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Biological Function of Fucosylation in Cancer Biology

Eiji Miyoshi*, Kenta Moriwaki and Tsutomu Nakagawa

Department of Molecular Biochemistry & Clinical Investigation, Osaka University Graduate School of Medicine, 1-7, Yamada-oka, Suita, 565-0871, Japan

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Fucosylation is one of the most common modifications involving oligosaccharides on glycoproteins or glycolipids. Fucosylation comprises the attachment of a fucose residue to *N*-glycans, *O*-glycans and glycolipids. *O*-Fucosylation, which is a special type of fucosylation, is very important for Notch signalling. The regulatory mechanisms for fucosylation are complicated. Many kinds of fucosyltransferases, the GDP-fucose synthesis pathway and GDP-fucose transporter are involved in the regulation of fucosylation. Increased levels of fucosylation have been reported in a number of pathological conditions, including inflammation and cancer. Therefore, certain types of fucosylated glycoproteins such as AFP-L3 or several kinds of antibodies, which recognize fucosylated oligosaccharides such as sialyl Lewis a/x, have been used as tumour markers. Furthermore, fucosylation of glycoproteins regulates the biological functions of adhesion molecules and growth factor receptors. Changes in fucosylation could provide a novel strategy for cancer therapy. In this review, the biological significance of and regulatory pathway for fucosylation have been described.

Key words: fucosylation, HCC, AFP-L3, fucosyltransferase, GDP-fucose.

INTRODUCTION

Fucosylation is one of the most important types of glycosylation in cancer. Hakomori *et al*. (*1*) presented the first paper on cancer and fucosylation in 1979. In this paper, the authors compared the fucosylation levels of glycolipids in hepatoma cells and normal hepatocytes. While certain kinds of fucosyltransferases involved differ between glycoproteins and glycolipids, their donor substrate, GDP-fucose, is common. Our recent findings regarding up-regulation of the GDP-fucose synthetic pathway would also reflect increases in glycolipid fucosylation in hepatoma cells. Fucosylation is regulated by several kinds of fucosyltransferases, the GDP-fucose synthetic pathway and GDP-fucose transporter. Before these complicated mechanisms of fucosylation were clarified, fucosylated target proteins were found and used as tumour markers. Increases in fucosylated alpha-fetoprotein (AFP) were reported by Dr Breborowicz and Dr Taketa (*2*, *3*). They first found microheterogeneity of AFP in several liver conditions and then found increases in α1-6 fucosylation (core-fucosylation) of AFP on lectin affino-electrophoresis (*4*, *5*). AFP is a well-known tumour marker for hepatocellular carcinomas (HCC), but it is sometimes also increased in benign liver diseases such as chronic hepatitis and liver cirrhosis. In contrast, AFP with core-fucosylation is a very specific marker for HCC (*6*, *7*). AFP with core-fucosylation was called AFP-L3, because it was detected the L3 fraction on LCA (Lensculinaris agglutinin) lectin-electorophoresis. Core-fucosylation comprises the attachment of fucose to the innermost *N*-acetylglucosamine in *N*-glycans. α1-6 fucosyltransferase (Fut8) catalyses the core-fucosylation reaction. We succeeded in the purification and cDNA cloning of Fut8 from porcine brain and the conditioned medium of a human gastric cancer cell line (*8*, *9*). Studies on cancer and fucosylation have moved to the second stage since that time.

Regulation of Fucosylation—The regulation of fucosylation appears to be complicated, and depends on the type of cells or organs involved. Basically, fucosyltransferases, GDP-fucose synthetic enzymes and GDP-fucose transporter are involved in the fucosylation pathway. There are 11 different, known fucosyltransferases (Fut) that have been cloned to date, and they are divided into four groups. Fut1 and Fut2 are involved in the synthesis of α1-2 fucose, Fut3, 4, 5, 6, 7 and 9 in the synthesis of α1-3/α1-4 fucose, and Fut8 in the synthesis of α1-6 fucose (core fucose) as described above, however, the fucosyltransferase activity has not been confirmed for either Fut10 or Fut11. When we cloned cDNA of Fut8 (*8*), we found that Fut8 exhibits little homology with other fucosyltransferases. Fut8 knockout mice showed no oligosaccharide structures with core fucose (*10*), suggesting that Fut8 is the only fucosyltransferase involved in core-fucosylation. Furthermore, 70–80% Fut8 knockout mice die at 2–3 days after birth although the detailed mechanisms remain unknown. Knockout mice as to other fucosyltransferases have not shown such drastic phenotypes. Fut7 controls leucocyte trafficking through an essential role in L-, E- and P-selectin ligand biosynthesis. Therefore, Fut7 knockout mice showed the abnormality of leukocyte extravasation during inflammation (*11*). Fut3 ~ Fut7 are involved in the synthesis of the Lewis X structure, which is a ligand for the selectin family. Fut9 knockout mice showed the disappearance of the

