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TOPIC HIGHLIGHT

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Clinicopathological utility of sialoglycoconjugates in diagnosing and treating colorectal cancer

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Abstract

Aberrant expression of glycoconjugates occurs during malignant transformation of cancer cells. Overexpression of sialoglycoconjugates in particular may play an important role in the progression, *i.e.*, invasion or metastasis, of cancer. Various types of sialoglycoconjugates have been investigated to clarify their biological significance and clinical utility in diagnosing and treating colorectal cancer. This review focuses specifically on expression of mucin (MUC) 1 and it suggests that MUC1 with the specific structure of a sialo-oligosaccharide has biological significance in determining the metastatic potential of colorectal cancer cells and clinicopathological utility in evaluating the effectiveness of treatments and the prognosis for patients with colorectal cancer. Further studies are expected to contribute to the expanded use of cancer-associated sialoglycoconjugates in cancer diagnosis and therapy.

Key words: Sialoglycoconjugates; Sialic acid; Mucin 1; Colorectal cancer; Invasion; Metastasis

Core tip: Many types of cancer-associated sialoglycoconjugates are produced during oncogenesis or in various stages of malignant transformation. Aberrant expression of sialoglycoconjugates has been evaluated in many histochemical and molecular biological studies. An overview of the current knowledge is crucial to understand its clinicopathological utility in diagnosing and treating colorectal cancer. The biological significance of sialoglycoconjugates in the progression of cancer is also discussed. This review may contribute to expanding the use of cancer-associated sialoglycoconjugates in cancer diagnosis and therapy.

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INTRODUCTION

Expression of various substances changes drastically during oncogenesis and the subsequent stages of cancer progression. The expression profile of components on the cell membrane in particular has a significant role in the proliferation and migration of cancer cells. Detecting cancer-associated molecules is an effective way to predict the prognosis for cancer patients.

Sialoglycoconjugates with a molecular structure containing sialo-oligosaccharides are expressed in many types of cells, where they participate in various biological events, *e.g.*, cell adhesion and recognition[1]. The overexpression of sialoglycoconjugates, however, has been

detected in cancer cells or tissues and may correlate with cancer behavior[2-4]. Many histochemical studies using colorectal cancer tissues have shown that elevated expression of sialoglycoconjugates was related to a worse prognosis for patients. Furthermore, molecular biological studies have revealed that those overexpressed sialoglycoconjugates had specific structures of sialo-oligosaccharides. The present article reviews the clinicopathological utility of sialoglycoconjugates in diagnosing and treating colorectal cancer and its metastatic foci, and discusses the biological significance of sialoglycoconjugates in the progression of cancer.

MOLECULAR CHARACTERISTICS AND BIOLOGICAL SIGNIFICANCE OF SIALOGLYCOCONJUGATES IN COLORECTAL CANCER

Sialo-oligosaccharides as a whole

There are three types of linkages between sialic acid and terminal galactose (Gal) or *N*-acetylgalactosamine (GalNAc) residues, but expression of glycoconjugates with α2,3- or α2,6-sialylated oligosaccharides in particular has often been investigated in relation to colorectal cancer. The sialic acid-binding lectins *Maackia amurensis* leukoagglutinin (MAL) and *Sambucus nigra* agglutinin (SNA) were used to respectively detect the expression of α2,3- and α2,6-sialoglycoconjugates[5,6]. Overexpression of sialoglycoconjugates recognized by those lectins was frequently detected in colorectal cancer tissue compared to surrounding non-cancerous tissue[7-9]. Various sialyltransferases contribute to creation of cancer-associated sialo-oligosaccharides, and some types of sialyltransferases such as β-galactoside α2,6-sialyltransferase (ST6Gal I) and α2,3-sialyltransferase (ST3Gal I) enhance their activity in colorectal cancer tissues[10-13]. Results of those studies suggested that overexpression of sialoglycoconjugates *via* activation of sialyltransferases occurs during the malignant transformation of cancer. Overexpression of sialoglycoconjugates has two patterns: (1) upregulating modification of sialo-oligosaccharides to glycoconjugates; and (2) upregulating expression of sialoglycoconjugates themselves. Alteration of the sialic acid moieties of glycoconjugates induces biological behavior of cancer cells, such as activation of motility and resistance to cell death and drugs (Figure 1). Several reports have shown that upregulation of α2,6 sialylation, and especially the sialylation of β1 integrins, is associated with the adhesion, migration, and invasion of colorectal cancer cells[14-16]. Swindall *et al*[17] revealed that the death receptor Fas is a substrate of ST6Gal I and that α2,6 sialylation of Fas confers protection against Fas-mediated apoptosis. ST6Gal I also catalyzed the sialylation of epidermal growth factor receptor (EGFR) and the loss of this sialylation by ST6Gal I knockdown increased the anticancer effect of the EGFR kinase inhibitor gefitinib[18]. In light of these findings, activation of sialyltransferases in colorectal cancer cells may change the function of various glycoconjugates and trigger events in cancer progression. Many previous studies also investigated altered expression of sialoglycoconjugates themselves. These sialoglycoconjugates have been designated cancer-associated molecules. Major cancer-associated sialo-oligosaccharides and sialoglycoconjugates that have been studied in relation to colorectal cancer are described later.

