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REVIEW

Fucosylation and gastrointestinal cancer

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Abstract

Fucose (6-deoxy-L-galactose) is a monosaccharide that is found on glycoproteins and glycolipids in vertebrates, invertebrates, plants, and bacteria. Fucosylation, which comprises the transfer of a fucose residue to oligosaccharides and proteins, is regulated by many kinds of molecules, including fucosyltransferases, GDP-fucose synthetic enzymes, and GDP-fucose transporter(s). Dramatic changes in the expression of fucosylated oligosaccharides have been observed in cancer and inflammation. Thus, monoclonal antibodies and lectins recognizing cancer-associated fucosylated oligosaccharides have been clinically used as tumor markers for the last few decades. Recent advanced glycomic approaches allow us to identify novel fucosylation-related tumor markers. Moreover, a growing body of evidence supports the functional significance of fucosylation at various pathophysiological steps of carcinogenesis and tumor progression. This review highlights the biological and medical significance of fucosylation in gastrointestinal cancer.

Key words: Fucosylation; Gastrointestinal cancer; Alpha-fetoprotein

INTRODUCTION

Oligosaccharides are one of the most important factors in the posttranslational modification of proteins and lipids. Glycomics, the systematic study of glycans and glycan-binding proteins in various biological systems, is an emerging field in the post-genomics and post-proteomics era[1-3]. It is well known that oligosaccharide structures change during malignant transformation[4]. The remodeling of cell surface glycoproteins and glycolipids through modification of oligosaccharide structures is associated with the biological behavior of tumor cells[5-8]. Fucose is a constituent of oligosaccharides, and is notably associated with cancer and inflammation[9]. In the 1980s, the development of monoclonal antibodies against carbohydrate antigens triggered research to detect cancer-associated aberrant glycosylation. Several antibodies recognizing fucosylated glycoproteins or glycolipids in the sera of patients with cancer have long been used as tumor markers, such as CA19-9[10]. Alpha-fetoprotein (AFP)-L3 fraction, which is fucosylated AFP, has also been clinically used as a tumor marker for hepatocellular carcinoma (HCC) since 1996 in Japan and 2005 in the United States[11,12]. In recent years, advances in the methodology for detection of glycan alteration in cancer cells and sera of patients with cancer have driven the development of various types of tumor markers. In this review, we summarize the history of fucosylation-