*To whom correspondence should be addressed. Tel: +81 6 6879 2590, Fax: +81 6 6879 2590,
E-mail: emiyoshi@sahs.med.osaka-u.ac.jp

Lewis X structure in the brain and increased anxiety-like behaviour (*12*), while these mice showed normal embryonic and germ cell development with disappearance of stage-specific embryonic antigen 1 (*13*).

For a GDP-fucose synthesis, there are two pathways. One is a *de novo* pathway, and the other is a salvage pathway (Fig. 1) The *de novo* pathway is dominant. The levels of GDP-fucose in cells or tissues are measured with HPLC systems using a fluorescent oligosaccharide and recombinant Fut8 (*14*). GDP-mannose-4, 6-dehydratase (GMD) (*15*) and GDP-fucose synthase, FX (*16*), play important roles in the synthesis of GDP-fucose. In particular, FX is a rate-limiting enzyme in the *de novo* pathway for GDP-fucose. A GMD mutant has been found in a CHO cell line, Lec13 (*15*). If there is a defect in the synthetic pathway for GDP-fucose, both Lewis-type and core-fucosylation disappear. FX knockout mice suffer from extreme neutrophilia, myeloproliferation and the absence of leucocyte selectin ligand expression (*17*). Interestingly, contingent restoration of leucocyte and endothelial selectin ligand expression, general cellular fucosylation and normal post-natal physiology is achieved by modulating dietary fucose to supply a salvage pathway for GDP-fucose synthesis. Both GMD and FX react in the cytosol, and cytosolic GDP-fucose is transported into the Golgi apparatus, where several fucosyltransferases can react. GDP-fucose transporter is a key factor for the transportation of GDP-fucose (*18*). An abnormality of GDP-fucose transporter has been reported in human congenital diseases involving glycosylation. In fact, GDP-fucose transporter knockout mice mimicked the congenital disorder of glycosylation IIc/leucocyte adhesion deficiency II (*19*).

Molecular Mechanisms for Producing AFP-L3 in HCC—Interestingly, the expression of Fut8 is quite low in normal liver (*20*), and increased levels of fucosylated proteins in serum can be used as tumour markers because numerous serum proteins are produced in the liver. A representative case is fucosylated α-fetoprotein (AFP), described above. AFP is a well-known tumour marker for HCC, but it is sometimes also increased in benign liver diseases such as chronic hepatitis and liver cirrhosis. In contrast, fucosylated AFP, referred to as AFP-L3 (Fig. 2), is very specific for HCC and was approved as a tumour marker for HCC by the FDA (Food and Drug Administration) in 2005. The molecular mechanism underlying the production of fucosylated AFP in HCC is complicated. The enhancement of Fut8 is required to produce fucosylated AFP, but this enhancement is insufficient for the production of fucosylated AFP in HCC (*21*). A donor substrate, GDP-fucose, is a more important regulatory factor for the fucosylation in HCC (*22*). FX plays a pivotal role in the synthesis of GDP-fucose, as described above. While the expression of Fut8 is increased in both HCC and liver cirrhosis, the levels of FX are significantly increased in HCC tissues (*22*). The levels of GDP-fucose in HCC tissues are significantly increased, compared to those in the surrounding tissue. In terms of the fucosylation pathway, many factors including fucosyltransferases, GMD, FX and the GDP-fucose transporter appear to be co-regulated. While gene expression of GMD was not significantly increased in