Cancer-associated sialyl-Lewis and sialyl-Tn antigens

Specific types of sialo-oligosaccharides and sialoglycoconjugates have garnered the attention of efforts to understand the biological and clinical significance of colorectal cancer behavior. Sialyl-Lewis-related antigens such as sialyl-Lewis x (sialyl-Le^x) and sialyl-Lewis a (sialyl-Le^a) antigens are the sialo-oligosaccharide complexes most often investigated in relation to colorectal cancer. The sialyl-Lewis structure consists of an *N*-acetylglucosamine (GlcNAc)-Gal backbone with an α2,3-linked sialic acid bound to Gal and fucose bound to GlcNAc. Elevated levels of sialyl-Lewis-related antigens are induced by down-regulation of ST6GalNAc VI, which transfers α2,6-linked sialic acid to GlcNAc to synthesize a disialyl Lewis structure[19,20]. This disialyl-Lewis structure-containing oligo-saccharide is expressed in normal tissue, so down-regulation of ST6GalNAc VI followed by formation of a sialyl-Lewis structure may be an important event during the malignant transformation of colorectal cancer. Furthermore, enhanced fucosyltransferase activity also leads to the stimulation of a cancer-associated sialyl-Lewis structure[21,22]. However, several studies have noted that expression of fucosyltransferases was not significantly enhanced in colorectal cancer tissues compared to adjacent normal tissue[23,24]. Although findings for colorectal cancer tissues are not consistent, the systematic regulation of glycosyltransferases plays an important role in expression of sialyl-Lewis-related antigens.

Another cancer-associated sialo-oligosaccharide antigen is sialyl-Tn antigen. This antigen is slightly expressed in normal epithelial tissue and therefore is highly specific as a cancer-associated molecule. The structure of sialyl-Tn consists of a terminal sialic acid α2,6-linked to GalNAc that is bound to the serine or threonine residue of a protein. Studies have suggested that the major regulator of sialyl-Tn antigen expression is ST6GalNAc I [25,26]. However, Vázquez-Martín *et al*[27] found that there was no correlation between ST6GalNAc I activity and the histological level of expression of sialyl-Tn antigen in colorectal cancer tissues. In addition, another sialyltransferase, ST6GalNAc Ⅱ, synthesizes sialyl-Tn antigen *in vitro* and may be related to expression of sialyl-Tn antigen, along with ST6GalNAc I, in colorectal cancer[28]. A systematic mechanism is thought to induce the overexpression of sialyl-Tn antigen in colorectal cancer tissue.