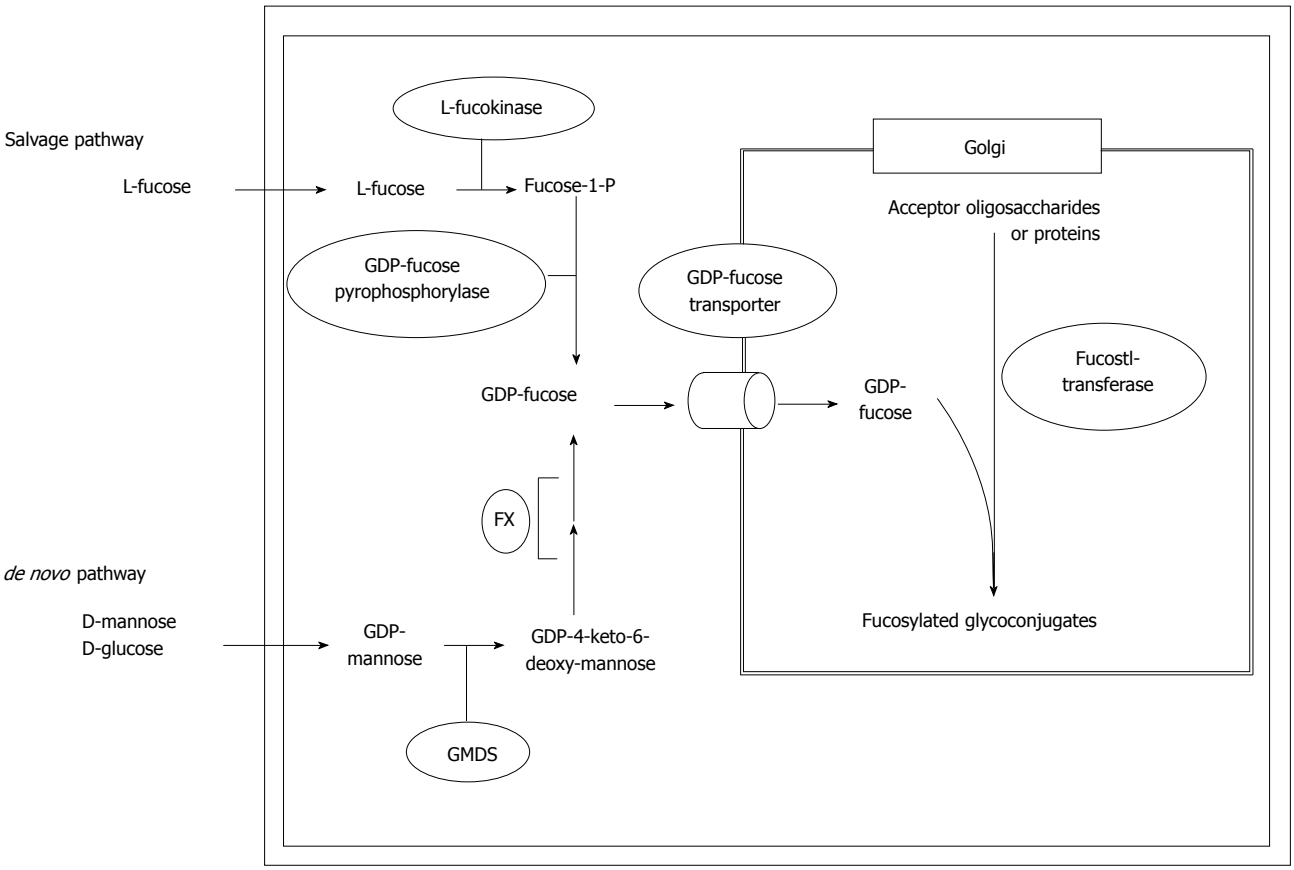

Figure 1 Fucose metabolism. GDP-fucose is mainly synthesized through the de novo pathway by three reactions catalyzed by GDP-4,6-dehydratase (GMDS) and GDP-4-keto-6-deoxy-mannose-3,5, epimerase-4-reductase (FX). Free L-fucose is converted to GDP-fucose through the salvage pathway, which is a minor pathway. GDP-fucose is subsequently transported from the cytosol to the Golgi lumen by GDP-fucose transporter, and then transferred to acceptor oligosaccharides and proteins by fucosyltransferases.

related tumor markers. Moreover, several research groups, including ours, have revealed the biological roles of fucose in several types of cancer. This review also focuses on the pathophysiological significance of fucosylation in gastrointestinal cancer.

REGULATORY MECHANISM FOR FUCOSYLATION

Fucosylation is catalyzed by fucosyltransferases, guanosine 5'-diphosphate (GDP)-fucose synthetic enzymes, and GDP-fucose transporter(s) (Figure 1). The thirteen fucosyltransferase genes which have thus far been identified in the human genome can be divided into five groups. Firstly, FUT1 and FUT2 have been shown to be responsible for the α1-2 linkage of fucose[13,14]. Secondly, a family of α1-3 fucosyltransferases, including FUT3[15], FUT4[16-18], FUT5[19], FUT6[20,21], FUT7[22,23], and FUT9[24,25], is involved in the synthesis of Lewis blood group antigens. FUTs3-7 can synthesize the sialyl Lewis X (sLe^x) structure, NeuAcα2-3Galβ1-4(Fucα1-3)GlcNAcβ-R, and FUTs3-6 and FUT9 (i.e. not FUT 7) can synthesize the Le^x structure, Galβ1-4(Fucα1-3)GlcNAcβ-R. FUT9 is the enzyme most responsible for the synthesis of Le^x in the brain[26]. Only FUT3 exhibits α1-4 fucosyltransferase activity, resulting in the synthesis of type 1 Lewis antigens such as Le^a [Galβ1-3(Fucα1-4)GlcNAcβ-R], Le^b [(Fucα1-2)Galβ1-3(Fucα1-4)GlcNAcβ-R], and sialyl Le^a [NeuAcα2-3Galβ1-3(Fucα1-4)GlcNAcβ-R]. Thirdly, FUT8 catalyzes the transfer of a fucose residue to the C6 position of the innermost GlcNAc residue of *N*-linked oligosaccharides on glycoproteins to produce core fucosylation[27,28]. Fourthly, it remains to be determined which kinds of fucosyltransferase activity FUT10 and FUT11 have[29]. Finally, protein *O*-fucosytransferases 1 and 2 (Pofut1 and Pofut2, respectively) transfer a fucose residue *via* an α-linkage to serine or threonine within epidermal growth factor (EGF)-like repeats containing an appropriate consensus sequence (C^2-$X_{(4-5)}$-[S/T]-C^3) and thrombospondin type 1 repeats containing a consensus sequence (C-X-X-[S/T]-C-X-X-G), respectively[30-33]. Notch and the ADAMTS superfamily were identified as proteins targeted by Pofut1 and 2, respectively[34-36]. Since these proteins have been reported to regulate carcinogenesis and cancer progression, *O*-fucose may be associated with cancer biology[37-39].

