Chapter 1
Roles of Fucosyltransferases in Cancer Phenotypes

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Abstract Fucosylation is one of the most important types of glycosylation in carcinogenesis. Fucosylation is linked to certain processes in cell-cell interaction and dynamic regulation of growth factor receptor signaling on cell surface, and changes in fucosylation result in differences of biological phenotype in cancer cells. Eleven fucosyltransferases are involved in the synthesis of fucosylated glycans and belong to some family of fucosyltransferases. To regulate cellular fucosylation, GDP-fucose, a donor substrate of fucosyltransferases, and GDP-fucose transporter are also important. Terminal fucosylation (Lewis-type fucosylation) is associated with the synthesis of sialyl Lewis antigens, leading to cancer metastasis. In contrast, core fucosylation is linked to the regulation of membrane-anchored glycoproteins, such as growth factor receptors and adhesion molecules. Target glycoproteins for each fucosyltransferase might be different in various kinds of cancer. In this chapter, we describe the roles of fucosyltransferase in several kinds of cancer, particularly gastroenterological cancers.

Keywords Fucosylation • Fucosyltransferases • Pancreatic cancer • Colon cancer • HCC • Lewis antigen • Cancer biomarker • CA19-9

1.1 Introduction

Fucosylation is one of the most important types of glycosylation involved in cancer and inflammation (Miyoshi et al. 2008). Cancer fucosylation is mainly divided into three types: α1-2 fucosylation, α1-3/1-4 fucosylation, and α1-6 fucosylation, as shown in Fig. 1.1. All fucosylations are regulated by orchestration of many fucosyltransferases (FUTs), guanosine 5′-diphosphate (GDP)-fucose synthetic enzymes, and GDP-fucose transporter(s). FUT1 and FUT2 have been shown to be responsible for α1-2 fucosylation (Larsen et al. 1990; Kelly et al. 1995). A family of

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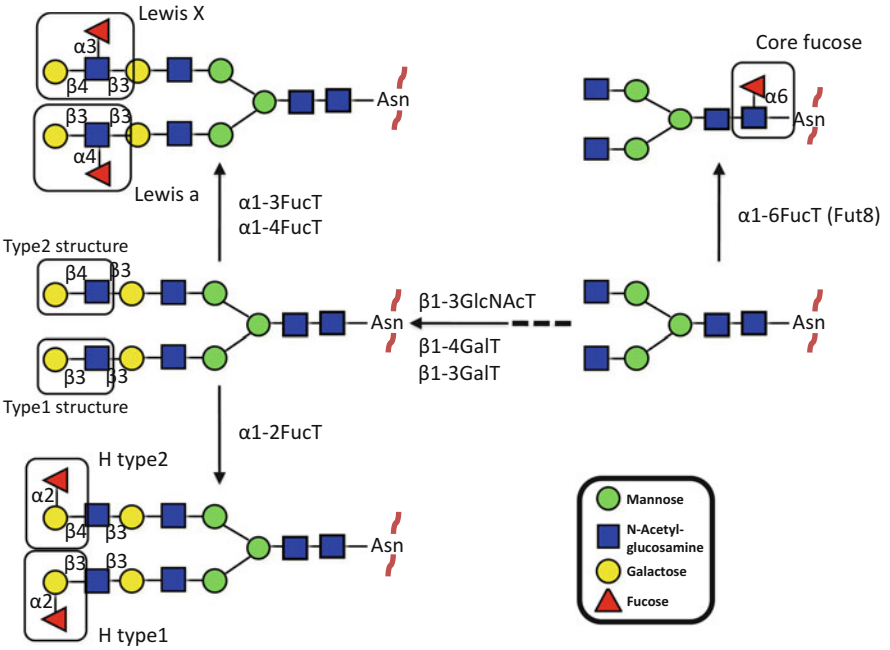