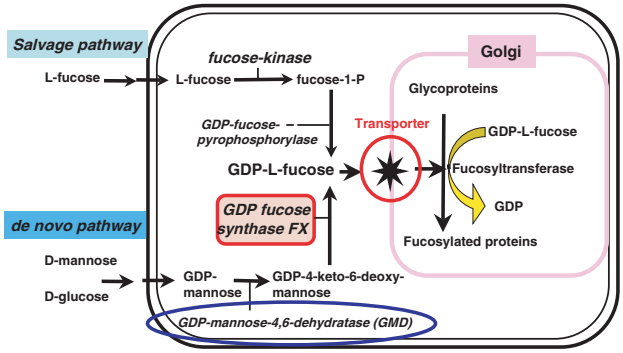

Fig. 1. **A synthetic pathway for GDP-fucose.** There are two different pathways for producing GDP-fucose in cells. While many enzymes are involved in the reaction, both GMD and FX play pivotal roles in production of the final product, GDP-fucose.

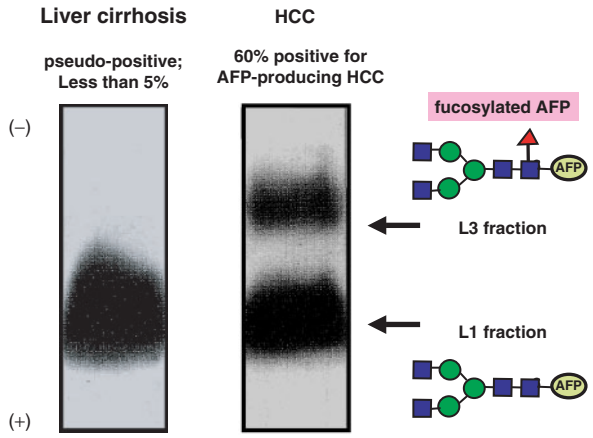

Fig. 2. **LCA lectin electrophoresis to identify AFP-L3 (fucosylated AFP).** WAKO Pure Chemical Industries established this system. The sera of patients with liver cirrhosis and HCC were elctrophoresed on an LCA agarose gel and western blot analysis was performed. Detail procedure was described previously (*4*, *5*). Since fucosylated AFP run more slowly on the LCA agarose gel, it was identified as AFP-L3. Levels of total AFP were increased in patients with HCC (~40–60%) as well as chronic liver diseases such as chronic hepatitis and liver cirrhosis. The AFP-L3 positive rate was ~60% in AFP-producing HCC, but was <5% in chronic liver diseases.

HCC tissues, western blot analyses of GMD showed dramatic increases in GMD proteins in HCC tissues, suggesting that post-translational modification of GMD is very important in the liver (*23*). Furthermore, a significant increase in the expression of GDP-fucose transporter mRNA was observed in HCC tissues. Overexpression of GDP-fucose transporter in hepatoma cells, Hep3B, caused a dramatic increase in cellular fucosylation. These data suggest that concomitant up-regulation of the expression of fucosylation-related genes is involved in the increases of fucosylated proteins including AFP-L3 in hepatomas.

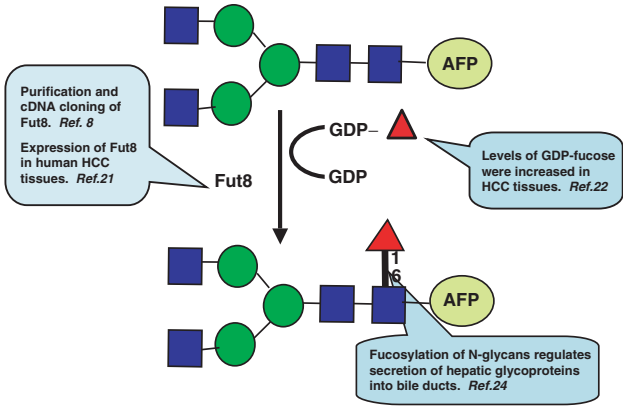

Fig. 3. **Molecular mechanisms for producing fucosylated AFP in patients with HCC.** The enhancement of Fut8 (*8*) is required to produce fucosylated AFP, but this enhancement is insufficient for the production of fucosylated AFP in HCC (*21*). A donor substrate, GDP-fucose is a more important regulatory factor for the fucosylation of HCC (*22*). FX plays a pivotal role in the synthesis of GDP-fucose. Another mechanism might exist in terms of an increase in fucosylated AFP in the sera of patients with HCC. Interestingly, fucosylated glycoproteins produced in hepatocytes are secreted into the bile, which is on the apical side of hepatocytes (*24*).