Sialo-oligosaccharides play a significant biological role in cancer progression, and especially in cancer invasion and metastasis (Figure 1). Sialyl-Le^x and sialyl-Le^a antigens function as a ligand of selectins. Sialyl-Le^x

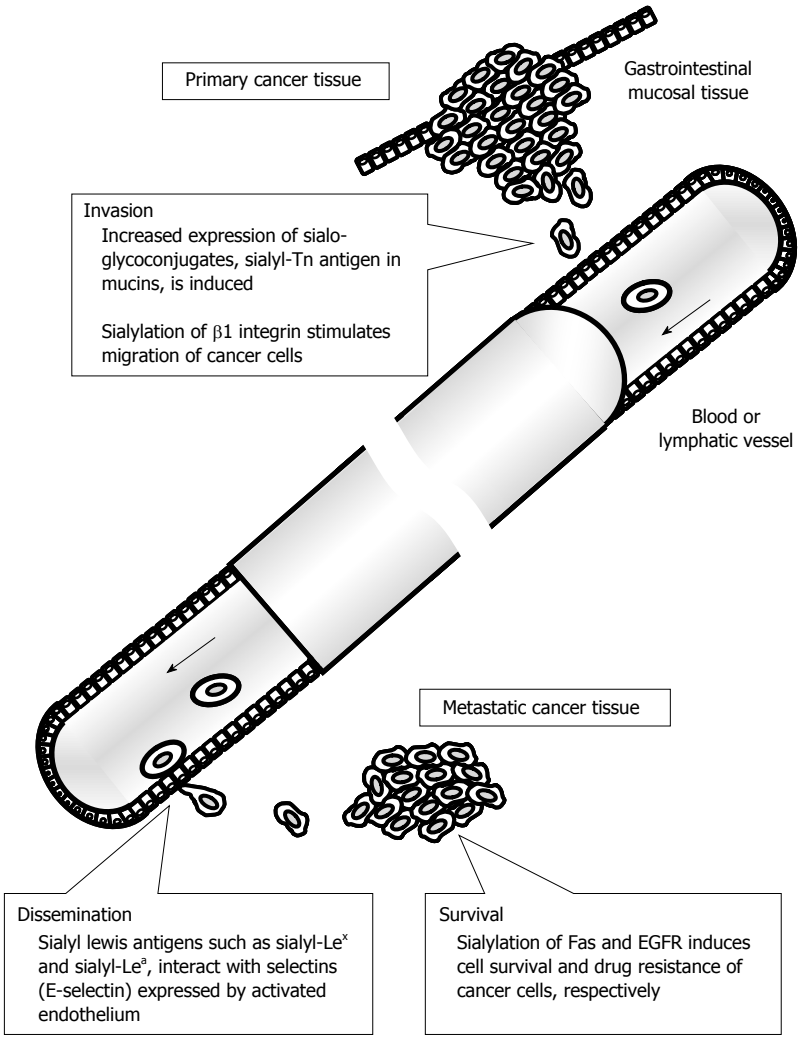

Figure 1 Relationship between altered expression of sialoglycoconjugates and various steps of metastasis. EGFR: Epidermal growth factor receptor.

antigen expressed on leukocytes interacts with selectins expressed on activated vascular endothelium, inducing the rolling of leukocytes and contributing to recruitment of leukocytes to inflammatory lesions[29]. The interaction of sialyl-Le^x and sialyl-Le^a antigens with E-selectin also contributes to the adhesion of cancer cells to the vascular endothelium[30,31]. Cancer cell lines expressing sialyl-Le^x and/or sialyl-Le^a antigens adhered to human umbilical vein endothelial cells, and this interaction was inhibited by use of anti-E-selectin antibody or benzyl *N*-acetyl-α-D-galactosaminide[31]. In addition, this effect depended on the expressed level of sialyl-Le^x antigen in colorectal cancer cells. Sialylation of glycoprotein CD44 and mucin may be altered in case of overexpression of sialyl-Tn antigen. CD44 is a transmembrane protein related to cell adhesion, and its splice variant (CD44v) carrying sialyl-Tn antigen was upregulated in colorectal cancer cells and was related to enhanced metastatic potential[32]. Sialo-mucins, and especially MUC1, also carry sialyl-Tn antigen in their extracellular highly glycosylated domains, and overexpression of sialyl-Tn antigen is related to worse tumor behavior, as described later. In other molecules, integrin β1, MUC1, and osteopontin may be sialyl-Tn antigen carriers and contribute to the stimulation of cell migration, but their biological significance in colorectal cancer is still a subject of debate[4]. Although additional evidence should be accumulated from biochemical and molecular biological studies, the upregulated modification of sialyl-Tn antigens may disable the primary function of those proteins and induce an invasive phenotype in colorectal cancer cells. Histochemical analysis indicated that tissues from colorectal metastases had a significant increase in sialyl-Tn and sialyl-Le^x expression compared to primary tumor tissues[33]. Alteration of the level of expression of glycoconjugates with those sialo-oligosaccharides occurs during the process of metastasis and is perpetuated in cancer cells in metastatic foci. This biological phenomenon can be utilized to develop sensitive methods for detecting metastatic tissues.