Fig. 1.1 Cancer fucosylation is mainly divided into 3 groups: α1-2 fucosylation, α1-3/1-4 fucosylation, and α1-6 fucosylation. Representative biosynthetic pathways and structures of the H, Lewis A, and Lewis X antigens. Type 1 and type 2 structures differ in the linkage of the outermost galactose (β1-3 and β1-4, respectively) and in the linkage of the fucose moiety to the internal GlcNAc (α1-4 and α1-3, respectively). The core fucose structure is synthesized by the glycosyltransferase FUT8, which catalyzes the transfer of a fucose residue from the donor substrate, guanosine 5′-diphosphate (GDP)-β-L-fucose, to the reducing terminal GlcNAc of the core structure of asparagine-linked oligosaccharide via an α1-6 linkage

α1-3 fucosyltransferases, including FUT3 (Kukowska-Latallo et al. 1990), FUT4 (Goelz et al. 1990), FUT5 (Weston et al. 1992), FUT6 (Koszdin and Bowen 1992), FUT7 (Natsuka et al. 1994), and FUT9 (Kudo et al. 1998), is involved in the synthesis of Lewis blood group antigens. FUTs 3–7 can synthesize the sialyl Lewis X (sLe^x) structure, NeuAcα2-3Galβ1-4(Fucα1-3)GlcNAcβ-R, and FUTs 3–6 and FUT9 can synthesize the Le^x structure, Galβ1-4(Fucα1-3)GlcNAcβ-R. Only FUT3 exhibits α1-4 fucosyltransferase activity, resulting in the synthesis of type 1 Lewis antigens such as Le^a, Le^b, and sialyl Le^a (sLe^a) (Galβ1-3(Fucα1-4)GlcNAcβ-R, (Fucα1-2)Galβ1-3(Fucα1-4)GlcNAcβ-R, and NeuAcα2-3Galβ1-3(Fucα1-4)GlcNAcβ-R, respectively). Therefore, individuals with FUT3 mutations, comprising approximately 10 % of the Japanese population, have a problem regarding diagnosis of pancreatic cancer using the CA19-9 antigen, sLe^a (Narimatsu et al. 1998). In contrast, FUT8 is the only α1-6 fucosyltransferase involved in core fucosylation at the innermost *N*-acetylglucosamine on *N*-glycans (Uozumi et al. 1996). Among the many fucosyltransferases, Fut8-deficient mice show severe phenotypes, including mortality rates of 70–80 % after birth, and the

survivors show severe growth disturbances and lung emphysema (Wang et al. 2005). The phenotype of Fut8 knockout mice is due to insufficient signaling via membrane-anchored receptors. Mice with a deficiency of FX (GDP-4-keto-6-deoxy-mannose-3, 5-epimerase-4-reductase), a rate-limiting enzyme for GDP-fucose synthesis, show severe phenotypes, which are mostly caused by the loss of Lewis-type fucosylation (Smith et al. 2002). There are two pathways of GDP-fucose synthesis: de novo and alternative (Miyoshi et al. 2008). Because FX is involved in the de novo pathway, the salvage pathway compensates the synthesis of GDP-fucose in FX knockout mice (Smith et al. 2002). These reports suggest that core fucosylation is associated with growth factor receptor-mediated cell signaling and Lewis-type fucosylation is linked to lymphocyte/white blood cell adhesion through selectin and $sLe^{x/a}$ interaction. In cases of many cancers, fucosylation levels are increased. The biological significance of increased fucosylation in each cancer has some common and some different aspects. In this review article, we discuss the roles of fucosyltransferase in several kinds of cancer, with a particular focus on gastroenterological cancers.

