have CVC-related complications before losing all sites of venous access. Patients with Crohn's disease clearly benefit from prolonged HPN. However, in all other situations we need better designed long term-studies of both survival and quality of life to advise the patient about the pros and cons of continued HPN versus IT. The future depends in part on progress in techniques, experience, and improvements in immunosuppression for IT.

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0016-5085/08/$34.00
doi:10.1053/j.gastro.2008.06.012

Aberrant Expression of Carbohydrate Antigens in Cancer: The Role of Genetic and Epigenetic Regulation

See "DNA hypermethylation contributes to incomplete synthesis of carbohydrate determinants in gastrointestinal cancer," by Kawamura Y, Toyota M, Kawashima R, et al, on page 142.

It has long been known that the cell surface is covered with abundant carbohydrates. In mammals, these carbohydrates are constructed from 9 monosaccharides that are connected through glycosidic linkages in many different combinations, thereby generating diverse glycan chains. Carbohydrates are linked to protein or lipid backbone structures by a series of glycosyltransferases and glycosidases. The combined effect of these enzymes is a diverse array of carbohydrate structures having the potential to generate many signals.[1–4] The major classes of carbohydrate structures are *N*-linked glycans that are attached to an asparagine residue of a protein moiety of nonmucin glycoprotein and *O*-linked glycans that are attached to serine or threonine residues of a protein backbone of mucin glycoprotein. Glycans are linked to

ceramide in glycolipids. Glycan chains are often branched with 1 to >20 sugars per chain and are arbitrarily divided into 3 regions: core, backbone, and periphery. Core region glycans are those near the linkage to protein backbone, peripheral region glycans are in the outer region, and backbone glycans are between core and peripheral regions. The synthesis of core region glycans varies considerably among *O*- and *N*-glycans and glycans of glycolipids, but peripheral region glycans are synthesized in a similar manner on glycoproteins and glycolipids by the stepwise addition of monosaccharide by the action of glycosyltransferases that are localized in the endoplasmic reticulum and Golgi apparatus. Each glycosyltransferase specifically catalyzes the addition of a nucleotide sugar donor (eg, UDP-Gal, UDP-GalNAc, and GDP-Fuc) to an acceptor/precursor. The peripheral region of all types of glycans on glycoproteins and glycolipids often contain glycan structures related to ABO, Lewis (Le) and Sd^a blood group antigens.[1–4] These antigens, originally described in erythrocytes, have later been found on epithelial and endothelial cells. These cell-surface antigens serve as receptors for pathogens, commensal bacteria and lectins, the carbohydrate-binding proteins such as selectins, galectins, and the Siglec family, and play an important role in cell–cell interaction and regulation of the function of cells in the innate and adaptive immunity.[4–8] Kawamura et al[9] in this issue of GASTROENTEROLOGY provide evidence for the importance of glycosyltransferases in the synthesis of cell-surface carbohydrate antigens in human gastrointestinal cancer cells that contribute to their clinicopathologic characteristics.

Altered Glycosylation in Cancer. Changes in the glycan structures of glycoproteins and glycolipids have been demonstrated during development, cellular differentiation, inflammation, and malignant transformation.[1–4] Two main mechanisms for the changes in carbohydrate determinants in tumors have been described: incomplete synthesis of preexisting carbohydrate determinants and neosynthesis of novel carbohydrate determinants.[2,3,10]

Incomplete Synthesis of Glycans. In tumors, incomplete synthesis of glycan chains may result in the reduction or loss of A and B antigens, disialyl Le^a, sialyl 6-Sulfo Le^x antigens, and Sd^a antigen and the appearance of core region carbohydrates T, Tn, sialyl Tn antigens, sialyl Le^a, and sialyl Le^x antigens.[2–4,7–11,12] Loss of A and B antigens in the tumor tissues are often correlated with an increase in H antigen expression indicating that loss of A and B antigens is the result of incomplete synthesis (Figure 1A). Down-regulation of A/B glycosyltransferases involved in the synthesis of A and B antigens has long been found in tumors.[2–4,7,11] However, the mechanisms involved in the down-regulation of this enzyme in tumors have recently been shown to be allelic loss or loss of heterozygosity (LOH) of A/B glycosyltransferase gene at chromosome 9q 34.1-2 and hypermethylation of the CpG islands in the proximal region of the promoter of A/B glycosyltransferase gene.[11] The observation that these 2 events frequently coincide in the same tumor is consistent with Knudson's 2-hit model that a phenotypic consequence of tumor suppressor gene loss is not seen unless both alleles of a gene are inactivated in a tumor[13] (Figure 1B). Kawamura et al[9] in this issue of GASTROENTEROLOGY confirmed the frequent occurrence of promoter methylation of α1,3-*N*-acetylgalactosominyltransferase (A3GalNT), an enzyme responsible for the expression of A determinant in gastric and colon cancer cell lines by reporting markedly elevated levels of the transcript of A3GALNT after the treatment with 5-aza-dC. Transfection studies in colon cancer cell lines as well as the comparison of A antigen–positive and –negative cancer cells have indicated that loss of expression of the A3GALNT enzyme can enhance the cell's motility and invasiveness, indicators of aggressive malignant phenotypes.[14]

Truncation of *O*-glycans in the tumors leads to the appearance of novel carbohydrate antigenic determinants such as T and sialyl Tn antigens, which consist of 2 sugars and Tn antigen with 1 sugar in the core region of *O*-glycans.[3,5] Under-expression of β1,6-*N*-acetylglucosaminyltransferase, branching enzyme or β1,3 galactosyltransferase (B3GALT) leads to the expression of T antigen or Tn and sialyl Tn antigens, respectively, in cancers, whereas up-regulation of GalNAc α2,6-sialyltransferase, which transfers sialic acid to Tn antigen, leads to the synthesis of siayl Tn antigen.[5] Recently, cancers expressing Tn and sialyl Tn antigens were found to have both mutations in a chaperone gene required for B3GALT expression and the LOH in its locus.[15] Expression of sialyl Tn, T, and Tn antigens is correlated with invasiveness, metastasis, and poor prognosis in colorectal, gastric, and breast cancers.[3,5]

Sialyl Le^a and sialyl Le^x have attracted considerable attention because they serve as ligands for vascular selectins that mediate adhesion of cancer cells to the endothelium, thereby facilitating hematogenous metastasis.[1–6,10] Recent studies indicate that the sialyl Le^a and sialyl Le^x antigens in cancers are expressed as precursor antigens that appear from down-regulation of 2 enzymes, namely GlcNAcα2,6 sialyltransferase and 6-sulfotransferase, that are responsible for the synthesis of more mature glycans such as disiayl Le^a and sialyl 6-sulfo Le^x antigens, respectively, which are expressed in normal stomach and intestine.[10] Recent studies indicate that this down-regulation is due mainly to promoter methylation because the treatment of cancer cells that express either sialyl Le^a or sialyl Le^x with a DNA methylation inhibitor, 5-aza-dC, induced surface expression of disiayl Le^a and sialyl 6-sulfo Le^x.[10] An additional mechanism for the increased expression of sialyl Le^a and sialyl Le^x antigenic determinants on cancer cells has been put forward recently by Kawamura et al.[16] Both sialyl Le^a and sialyl Le^x antigens and Sd^a antigen arise from a common precursor trisaccharide, NeuAc 2-3Gal 1-4(3)GlcNAc-R. The addition of fucose (Fuc) in