GDP-fucose, which is a common donor substrate to all fucosyltransferases, is synthesized in the cytosol *via* two pathways, namely the salvage pathway and the *de novo*

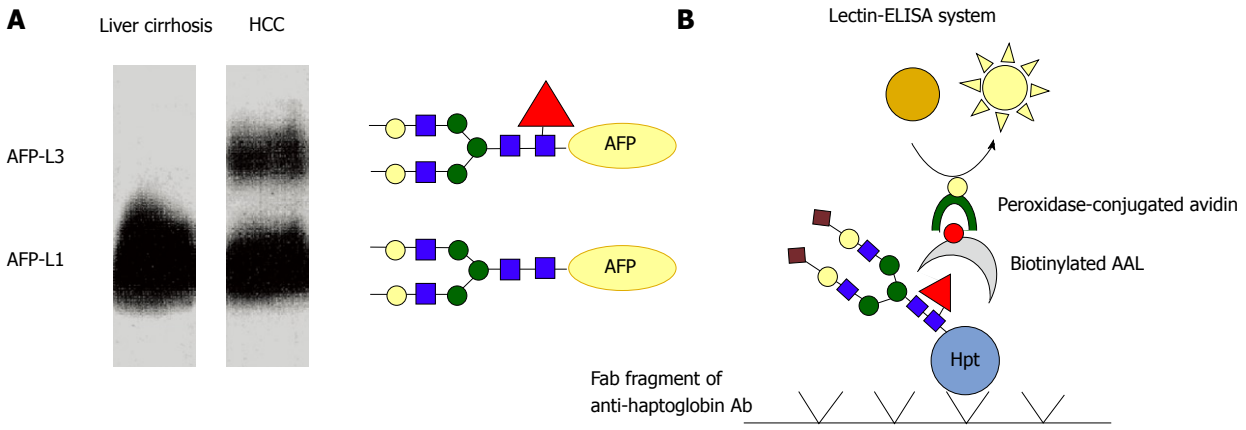

Figure 2 Measurement of fucosylation-related tumor markers in gastrointestinal cancer. A: The sera of patients with liver diseases were electrophoresed on an LCA agarose gel, followed by reaction with anti-AFP antibody. Since LCA specifically binds to fucosylated oligosaccharides on AFP, fucosylated AFP runs slowly on an LCA agarose gel; B: Since IgG has a fucosylated oligosaccharide in its Fc portion, a Fab fragment of anti-human haptoglobin IgG was coated on the bottom of a 96-well ELISA plate. After the sera of patients had been loaded into individual wells, the reaction with biotinylated AAL was performed to detect specifically fucosylated haptoglobin. Peroxidase-conjugated avidin and 3,3',5,5' tetramethylbenzisine were used for development.

pathway. The salvage pathway synthesizes GDP-fucose from free L-fucose, derived from extracellular or lysosomal sources *via* two steps: catalyzation by L-fucokinase[40] and then GDP-fucose pyrophosphorylase[41]. The *de novo* pathway transforms GDP-mannose into GDP-fucose *via* three steps: catalyzation by GDP-mannose-4,6-dehydratase (GMDS)[42,43] and GDP-4-keto-6-deoxymannose-3, 5-epimerase-4-reductase (FX)[44]. The salvage pathway is responsible for only about 10% of the cellular pool of GDP-fucose. Thus, cellular GDP-fucose is mainly produced by the *de novo* pathway. A defect of this pathway leads to a virtually complete deficiency of cellular global fucosylation, including α1-2, 1-3/4, 1-6, and *O*-fucose[42,43,45]. After GDP-fucose has been synthesized in the cytosol, it is transported to the Golgi apparatus through GDP-fucose transporter to serve as a substrate for fucosyltransferases[46,47].