Carcinoembryonic antigen

Carcinoembryonic antigen (CEA) was first identified by Gold and Freedman and its expression was detected in colon cancer and other cancers of digestive organs as well as fetal digestive system tissues[34,35]. A subsequent study indicated that CEA was expressed in normal body

Table 1 Antibodies against mucin 1 recognizing various epitopes

Antibody	Epitope	Antigen
DF3	Core peptide sequence (DTRPAPGS) in the extracellular tandem repeat	Poorly glycosylated MUC1
NCL-MUC-1-CORE	Core peptide sequence (GVTSAPDTRPAP) in the extracellular tandem repeat	Poorly glycosylated MUC1
MY.1E12	O-linked Sialyl T1 antigen in the extracellular tandem repeat	Sialylated MUC1
NCL-MUC-1-GP	Carbohydrate in the extracellular tandem repeat	Sialylated MUC1
KL-6	Core peptide sequence (PDTRPAP) with *O*-linked Sialyl T[1] antigen in the extracellular tandem repeat 3'-sialylated, 6'-sulfated LNnT[2] and 3'-sialylated, 6-sulfated T antigen[3]	Sialylated MUC1
HMFG-1	Core peptide sequence (PDTR) in the extracellular tandem repeat	Highly-glycosylated MUC1

[1]Sialyl T: Neu5Acα2,3Galβ1,3GalNAc; [2]3'-Sialylated, 6'-sulfated LNnT: Neu5Acα2-3(SO_3^--6)Galβ1-4GlcNAcβ1-3Galβ1-4Glc; [3]3'-Sialylated, 6'-sulfated T: Neu5Acα2-3Galβ1-3(SO_3^--6)GalNAc. MUC1: Mucin 1.

fluids and mucosal tissues and had a variety of cross-reacting forms that induced variable expression patterns[36]. Sanders *et al*[37] showed that Le^x and sialyl-Le^x were coexpressed on CEA-related glycoproteins, thus suggesting that CEA is a transmembrane sialoglycoconjugate. CEA expressed on the cell surface was found to act as a homotypic intercellular adhesion molecule, and CEA may contribute to colon carcinogenesis by inhibiting differentiation of colonic epithelium[38]. Alteration of the expression and distribution of CEA may have an important role in the metastasis of colon cancer to the liver[39]. Colorectal cancer cells with elevated expression of CEA by transfection of cDNA had an enhanced potential for metastasis to the liver in nude mice[40]. In addition, circulating CEA, which is elevated in patients with various gastrointestinal cancers, was recognized by a receptor expressed on the liver cell surface[41]. This biological phenomenon may lead to the induction of a receptor for circulating cancer cells that express CEA-related glycoproteins, enhancing the metastatic potential of cancer cells.