1.2 Fucosylation in Colorectal Cancer

α1-2 Fucosylation, as seen in H, Lewis B, and Lewis Y antigens, is regulated by FUT1 and FUT2 and plays pivotal roles in colorectal cancer. Increased α1-2 fucosylation is observed in the progression of colorectal cancer (Misonou et al. 2009). Based on mass spectrometry analysis of neutral and acidic glycosphingolipids, structures of normal colorectal epithelial cells are characterized by the dominant expression of neutral type-1 chain oligosaccharides. Three specific alterations were observed in malignant transformation: increased ratios of type-2 oligosaccharides, increased α2-3 and/or α2-6 sialylation, and increased α1-2 fucosylation. Pendu et al. have published several papers regarding the biological function of α1-2 fucosylation in colorectal cancer cells (Goupille et al. 2000; Cordel et al. 2000). They used gene manipulation techniques, but did not identify target glycoproteins/glycolipids for α1-2 fucosylation, which regulates biological functions. When the FUT1 expression vector was transfected into colorectal cancer cell lines, the cells showed resistance to serum-starved apoptosis and anticancer drug treatment. In contrast, transfection with antisense cDNA against FUT1 induces apoptosis under these conditions. An increase in tumorigenicity was observed in rat colon carcinoma cells after transfection with rat α1, 2-fucosyltransferase FTA (human FUT1) antisense cDNA (Hallouin et al. 1999). Antisense transfection of a cDNA fragment of the FTB enzyme (human FUT2) decreased the cell-surface levels of H-antigen and concomitantly decreased tumorigenicity. Interestingly, these phenomena were observed only in synergic animals but not in immunodeficient mice. These results suggest that FTA and FTB fucosylate distinct glycan chains in the same cell, leading to opposite effects, under the control of the immune system. The immune system regulated by α1-2 fucosylation is not mediated by NK

cell cytotoxicity, but lymphokine-activated killer cytotoxicity (Marionneau et al. 2000). In the case of α1-3 fucosylation, increased expression of sLe^x in colorectal cancer is associated with liver metastasis (Nakamori et al. 1993). This is due to enhanced selectin-mediated cell adhesion. Selectins are intrinsic ligands for sLe^x, and the interaction between selectin and oligosaccharides plays a pivotal role in the rolling of white blood cells and the initial adhesion of cancer cells to metastatic organs. Overexpression of FUT7 induces the expression of sLe^x antigen, resulting in the promotion of cell migration and invasion in a colon cancer cell line, LoVo (Li et al. 2010). The authors identified CD24 as a carrier molecule for the sLe^x antigen, which is a well-known cell-surface marker for cancer stem cells. Administration of disaccharides blocked colorectal cancer cells from forming selectin ligands and inhibited adhesion to immobilized selectins, suggesting that glycosides might prove useful for interfering with tumor cell adhesion and metastasis (Brown et al. 2003). This approach opens up the possibility of clinical glycotherapy with no gene manipulations. Apart from fucosyltransferases, the sialidase NEU4 inhibits the synthesis of Le^x antigens on *O*-glycans (Shiozaki et al. 2011). Cell adhesion to and motility and growth on E-selectin are significantly reduced by NEU4. Under hypoxia conditions, whereby sLe^x antigens are increased concomitantly with several sialyl- and fucosyltransferases, NEU4 expression is markedly decreased. These results suggest that NEU4 plays an important role in the control of sLe^x expression and its impairment is involved in colon cancer progression. The epithelial-mesenchymal transition (EMT) is involved in cancer metastasis, and fibroblast growth factor (FGF)/basic FGF (bFGF)-mediated EMT induced increases cancer invasion and metastasis. During the EMT, transcript levels of the glycosyltransferase genes ST3GAL1/3/4 and FUT3 were significantly elevated, and that of FUT2 was markedly suppressed (Sakuma et al. 2012). GDP-mannose-4,6-dehydratase (GMDS) is a rate-limiting enzyme in GDP-fucose synthesis, in addition to FX (Miyoshi et al. 2008). Mutation of the GMDS gene was found in the colon cancer cell line HCT116 (Moriwaki et al. 2009). HCT116 cells showed complete loss of all types of fucosylation, and the fucosylation level was recovered upon transfection of a wild-type GMDS expression vector. Unexpectedly, HCT116 cells showed higher metastatic potential through escape from NK cell-mediated immune surveillance. The molecular mechanisms underlying the inhibition of cell death by NK cell killing are suppressed during death signaling through the Fas or tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors. Interestingly DR5, a TRAIL receptor, has neither *N*-glycans nor *O*-glycans, although DR5-mediated cell death is inhibited in HCT116 cells, but not in fucosylation-rescued HCT116 cells (Moriwaki et al. 2011). There is an unknown pathway in fucosylation and receptor-mediated cell signaling. Mutation of the GMDS gene was found in approximately 10 % of original colorectal cancer tissues and 15 % of metastatic colorectal cancer tissues, but not in the normal colon (Nakayama et al. 2013). This report suggests a novel type of metastatic pathway due to the loss of fucosylation in colon carcinogenesis.