While the GDP-fucose level is up-regulated in HCC tissues, the level was only twice or three times, compared to in surrounding tissues (*22*). Another mechanism might exist in terms of an increase in fucosylated AFP in the sera of patients with HCC. Interestingly, fucosylated glycoproteins produced in hepatocytes are secreted into the bile, which is on the apical side of hepatocytes (*24*). When the oligosaccharide structures of bile and serum glycoproteins were compared by means of lectin blotting or 2D mapping, dramatic increases in fucosylation were observed for bile glycoproteins. Fut8 knockout mice show decreased levels of hepatic glycoproteins such as α1-acid glycoprotein and α1-antitrypsin in their bile, suggesting that fucosylation regulates the secretion of certain types of hepatic glycoproteins into the bile. The disruption of this system could be one of the mechanisms underlying the increases in fucosylated protein levels, including that of AFP-L3, in the sera of patients with HCC. HCC cells lose their polarity because they are rapidly proliferating. There are often no bile duct structures in HCC tissues. Therefore, selective secretion of fucosylated glycoproteins was not observed in HCC tissues, which led to the production of AFP-L3. AFP-L3 has also been detected in severe acute hepatitis (*25*).

Fucosylation and Lewis Antigen—Fut3, 4, 5, 6, 7 and 9 are involved in the synthesis of the Lewis antigen. They function in a cell- or organ- specific manner. Sialyl Lewis X or sialyl Lewis A is used as a tumour marker for certain types of cancer. Increases in these Lewis antigens in cancer tissues are correlated with a poor prognosis in colon cancer, due to the high incidence of liver metastasis. The reason for this is that Sialyl Lewis X is a ligand for selectins, which are expressed in endothelial cells. The first step of tumour metastasis is weak binding through an oligosaccharide and a lectin, followed by strong binding *via* integrins. Although these Lewis antigens are fucosylated oligosaccharides, other glycosyltransferases except fucosyltransferases are involved in its synthesis. The donor substrate, GDP-fucose, is also important for their synthesis, but the K_m values for these Lewis enzymes are different from that of Fut8. This type of fucosylation is also a signal for sorting hepatic glycoproteins into the bile (*24*). In the human liver, Fut6 is involved in the synthesis of Lewis types of fucosylation and hepatic glycoproteins with this oligosaccharide structure are present in the bile. In the case of mice, Fut6 is a pseudo-gene, and therefore the secretion of certain kinds of hepatic glycoproteins into the bile is disrupted in Fut8 knockout mice.

Fucosylated Haptoglobin and Pancreatic Cancer—In terms of glycomics, fucosylated glycoproteins are recognized by several types of lectins. These lectins include AAL, UEA, LCA and AOL. AAL recognizes α1-3/α1-4 and α1-6 fucose, UEA recognizes α1-2 fucose, LCA recognizes the native form of α1-6 fucose with a mannose arm and AOL recognizes α1-6 fucose more specifically (*26*). These lectins could imply a diagnosis of cancer. On western blotting of the AAL lectin using serum from patients with pancreatic cancer, ~40 kDa protein was found to be highly fucosylated. The N-terminal sequence revealed that this protein was the haptoglobin β chain (*27*). The positive rate of fucosylated haptoglobin is 60–80% and the rate increases progressively with the stage of the disease. Increases in fucosylated haptoglobin levels have been observed in several types of cancer (20–40%), and it has been reported that high levels of fucosylated haptoglobin were produced in the advanced stages of ovarian cancer, lung cancer and breast cancer (*28*). Basically, haptoglobin is produced in the liver and exhibits a low level of fucosylation of its glycans, since the expression of Fut8 is quite low in the normal liver. The ectopic expression of haptoglobin is observed in special conditions such as infections, inflammation and cancer. The question here is where fucosylated haptoglobin is produced in patients with pancreatic cancer. A special pancreatic cancer cell, PSN-1, expresses haptoglobin mRNA and produces fucosylated haptoglobin in conditioned medium. However, this case is very rare in comparison with the positive rate for fucosylated haptoglobin (60–80%). If white blood cells that have infiltrated around pancreatic cancer cells produce haptoglobin, they would be fucosylated, because blood cells express high levels of Fut8. The third hypothesis is that fucosylated haptoglobin produced in the liver is missorted into the blood due to a factor that is secreted from pancreatic cancer cells. To determine which theory is correct, detailed analyses of oligosaccharide structures including site-directed analysis of haptoglobin oligosaccharides need to be performed. Collectively, fucosylation is highly associated with cancer and additional information regarding the mechanism involved would be highly desirable, since it could be a target for novel cancer therapy.