Cancer-associated mucin

Mucins are expressed in gastrointestinal tissues, including the large intestine[42]. Mucins are categorized as transmembrane (MUC1, MUC3A, MUC3B, MUC4, MUC12, MUC13, MUC15, MUC16, and MUC17) or secreted (MUC2, MUC5AC, MUC5B, MUC6, MUC7, and MUC19). The level of each mucin's expression or secretion differs in different types of tissues and organs. Colorectal tissue mainly contains several types of secreted mucins (MUC2, MUC5AC) and transmembrane mucins (MUC1, MUC3, MUC4, and MUC12), and alteration of their expression may be related to the malignancy of colorectal cancer. MUC2 and MUC5AC are clustered at the same chromosomal locus (11p15.5), and their expression may be regulated by a common mechanism[43]. In colorectal cancer cells, however, repression of mucin transcription is controlled by the epigenetic mechanism of methylation[44,45]. MUC2 expression decreases in differentiated colorectal adenocarcinoma tissues but not in mucinous carcinoma tissues, whereas MUC5AC expression increases in differentiated colorectal adenocarcinoma but decreases in mucinous carcinoma tissues[46]. A study of *Muc2*-deficient mice showed that decreased expression of MUC2 induced tumor formation in the small intestine and the colon[47]. MUC5AC is not expressed in normal colonic epithelium whereas *de novo* expression was frequently detected in adenoma and carcinoma tissues of the colon[48,49]. As a transmembrane mucin, MUC1 has often been investigated to clarify its significance in the progression, *i.e.*, invasion or metastasis, of colorectal cancer. MUC1 has a variable number of tandem repeats of the 20 amino acids in its extracellular domain. This tandem repeat sequence contains a number of *O*-linked glycosylation sites, and the level of glycosylation of those tandem repeats is a characteristic of MUC1[50]. There are various antibodies that can recognize different types of MUC1 molecules (Table 1). Antibodies recognizing the core peptide sequence can detect poorly glycosylated MUC1 while antibodies recognizing glycosides on the tandem repeat domain can detect highly glycosylated MUC1[51-56]. Various forms of MUC1 with different glycoforms are expressed in colonic epithelium and tumor cells, and those glycoforms may change during disease progression. The present review has focused on alteration of sialo-oligosaccharide expression. There are several antibodies recognizing sialylated MUC1, such as monoclonal antibody MY.1E12 and KL-6. Monoclonal antibody MY.1E12 was established by immunizing mice with human milk fat globules and was found to recognize α2,3-sialylated *O*-linked oligosaccharides[55,57]. The latter monoclonal antibody, KL-6 antibody, also recognizes MUC1 and was obtained by Kohno *et al*[58,59] from a hybridoma established from the splenocytes of a BALB/c mouse immunized with a human pulmonary adenocarcinoma cell line, VMRC-LCR. The epitope structure of KL-6 antibody is still being studied. A chemical study by Ohyabu *et al*[60] showed that the minimal antigenic structure recognized by KL-6 antibody was a heptapeptide sequence (PDTRPAP) with the sialo-oligosaccharide Neu5Acα2,3Galβ1,3GalNAcα. A recent study by Seko *et al*[61] showed that the epitope of KL-6 antibody has a 3'-sialylated, 6'-sulfated lacto-*N*-neotetraose (LNnT) and 3'-sialylated, 6'-sulfated core 1 structure. A previous study by the current authors confirmed this relationship between expression of KL-6 mucin and metastatic potential through analysis using colorectal cancer cell lines[62]. A cytochemical assay detected KL-6 mucin in the surrounding membrane and cytoplasm of cell lines with a high metastatic potential but not in cell lines with

a low metastatic potential. Thus, this study indicated that expression of KL-6 mucin affected cancer cell morphology and metastatic potential. The clinicopathological significance of the expression of KL-6 mucin in the surrounding membrane and/or cytoplasm, which may be an important indicator of the liver metastasis of colorectal carcinoma, is discussed later.

CLINICAL UTILITY OF SIALOGLYCOCONJUGATES IN DIAGNOSING AND TREATING COLORECTAL CANCER

Cancer-associated molecules have been used to detect cancer and diagnose cancer behavior[63,64]. Molecules secreted by cancer cells into a patient's blood in particular are effective as serological markers to screen for cancer and predict patient outcomes[63,65]. Furthermore, the levels of those molecules in serum may be related to cancer behavior and patient prognosis. Clinicopathological analysis of levels of serological and histological markers has suggested that marker expression plays a functional role in cancer progression, such as cancer cell invasion and metastasis[66-71].