1.3 Fucosylation in Pancreatic Cancer

Pancreatic cancer is one of the worst diseases in terms of prognosis. The reason for the poor prognosis of pancreatic cancer is the difficulty in early diagnosis and high metastatic potential. Sialyl Lewis A, referred to as CA19-9, is a representative cancer biomarker for pancreatic cancer and is a fucosylated glycan (Kannagi et al. 2004). Measurement of serum CA19-9 levels in patients with pancreatic cancer is dependent on the levels of several kinds of mucins that carry many sialyl Lewis A molecules. Recently, we identified another type of CA19-9 carrier molecule, microlipid membranes, in both bile and sera of patients with pancreatic cancer (Uozumi et al. 2010). Details of the synthetic pathway of CA19-9, as well as its carrier molecules, remain unknown, but this appears to be one of the most interesting topics in glycobiology research. Fucosylated haptoglobin has been found in the sera of patients with pancreatic cancer (Okuyama et al. 2006), and we have developed a lectin ELISA system for measuring fucosylated haptoglobin (Kamada et al. 2013b). Various screening analyses using this ELISA assay have revealed that fucosylated haptoglobin is increased in several cancers and liver diseases (Kamada et al. 2013a; Takeda et al. 2012). Fucosylated haptoglobin is probably produced in the liver upon metastasis of colon/pancreatic cancers, and this is the reason why the positive rate of fucosylated haptoglobin is much higher in pancreatic cancer, which easily metastasizes at the early clinical stages (Okuyama et al. 2006). Detailed oligosaccharide analysis of fucosylated haptoglobin showed that most of the fucosylation is the Lewis type, and there are small amounts of core fucosylation. Interestingly, site 3 of the *N*-glycan on haptoglobin has a unique oligosaccharide structure with unique fucosylation, compared to the other 3 sites (Nakano et al. 2008). High expression of sLe^x antigen is involved in the metastasis of pancreatic cancer as well as colorectal cancer (Mas et al. 1998). The restoration of α1-2 fucosyltransferase (FUT1) activity decreases the adhesive and metastatic properties of human pancreatic cancer cells, although the molecular mechanisms are not clarified (Aubert et al. 2000; Mathieu et al. 2004).

1.4 Fucosylation in Hepatocellular Carcinoma

Fucosylation in the liver is different from that in other organs because the expression of α1-6 fucosyltransferase (FUT8) is quite low in normal hepatocytes (Noda et al. 1998a). Inflammation induces the expression of fucosylation regulatory genes, resulting in increases in Lewis-type fucosylation on hepatic glycoproteins. FUT6 is important in the synthesis of Lewis-type fucosylation in the liver but is a pseudogene in the mouse. Therefore, FUT8 is the main fucosyltransferase involved in cellular fucosylation in the mouse liver. FUT8-deficient mice show dramatic inhibition of hepatic glycoproteins in bile (Nakagawa et al. 2006), suggesting that fucosylation might be a sorting signal for the secretion of liver glycoproteins into bile. This hypothesis could explain the molecular mechanisms underlying the production of