Core Fucose Directly Regulates ADCC Activity, Growth Factor Receptor Signalling and Adhesion Molecule Activity—Antibody-dependent cellular cytotoxicity (ADCC), *i.e.* a lytic attack on antibody-targeted cells, has been found to be one of the critical effector functions

responsible for the clinical efficacy of therapeutic antibodies and is dramatically enhanced by fucose-negative oligosaccharides attached to the Fc region (*29*, *30*). This concept could provide us with a novel strategy for antibody therapy of lower cost. While the detailed mechanism underlying the growth retardation of Fut8 knockout mice remains unknown (*10*), it has been shown that the signalling of the EGF receptor was reduced with MEF (murine embryonic fibroblast) cells of Fut8 knockout mice. Phosphorylation of the EGF receptor after EGF stimulation was dramatically reduced in Fut8 (–/–) MEF cells as compared to in wild type MEF cells (*31*). Reintroduction of Fut8 reversed this delay in the EGF receptor reaction. Furthermore, down-regulation of EGF receptor in Fut8 deficiency suppressed the activation of trypsin, leading to a delay in cell growth via the PAR2 (proteinase-activated receptor 2) system (*32*). The DNA micro array and real-time polymerase chain reaction (PCR) analyses showed that a group of genes, including those of trypsinogens 4, 7, 8, 11, 16 and 20, were down-regulated in Fut8 (–/–) embryos. Consistently, the expression of trypsinogen proteins was found to be lower in Fut8 (–/–) mice in the duodenum, small intestine and pancreas. Trypsin, an active form of trypsinogen, regulates cell growth through a G-protein-coupled receptor, PAR-2. Many factors due to dysregulation of growth factor receptors might greatly influence the growth of Fut8-deficient mice. The activity of integrin also decreased with reduction in core-fucosylation (*33*). Integrins are adhesion molecules which have many *N*-glycans. Interestingly most of the *N*-glycans are core-fucosylated in wild type MEF cells. Fut8 (–/–) MEF cells showed a dramatic decrease in adhesion to the extracellular matrix and the reintroduction of Fut8 caused recovery of the activity. Overall, many glycoproteins on the cell surface would be controlled by core-fucosylation.

Closing, Functional Glycomics and Core-Fucosylation—Recent techniques for glycomics (proteomics with glycobiology techniques) will provide several kinds of glyco-biomarker. In particular, core-fucosylated glycoproteins would be one of the targets for glycomics because the expression level of Fut8 is quite low in normal liver, where most glycoproteins in the serum are produced. GP73 was found to be a novel tumour marker for HCC in a glycomics study (*34*). GP73 is a phosphoprotein in the Golgi apparatus, but its function is unknown. The secretion pathway for GP73 would be different from those for other glycoproteins in the liver. It is also reported that fucosylation of GP73 was increased in sera of patients with HCC. Recently, the traffic pathway for GP73 was clarified and furin was found to be a key protease that cleaves GP73 in the Golgi (*35*). One goal of functional glycomics is to identify a target glycoprotein for a glycosyltransferase, which functionally changes on the addition of specific oligosaccharide structure (*36*). While IgG is one such glycoprotein, other fucosylated glycoproteins such as AFP, haptoglobin and GP73 should be functionally analysed. Collectively, fucosylation is one of the most exciting types of glycosylation in cancer, the immune system and cell growth. Recent advances in glycotechnology will find more number of fucosylated glycoproteins as tumour markers. The most important issues in cancer and fucosylation would answer to a question, why a specific type of fucosylated proteins is increased in each cancer.

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