Sialoglycoconjugates as a whole

Lectin-immunohistochemical studies have revealed aberrant expression of sialoglycoconjugates in colorectal cancer tissue. Compared to α2,3-linked sialoglycoconjugates (recognized by MAL lectin), α2,6-linked sialoglycoconjugates (recognized by SNA lectin) are significantly related to a worse prognosis for patients with colorectal cancer[7,8]. In a previous study, the current authors detected overexpression of α2,3- and α2,6-linked sialoglycoconjugates in colorectal cancer tissues and found that this overexpression was associated with worse patient survival[9]. Elevated expression of α2,6-linked sialoglycoconjugates was detected in cancerous tissue with lymphatic vessel and venous invasion, lymph node metastasis, and a more advanced tumor stage. Metastatic lymph node tissues also exhibited overexpression of those sialoglycoconjugates. The histological significance of expression profiles of those sialoglycoconjugates is still a subject of debate. An elevated level of total sialic acid was also detected in serum from patients with colorectal cancer[72,73]. In a study of patients with distant metastasis of colorectal cancer, an elevated level of total sialic acid in plasma decreased significantly as a result of 5-fluorouracil administration, eventually dropping below normal levels[73]. Although the correlation between overexpression in cancerous tissue and elevated levels in serum is still not clear, sialoglycoconjugates may be used to screen for patients with metastasis and evaluate the effectiveness of treatments.

Sialoglycoconjugates with cancer-associated sialo-oligosaccharides

Because sialoglycoconjugates have various moieties of the oligosaccharide structure, specific molecules of sialoglycoconjugates have been used as diagnostic markers with a high level of sensitivity. Antibodies against various sialo-oligosaccharides, such as sialyl-Le^x, sialyl-Le^a, and sialyl-Tn antigens, have been used in histochemical and serological analyses of colorectal cancer. Several histochemical studies suggested that the overexpression of sialyl-Le^x or sialyl-Le^a antigen can be used to evaluate worse tumor behavior, such as cancer cell invasion and metastasis, as well as worse patient survival[74-77]. Histochemical expression of sialyl-Tn antigen was also analyzed and may be related to worse patient survival[78]. However, other studies have found no significant association between sialyl-Tn antigen expression and prognosis for patients with colorectal cancer[79]. Nakagoe *et al*[80] compared the clinicopathological significance of those three antigens and found that patients with overexpression of sialyl-Le^x antigen had a shorter disease-free survival time than those with low levels of expression of sialyl-Le^x antigen. In another study, the same authors found that overexpression of sialyl-Le^x antigen was significantly related to a worse overall survival rate[81]. Although studies have described varying clinicopathological significance, the histochemical expression of those antigens, especially sialyl-Le^x antigen, is considered an effective way to predict recurrence and worse patient survival. Numerous serological studies of sialo-oligosaccharide antigens have been conducted, and those studies have cited their clinical utility as markers of colorectal cancer. Elevated levels of serum sialyl-Le^x, sialyl-Le^a, and sialyl-Tn antigen may be useful markers for predicting the metastasis of colorectal cancer along with serum CEA levels[82]. Carbohydrate antigen (CA) 19-9 (identical to sialyl-Le^a) and CEA have frequently been studied to clarify their effectiveness as markers to determine the prognosis for patients with colorectal cancer. These antigens could possibly be used to predict the recurrence of colorectal cancer. Many studies have suggested that patients with elevated preoperative serum levels of CEA and/or CA19-9 frequently experience recurrence[83-86]. The combined evaluation of CEA and CA19-9 is recommended for better sensitivity[87,88]. If the preoperative levels of CEA and/or CA19-9 are elevated, a decrease in the postoperative levels of these antigens could be used to evaluate the effectiveness of surgery. Furthermore, measurement of these antigen levels in serum during chemotherapy in patients with colorectal liver metastases helps to evaluate the effectiveness of treatment[89-91]. Recurrent elevation of antigen levels is significantly related to recurrence or progression of disease. According to studies, monitoring serum levels of CEA and CA19-9 perioperatively or during treatment such as chemotherapy may be a method to detect recurrence or measure therapeutic efficacy[92].

Cancer-associated sialo-mucin, MUC1

The structure and level of expression of various sialoglycoconjugates change during cancer formation and progression. Several types of mucins have been studied

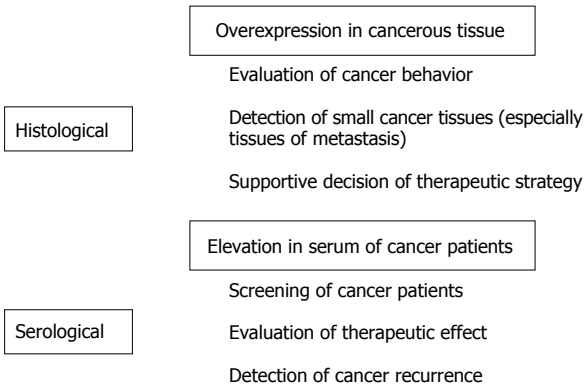

Figure 2 Clinical utility of sialoglycoconjugates as histological and serological markers in colorectal cancer.