fucosylated cancer biomarkers in hepatocellular carcinoma (HCC). α-Fetoprotein (AFP) is clinically used as cancer biomarker but has the drawback that serum AFP levels are increased in certain cases of chronic liver disease such as chronic hepatitis and liver cirrhosis (Taketa 1990). In contrast, fucosylated AFP, referred to as AFP-L3, is specifically increased in the sera of patients with HCC. AFP-L3-positive HCC showed worse prognosis than did AFP-L3-negative HCC (Yamashita et al. 1996). Although it has been reported that AFP-L3 could be a cancer biomarker for early HCC (Sato et al. 1993), many clinicians think that AFP-L3 is a marker for HCC with poor prognosis and that AFP-L3-positive HCC should be treated with hepatic resection, but not percutaneous radiofrequency ablation. However, a highly sensitive AFP-L3 assay might provide another possibility as a biomarker for the early diagnosis of HCC (Kumada et al. 2013). While FUT8 is involved in the synthesis of AFP-L3, the expression of FUT8 is increased in chronic liver disease (Noda et al. 1998b). In contrast, the level of GDP-fucose, a donor substrate of FUT8, is higher in HCC tissue than in the surrounding tissue (Noda et al. 2003). Increased levels of GDP-fucose are caused by high FX expression in HCC tissue. However, the most important factor involved in the production of AFP-L3 seems to be an abnormal sorting system for fucosylated proteins in HCC (Nakagawa et al. 2012). Fucosylated proteins produced by normal hepatocytes are secreted into bile, but this system is disrupted in HCC. This disruption might be due to the loss of the intrahepatic bile duct or the loss of cargo receptors for core fucose in HCC. In the case of hepatitis B virus-related HCC, it is reported that FUT8 is directly involved in the progression of HCC (Ji et al. 2013). In this report, downregulation of FUT8 in cancer cells was found to cause a decrease in cell growth in HCC cell lines as in other cancer cell lines. Although liver diseases have different etiologies and each disease has a characteristic biomarker, common changes in protein glycosylation in liver diseases are hyperfucosylation and an increase in the branching structure of *N*-glycans (Blomme et al. 2009). Moreover, mass spectrometry analysis of *N*-glycans on hepatic glycoproteins in HCC tissue revealed that the characteristic changes in glycan structure involve increases in tetra-antennary *N*-linked glycan but not in core fucosylation (Mehta et al. 2012). These papers further support the presence of an abnormal sorting system of fucosylated proteins in liver diseases. A previous report suggests that fucosyltransferase activity in serum, plasma, and tissue is different in patients with liver cirrhosis and HCC (Hutchinson et al. 1991), although its biological significance remains unknown.

1.5 Fucosylation in Other Cancers

Gastric cancer is the most popular carcinoma and the second cause of cancer-related death in Japan. In addition to hepatocarcinogenesis, inflammation induced by *Helicobacter pylori* infection plays a key role in the carcinogenesis of gastric cancer (Wang et al. 2013). Interestingly, polymorphisms of fucosyltransferases are involved in infection by *Helicobacter pylori* (Ikehara et al. 2001). Both IL-1 and IL-6, which are associated with inflammation-related cytokines, regulate the expression of

fucosyltransferases in gastric cancer cell lines (Padro et al. 2011). This finding is similar to the observed induction of fucosylation regulatory genes in HCC cell lines with IL-6 treatment (Narisada et al. 2008). Interestingly, FUT3 gene expression, involved in the synthesis of the sialyl Lewis A antigen, CA19-9, is regulated by DNA methylation (Serpa et al. 2006). Hypo-methylation of the FUT3 gene promoter in gastric cancer leads to the production of CA19-9. The expression pattern of fucosyltransferases alters oligosaccharides of mucins produced in normal and cancer tissue (Lopez-Ferrer et al. 2000). In the case of prostate cancer, α1-3 fucosyltransferases are very important in the regulation of cell behaviors such as adhesion, trafficking, and cell growth (Barthel et al. 2009; Inaba et al. 2003). Furthermore, FUT6 is involved in the bone metastasis of prostate cancer (Li et al. 2013). It has recently been reported that the high expression of GnT-IX and FUT8 is associated with the malignant phenotype of prostate cancer (Lange et al. 2012). Serum levels of fucosylated haptoglobin are also increased in patients with prostate cancer (Fujimura et al. 2008). Several papers on mammary cancer and fucosylation have been published, and their contents are similar to observations in other cancers (Yang et al. 2013, 2014; Julien et al. 2011). A very old article reported in *Science* indicates that a decrease in human serum fucosyltransferase is an indicator of successful tumor therapy in breast cancer (Bauer et al. 1978). A recent interesting paper on cholangiocarcinoma suggests that FUT2 and FUT3 genotypes determine the cutoff value for CA19-9 in differential diagnosis of cancer in patients with sclerosing cholangitis (Wannhoff et al. 2013). The involvement of FUT8 in EMT and EGF signaling has been reported in lung cancer (Liu et al. 2011; Chen et al. 2013).