APPLICATION OF FUCOSYLATED GLYCANS AS TUMOR MARKERS

AFP is a glycoprotein produced in the mammalian embryonic liver and is a major serum protein in the developing fetus. While the expression of AFP is absent in the normal adult, its reappearance is observed in patients with HCC. Therefore, AFP has been clinically used as a tumor marker for HCC[48,49]. However, determination of the AFP level is of limited value for the diagnosis of HCC since AFP is often elevated in chronic liver diseases, such as chronic hepatitis (CH) and liver cirrhosis (LC). It is difficult to make a differential diagnosis of HCC from benign liver diseases based on low or moderate elevation of AFP. Under these circumstances, the fucosylated AFP (AFP-L3 fraction) is more effective for the specific diagnosis of HCC because it increases in patients with HCC, but not in ones with CH and LC[11,12] (Figure 2A). LCA (*Lensculinaris agglutinin*) lectin-electrophoresis has been used for the measurement of AFP-L3[50]. Recently, the fully automated and high-performance micro-total analysis system (μTAS) developed by Wako Pure Chemical Industries has increased the analytical sensitivity for AFP-L3 and shortened the measurement time from the 1h required for the conventional assay to less than 10 min[51]. The molecular mechanism underlying the production of fucosylated AFP in HCC is complicated. Fucosylation at an *N*-glycan of AFP is mediated by FUT8, which has been purified and cloned by our group[27,28]. The expression of FUT8 is quite low in the normal liver and increases in HCC[52,53]. The up-regulation of FUT8 expression is required for the production of fucosylated AFP, but such enhancement is insufficient to explain the specific production of fucosylated AFP in HCC due to the broad increased expression of FUT8 in benign liver diseases[54]. We have shown that GDP-fucose is a more important regulatory factor for fucosylation in HCC. The level of GDP-fucose, and the expression of FX and GDP-fucose transporter are significantly increased in HCC tissue compared with that in adjacent chronic inflamed tissue or normal liver tissue[55-57]. As a result of cell experiments, the most important factor for the increase in fucosylation in HCC is thought to be the transport of GDP-fucose. However, a problem is that the level of GDP-fucose is increased only by two or three-fold, which does not explain the fact that the level of serum AFP-L3 is increased in HCC to dozens of times its normal level. Recently, we proposed an additional mechanism by which AFP-L3 increases in sera of patients with HCC[58]. Fucosylated glycoproteins, such as α1-acid glycoprotein and α1-antitrypsin, produced in hepatocytes are secreted into the bile. FUT8 knockout mice show decreased levels of these proteins in their bile, suggesting that fucosylation regulates the secretion of certain types of hepatic fucosylated glycoproteins, including AFP, into the bile. The disruption of this sorting system could be an additional mechanism und-

Table 1 Positive ratio of fucosylated haptoglobin in sera of patients with various diseases[63]

	n	Negative	Positive	%
Normal	30	29	1	3
[a]Pancreatic cancer	87	30	57	66
[a,c]HCC	23	18	5	22
[a,c]Liver cirrhosis	12	9	3	25
[c]Gastric cancer	10	8	2	20
[a]Colon cancer	100	59	41	41
[a,c]Chronic pancreatitis	9	7	2	22

Statistic analysis was performed according to the program for StatView software. [a]$P < 0.05$ *vs* normal; [c]$P < 0.05$ *vs* pancreatic cancer (χ^2 test).

erlying the increase in AFP-L3 in sera of patients with HCC.

Recently, large-scale analytical methods have been developed for the human serum glycoproteome which are also powerful tools for the discovery of diagnostic and therapeutic targets. Glycoprotein (GP) 73 was found to be a novel tumor marker for HCC through lectin-based glycoproteomic analysis[59]. The serum GP73 level was significantly increased in patients with HCC, even in HCC patients who had serum AFP levels less than 20 ng/mL[60]. It has also been reported that the fucosylation of GP73 was increased in patients with HCC[59]. Moreover, other fucosylated glycoproteins, kininogen and α1-antitrypsin, were identified as candidate hepatic tumor markers[61]. The best performance was obtained with the combination of fucosylated kininogen, AFP and GP73, the optimal sensitivity being 95% and the specificity 70%.

Pancreatic cancer is currently one of the leading causes of cancer-related deaths and the overall 5-year survival has been reported to be less than 5%[62]. CA19-9, which is a monoclonal antibody against the sLe^a structure, has been used as a tumor marker for pancreatic cancer[10]. However, false positives are a problem and an early diagnosis based on the CA19-9 level is quite difficult. Under these circumstances, we reported on the potential use of fucosylated haptoglobin as a novel tumor marker for pancreatic cancer[63]. The positive rate for fucosylated haptoglobin is 60%-70% (Table 1) and the rate increases progressively with the stage of the disease. For clinical applications, we established and validated the original lectin-ELISA system (Figure 2B). After our report, several groups reported that fucosylated haptoglobin was increased in sera of patients with lung, prostate, and liver cancer[64-66]. Thus, our established lectin-ELISA system is available for detecting fucosylated haptoglobin in several types of tumors. Haptoglobin is a glycoprotein produced in the liver. Thus, increases in fucosylated haptoglobin in sera of patients with pancreatic cancer are thought to be caused by a soluble factor secreted from pancreatic cancer tissue. Recently, we found that interleukin-6 (IL-6) secreted from pancreatic cancer cells induced the production of fucosylated haptoglobin in the liver[67]. IL-6 could be one of the factors that induce the production of fucosylated haptoglobin in sera of patients with pancreatic cancer.