exhaustively to understand their clinical utility. Decreased expression of MUC2, a secreted mucin, was frequently detected in colorectal adenocarcinoma tissues and significantly related to recurrence and worse survival[93,94]. MUC1, a transmembrane mucin, has often been investigated as a cancer-associated mucin antigen while a few studies have analyzed the pathological utility of other antigens. Shanmugam *et al*[95] immunohistochemically analyzed MUC4 in colorectal cancer tissue and found that a high level of MUC4 expression was significantly related to shorter survival for patients with colorectal cancer, especially for those with early stages of cancer. The present review has focused on expression of MUC1 in colorectal cancer and its clinicopathological significance. A number of studies have examined MUC1 expression in colorectal cancer tissue and analyzed its pathological significance and clinical utility[96-98]. Baldus *et al*[99] histochemically analyzed MUC1 (detected using antibodies recognizing the tandem repeat peptide), MUC2, sialyl-Le^x, and sialyl-Le^a antigens in colorectal cancer tissues. They found that strong immunoreactivity for MUC1 was correlated with an advanced tumor stage and the presence of distant metastasis and they posited that MUC1 may be an independent predictor of survival.

However, some reports have noted that aberrant expression of MUC1 is more prevalent in advanced stages of colorectal cancer tissue but is not significantly related to various clinicopathological features[100]. Studies have differing views on the clinicopathological significance of MUC1 expression overall in cancerous tissue. MUC1 has been localized in cancer cells and tissue. Stromal MUC1/MY.1E12 (detected using the monoclonal antibody MY.1E12) was frequently detected in advanced-stage cancer tissue and was significantly related to the presence of distant metastasis[101]. Expression of MUC1/KL-6 (detected using the monoclonal antibody KL-6) at the deepest site of invasion by colorectal cancer was significantly associated with the presence of lymphatic or venous invasion, lymph node and distal metastasis, and an advanced Duke's stage[102]. According to these studies, specific types of MUC1 expression could be used clinicopathologically to evaluate the behavior of colorectal cancer. Moreover, recent studies by the current authors and their colleagues have analyzed the clinicopathology of MUC1/KL-6 in colorectal cancer and liver metastases[103-105]. Localization of MUC1/KL-6 in the surrounding membrane and/or cytoplasm of colorectal cancer cells was significantly related to the presence of lymphatic vessel invasion, venous invasion, lymph node metastasis, and an advanced TNM stage as well as worse overall survival[103]. Although further studies should be conducted to determine its specificity, detection of subcellular localization of MUC1/KL-6 might help to evaluate cancer behavior and the prognosis for patients. In addition, analysis of colorectal metastasis to the liver indicated that the surrounding membrane and/or cytoplasm of cancer cells had immunoreactivity for MUC1/KL-6 while the surrounding non-cancerous liver tissue had no immunoreactivity for MUC1/KL-6[105]. This result suggested that MUC1/KL-6 is effective in sensitive detection of liver metastasis. Although further studies should be conducted with larger samples, MUC1/KL-6 may possibly be used to detect the foci of liver metastasis of colorectal cancer.

CONCLUSION

Many types of cancer-associated sialoglycoconjugates are produced during oncogenesis or in various stages of malignant transformation. Each of these sialoglycoconjugates has a characteristic role, such as cancer cell invasion or metastasis, that contributes to the progression of cancer. That said, these sialoglycoconjugates can also be used to evaluate cancer behavior, and clinicians have used several sialoglycoconjugates as markers to evaluate the effectiveness of treatments or detect the recurrence of cancer (Figure 2). Further verification of the utility of sialoglycoconjugates will encourage their continued use and highlight their clinical utility. Furthermore, use of sialoglycoconjugates in combination with unique imaging techniques such as molecular fluorescent imaging may lead to establishment of novel methods for diagnosing cancer with a high level of sensitivity. Use of cancer-associated sialoglycoconjugates is expected to expand in the future.

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