1.6 Closing

Both FUT10 and FUT11 are novel types of α1-3 fucosyltransferases (Mollicone et al. 2009; Kumar et al. 2013; Both et al. 2011). These FUTs might play specific roles in carcinogenesis or may have other pathological functions that have not been mentioned in this review. A summary of FUT genes, including their chromosomal localization, is provided in Table 1.1. Interestingly, many fucosyltransferase genes are localized on chromosome 19. The amino acid homology of α1-3/1-4 fucosyltransferases is shown in Fig. 1.2. Here, we should note the structural characteristics of α1-3 fucosyltransferases. FUT3 is a unique glycosyltransferase that has the enzymatic activities of both α1-3 and 1-4 fucosyltransferase. FUT3 plays an important role in the synthesis of Lewis antigen in blood type, and loss of Fut3 activity leads to deficiency of the Lewis antigen in blood type, as well as of the Lewis A antigen (CA19-9). However, the amino acid sequence of FUT3 is very similar to those of other α1-3 fucosyltransferases. PCR primers for each fucosyltransferase should be designed carefully, due to their high gene/amino acid homologies. While this number is not so much, compared to other research fields, the number is relatively high in glycobiology research. Recently, O-fucosylation and notch signaling are two of the most important issues in glycobiology (Stanley 2007). Since notch signaling is involved in EGF

Table 1.1 Papers on the chromosomal localization and cloning of fucosyltransferases (FUTs)

FUTs	Official full name	Location (Human)	Gene ID (Human)	References (cDNA cloning)
FUT1	Fucosyltransferase 1 (galactoside 2-alpha-L-fucosyltransferase, H blood group)	19q13.3	2523	Larsen RD, et al. *Proc Natl Acad Sci U S A* 87, 6674–6678 (1990)
FUT2	Fucosyltransferase 2 (secretor status included)	19q13.3	2524	Kelly RJ, et al. *J Biol Chem* 270, 4640–4649 (1995)
FUT3	Fucosyltransferase 3 (galactoside 3(4)-L-fucosyltransferase, Lewis blood group)	19p13.3	2525	Kukowska-Latallo JF, et al. *Genes Dev* 4, 1288–1303 (1990)
FUT4	Fucosyltransferase 4 (alpha (1,3) fucosyltransferase, myeloid specific)	11q21	2526	Goelz SE, et al. *Cell* 63, 1349–1356 (1990)
FUT5	Fucosyltransferase 5 (alpha (1,3) fucosyltransferase)	19p13.3	2527	Weston BW, et al. *J Biol Chem* 267, 4152–4160 (1992)
FUT6	Fucosyltransferase 6 (alpha (1,3) fucosyltransferase)	19p13.3	2528	Koszdin KL, et al. *Biochem Biophys Res Commun* 187, 152–157 (1992)
FUT7	Fucosyltransferase 7 (alpha (1,3) fucosyltransferase)	9q34.3	2529	Natsuka S, et al. *J Biol Chem* 269, 16789–16794 (1994),
FUT8	Fucosyltransferase 8 (alpha (1,6) fucosyltransferase)	14q24.3	2530	Uozumi N, et al. *J Biol Chem* 271, 27810–27817 (1996)
FUT9	Fucosyltransferase 9 (alpha (1,3) fucosyltransferase)	6q16	10690	Kudo T, et al. *J Biol Chem* 273, 26729–26738 (1998)
FUT10	Fucosyltransferase 10 (alpha (1,3) fucosyltransferase)	8p12	84750	Mollicone R, et al. *J Biol Chem* 284, 4723–4738 (2009)
FUT11	Fucosyltransferase 11 (alpha (1,3) fucosyltransferase)	10q22.2	170384	Mollicone R, et al. *J Biol Chem* 284, 4723–4738 (2009)

receptor-mediated cell signaling, O-fucosylation might be important in cancer biology. Globally, if we search for all fucosyltransferases and cancer, the number is 588. If we search for all sialyltransferases and cancer, the number is 780. We believe that fucosylation, sialylation, and branching are three major glycosylations involved in cancer. Taken together, each fucosylation shows commonalities in each gastroenterological cancer and also shows differences in different cancers, suggesting that the target glycoproteins for fucosylation might be different in each cancer phenotype.

Fig. 1.2 Amino acid homology of α1-3 fucosyltransferases (Fut3–Fut11). (**A**) High-homology region of α1-3 fucosyltransferases (Fut3–Fut11). (**B**) Total amino acid structure of α1-3 fucosyltransferases (Fut3–Fut11)

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