BIOLOGICAL ROLE OF THE INTERACTION BETWEEN LEWIS ANTIGEN AND SELECTIN IN TUMOR METASTASIS

Inflammation and cancer metastasis are associated with extravasation of leukocytes or cancer cells from blood vessels into tissues. The interaction between cancer cells and vascular endothelial cells is mediated by a coordinated and sequential molecular cascade initiated, in part, by selectins, carbohydrate-binding proteins[68-71]. The initial adhesion mediated by these molecules triggers activation of integrin molecules through the action of several cytokines, leading to the extravasation of cancer cells. In addition, leukocyte-endothelial interactions *via* selectins are associated with tumor angiogenesis and progression[72]. Carbohydrate ligands for selectins, such as sLe^x[73-75] and sLe^a[76,77], are expressed on cancer cells. sLe^x and sLe^a have been used as tumor markers for certain types of cancer. Increases in sLe^x and sLe^a in cancer tissues are correlated with a poor prognosis in several types of cancers, including colon, bladder, and breast cancers[78-80]. Two principal mechanisms underlying the accelerated expression of sLe^x and sLe^a in cancers are known: "neosynthesis" and "incomplete synthesis"[81]. During "neosynthesis", cancer-associated induction of some glycosyltransferases, including fucosyltransferases, has been assumed to influence expression of the determinants. Certain types of fucosyltransferases are up-regulated in cancer tissues, and are responsible for the final step in the synthesis of sLe^a and sLe^x[82,83]. On the other hand, recent results have indicated that normal epithelial cells of several organs contain sufficient amounts of enzymes required for the synthesis of sLe^a and sLe^x. The difference between normal epithelial cells and cancer cells is that normal epithelial cells have additional enzymes to further modify these determinants into more complicated entities, such as disialyl Le^a[84,85] and sialyl 6-sulfo Le^x[86]. The impaired expression of glycosyltransferases, which are involved in the synthesis of complex carbohydrate determinants in normal epithelial cells, leads to the accumulation of less-complex cancer-associated carbohydrates in cancer cells (incomplete synthesis)[87-89].

RELATIONSHIP BETWEEN LEWIS ANTIGEN AND INFECTION BY *HELICOBACTER PYLORI*

Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium that colonizes the human gastric mucosa, and infects over 50% of the world's population[90]. The infection outcome is diverse, and includes the development and recurrence of gastritis, gastric and duodenal ulcers, and an increased risk of gastric adenocarcinomas and

mucosa-associated lymphoid tissue (MALT) lymphomas[91-93]. The lipopolysaccharides (LPSs) of *H. pylori* contain fucosylated oligosaccharides, predominantly type Ⅱ blood group antigens, such as Le^x and Le^y, in addition to minor amounts of type Ⅰ antigens, such as Le^a and Le^b[94,95]. Lewis blood group antigens are also present in the normal human gastric mucosa. The molecular mimicry of host cell surface antigens has been suggested to mask the pathogen from host immune surveillance, and thus plays an important role in colonization and long term infection in the stomach[96]. These Lewis antigens are synthesized by *H. pylori* fucosyltransferases using GDP-fucose as a donor substrate. A recent report suggested that L-fucose released from the surface of host cells by secreted human α-L-fucosidase is used as a source for the production of Le^x in *H. pylori*[97]. Successful *H. pylori* infection is dependent on tight adherence to the mucous epithelial cells and the mucus layer lining the gastric epithelium. Two oligosaccharide structures, Le^b and $sLe^{x/a}$, on the surface of mucous cells serve as specific ligands for blood group antigen-binding adhesin (BabA) and sialic acid-binding adhesin (SabA) respectively, expressed on the surface of *H. pylori*[98,99]. *H. pylori* adhesins, such as BabA, may have evolved an ability to distinguish between host and bacterial ligands based on the differences in their core sugar structures in order to avoid bacterial autoaggregation[100]. These findings show that certain oligosaccharide structures expressed on *H. pylori* and gastric epithelial cells are closely associated with the pathogenesis and prevention of *H. pylori*-related disease, suggesting their therapeutic potential through modification of the determinants.

MODIFICATION OF GROWTH FACTOR RECEPTORS AND ADHESION MOLECULES THROUGH CORE-FUCOSYLATION

Most receptors on the cell surface, including EGF receptor (EGFR), transforming growth factor β receptor (TGFβR), E-cadherin, and integrins, are core-fucosylated. Core-fucosylated oligosaccharides affect protein folding and structure, and as a result, regulate many physiological and pathological events, including cell growth, migration, embryogenesis, and tumor invasion. The importance of core-fucosylation for the functions of several membrane-associated proteins has been demonstrated through glycomic analyses of Fut8-deficient mice. TGF-β is a pleiotropic cytokine that is especially important for cancer biology and the immune system[101,102]. Fut8-deficient mice show marked dysregulation of TGFβR activation and signaling due to impaired binding between a receptor and a ligand[103]. Since TGF-β signaling also controls extracellular matrix homeostasis[104], Fut8-deficient mice show an emphysema-like phenotype in the lungs. Further studies by our group revealed that core-fucosylation was required for the binding of the EGF to EGFR, which contains 12 potential *N*-glycosylation sites[5,105]. The growth retardation observed in Fut8-deficient mice might be caused partly by impaired EGF signaling. Both integrins and E-cadherin are associated with the characteristics of cancer cells through regulation of the cell-extracellular matrix interaction and homotypic cell-cell adhesion, respectively[106,107]. Recent reports showed that a loss or decrease in core-fucosylation on *N*-glycans in integrins and E-cadherin resulted in defects in their functions[6,108]. Thus, core-fucosylation would be closely involved in the biological behavior of cancer cells through regulation of the functions of many membrane-associated proteins.

BIOLOGICAL ROLE OF FUCOSYLATED GLYCANS IN TUMOR IMMUNE SURVEILLANCE *VIA* TRAIL SIGNALING

While many studies have revealed that fucosylation is closely associated with cancer biology through modulation of signal transduction and the cell-cell adhesion pathway, we recently provided new evidence that fucosylation affects tumor immune surveillance *via* another signaling pathway: TRAIL signaling[109,110].

When we examined the global fucosylation level in several colon cancer cells using *Aleuria aurantia* (AAL) lectin, which recognizes fucosylated oligosaccharides, little binding to AAL lectin was found in HCT116 cells (Figure 3A). Further analysis revealed that HCT116 cells had a deleted GMDS transcript which eliminated their ability to synthesize GDP-fucose, and resulted in a virtually complete deficiency of fucosylation. Tranfection of the wild-type GMDS gene into HCT116 cells restored the cellular fucosylation. GMDS-rescued cells showed dramatically suppressed tumor formation and metastasis compared with mock cells when they were inoculated into athymic nude mice (Figure 3B). Depletion of natural killer (NK) cells stimulated tumor growth of the GMDS-rescued cells, but not that of the mock cells, indicating that a deficiency of fucosylation leads to escape from NK cell-mediated tumor immune surveillance (Figure 3C). Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is expressed mainly on the surface of immune cells, where it functions in T-cell homeostasis and NK cell-mediated killing of virally infected or oncogenically transformed cells[111-114]. The engagement of TRAIL receptors by the ligand leads to apoptosis through a specific signaling cascade[115]. Subsequent studies revealed that the GMDS-rescued cells were significantly more susceptible to TRAIL-induced apoptosis (Figure 3D), which caused the increased sensitivity of the GMDS-rescued cells to NK cells. Aberrant transcripts of the GMDS gene were found in three other cancer cell lines (two human colon cancers and one gastric choriocarcinoma) as well as several colon and ovarian cancer tissues. Thus, loss of GMD might be a common mechanism for cancer cells to evade TRAIL-

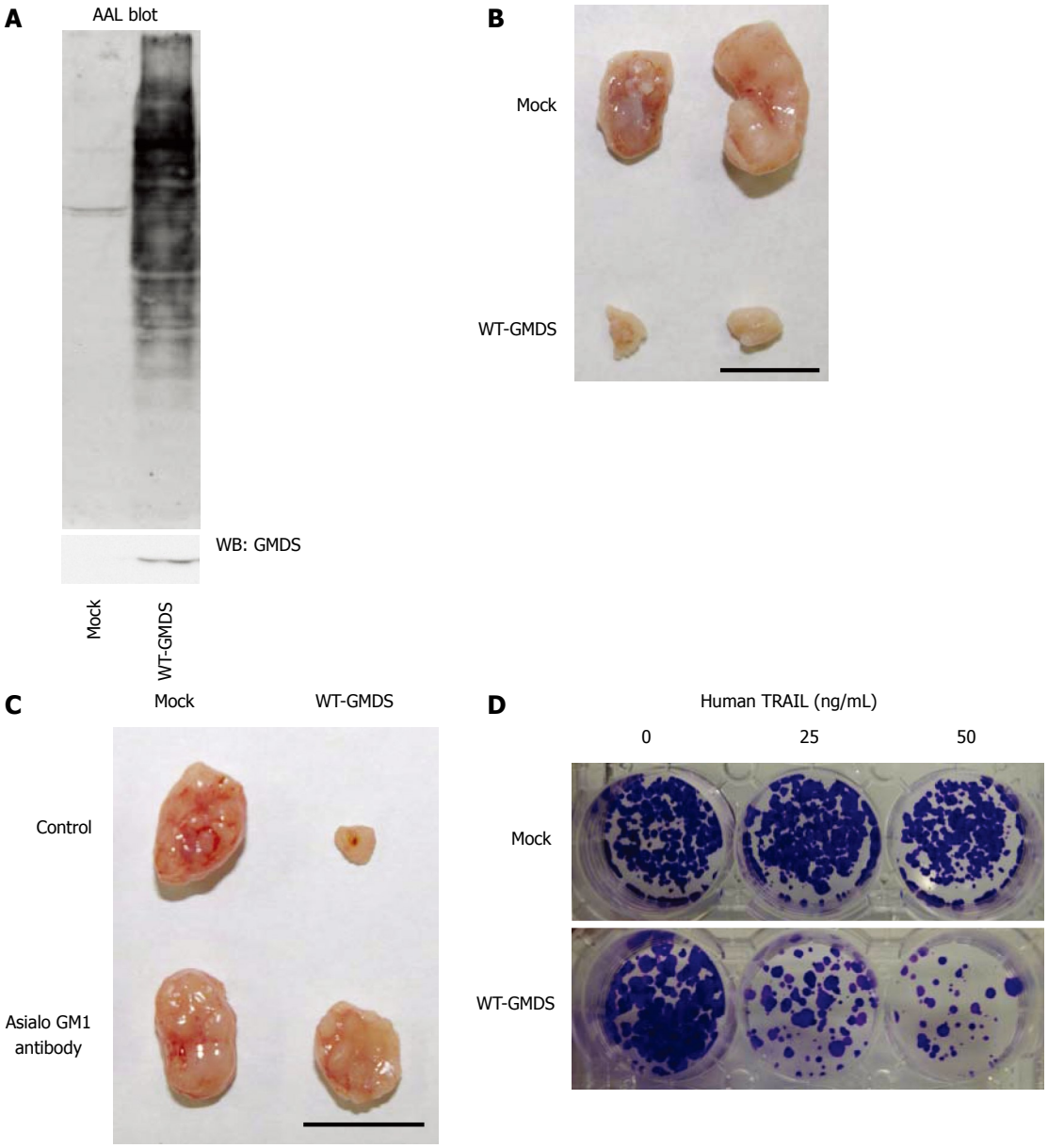

Figure 3 Deficiency of GMDS leads to escape from NK cell-mediated tumor surveillance through modulation of TRAIL signaling[109]. A: After trasnfection of the wild-type GMDS gene into HCT116 cells, Western blot analysis of GMDS and AAL blot analysis were performed. The binding to AAL was restored in transfected cells (WT-GMDS); B: Tumor growth of the GMDS-rescued cells on the backs of athymic nude mice was significantly suppressed compared to mock cells. The bar indicates 10 mm; C: When athymic nude mice were treated with anti-asialo GM1 antibody to deplete NK cells, the tumor growth of the GMDS-rescued cells was accelerated, but not in the case of mock cells. D: The higher susceptibility of the GMDS-rescued cells to TRAIL was confirmed by clonogenic survival assays. These figures are modified from the data in reference 109.

mediated killing. While the increase in fucosylation is important at an early stage of carcinogenesis, defucosylation through genetic mutation in certain types of advanced cancer would lead to escape from NK-cell mediated tumor surveillance and the acquisition of more malignant characteristics (Figure 4).

Currently, because of their ability to kill cancer cells, optimized soluble recombinant human TRAIL or agonistic antibodies targeting TRAIL receptors are undergoing phase 1 or 2 clinical evaluation as promising pro-apoptotic antitumor therapeutic agents in patients with several types of tumors[116]. However, it has now become clear that many types of tumor cells are resistant to TRAIL[117-119]. Thus, studies are now underway to identify and characterize potential biomarkers of sensitivity to TRAIL. Our findings demonstrated that examination of the fucosylation levels in tumor tissues might be promising for predicting the efficiencies of TRAIL-targeted therapies. Furthermore, the combination of TRAIL-targeting medicine with a therapy, which could up-regulate fucosylation level, might have a synergistic therapeutic effect.

CONCLUSION

Fucosylation has been thought to play important roles

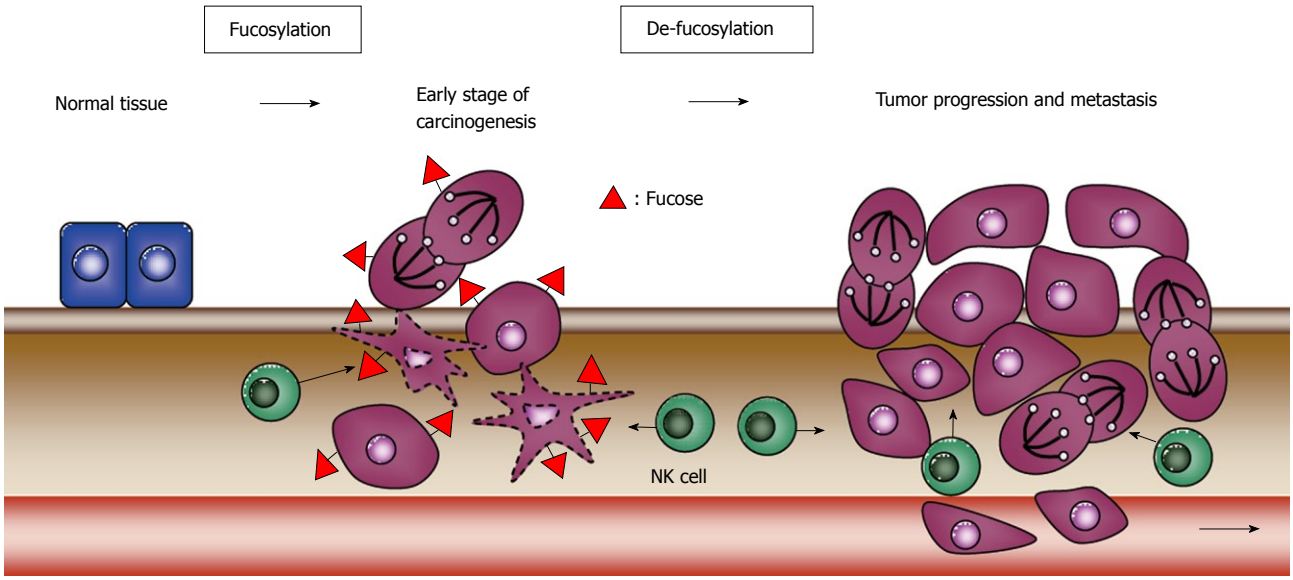

Figure 4 Schematic model of the biological function of fucosylation and de-fucosylation in modulating immune surveillance during colon carcinogenesis[109]. The level of fucosylation is not high in normal colon tissues, but is increased at an early stage in colon cancer. The cancer cells represented by the dotted line are apoptotic ones, which are attacked by NK cells. In certain types of advanced cancer, de-fucosylation through genetic mutation leads to escape from NK cell-mediated tumor surveillance and the acquisition of more malignant characteristics. This figure is modified from the data in reference 109.

in a wide variety of events in cancer biology, but only AFP-L3 and CA19-9 have been used for the diagnosis of cancer. In the case of cancer therapy, fucosylation has never been clinically applied so far. Our recent study indicates that modulation of fucosylation might be a promising target for cancer immune therapy. Recently identified fuocsylation-related tumor markers need to be validated using hundreds of clinical specimens. In addition, tumor markers are not only monitors for diagnosis or therapy, but also represent the biological characters of cancer cells. Thus, the mechanisms underlying the production of any tumor markers should be revealed. While we have investigated the biological significance of fucosylation in carcinogenesis and cancer progression, as described in this review, further analyses are required for its application to clinical tumor therapy. What molecules are the targets of fucosylation? Which linkages, α1-2, α1-3/4, α1-6, and/or *O*-fucose, are important? When is fucosylation up- or down-regulated during carcinogenesis and cancer progression? We would like to pose these questions to anyone studying cancer fucosylation. We believe that fucosylation is not just a tumor marker, but is also a possible factor determining the characteristics of cancer cells.

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