

Cancer-associated carbohydrate antigens for clinical diagnostic markers – its effectiveness and limitations

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Summary

Cancer cells express various aberrant glycoconjugates. Several kinds of carbohydrate antigens have been used for the serological tumor markers. In particular, the serological level of sialylated carbohydrate antigens, which contain the sialic acid residue in their structure, showed effectiveness in diagnosing cancer behavior. Although large number of carbohydrate antigens in serum of cancer patients was elevated broadly in various cancers, each tumor marker has different sensitivity and specificity for each cancer. Therefore, the combined use of several tumor markers which have different characteristics is effective for better sensitivity in diagnosing cancer behavior. The mechanism of synthesizing cancer-associated carbohydrate antigens is not fully understood because it is very complex. In addition, new cancer-associated carbohydrate antigens are also identified by molecular oncological studies. Those investigations are considered to develop more effective tumor markers to diagnose cancer behavior.

Keywords: Tumor marker, sialylated carbohydrate antigens, clinical diagnosis

Glycoconjugates are important factors for various biological events in an organism. Aberrance of glycoconjugates, e.g. the change of structure or expression level, is detected in diseased patients and suggested to associate with the progression of diseases. In cancer, various aberrant glycoconjugates are expressed in cancerous tissues and investigated in relation to cancer behavior such as invasion and metastasis. Several kinds of those overexpressed glycoconjugates are detected in the serum of cancer patients and used as clinical diagnostic markers. The serological tumor markers are considered to be effective tools for screening cancer patients in routine medical care and monitoring the state of cancer patients.

In clinical tumor markers, there are many kinds of cancer associated carbohydrate antigens (Table 1). Each tumor marker has different sensitivity and specificity for various cancers. A large number of those carbohydrate antigens in serum of cancer patients is elevated broadly

in several gastrointestinal and gynecological cancers. Carbohydrate antigen (CA) 15-3 has been used for the evaluation of metastasis and recurrence of breast cancer although its sensitivity is poor (1,2). CA125, whose epitope is on the tandem repeat peptide in MUC16, is suggested to be effective for longitudinal monitoring of ovarian cancer (3). Patients with cardiovascular disease are also suggested to show the elevation of CA125. In a study of patients with congestive heart failure, patients in a more advanced stage showed elevation of CA125 level (4). Therefore, CA125 shows a false positive if the patients suffered from those diseases. On the other hand, alpha-fetoprotein (AFP), which is frequently used as the diagnostic marker of hepatocellular carcinoma (HCC), also has carbohydrate structures. Elevation of AFP level also detects in benign liver diseases such as hepatitis and liver cirrhosis. The *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3), which receives the structural change of carbohydrate (addition of fucose residue), contributes to an increase in sensitivity in screening HCC patients (5,6). The peptide structure or glycoform of the epitope of these antigens have been investigated insufficiently.

Sialylated carbohydrate antigens, which contain sialic acid residues in their structure, frequently overexpress in cancer and are used for diagnosing cancer behavior.

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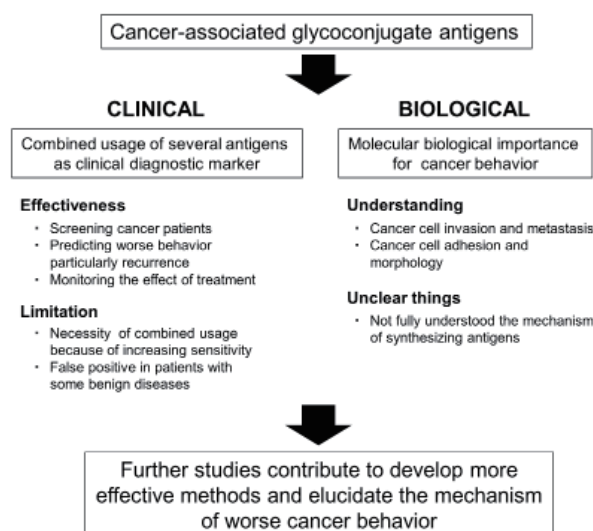
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Table 1. Carbohydrate antigens that are used for clinical tumor marker

Tumor markers	Cancers which show significant elevation	References
CA15-3	Breast cancer	(1,2)
CA125	Ovarian cancer, Uterus cancer	(3, 27-29)
CA72-4	Ovarian cancer, Uterus cancer, Gastric cancer	(17-19)
CA19-9	Colorectal cancer, Gastric cancer, Pancreatic cancer, Bile duct cancer	(12-14, 30)
sialyl Le ^x	Lung cancer, Gastric cancer, Bile duct cancer	(31-33)
sialyl Tn	Ovarian cancer, Uterus cancer, Gastric cancer	(16,32-34)
DUPAN-2	Pancreatic cancer, Bile duct cancer	(20-22)
SPan-1	Pancreatic cancer, Bile duct cancer	(35,36)

Many immunohistochemical studies showed the overexpression of sialylated carbohydrate antigens in cancer tissues by using lectins (7-10). Sialylation, the moiety of sialic acid, is considered to play an important role in tumor progression. Although various structures of sialylated carbohydrate are considered to be synthesized in cancer cells, specific types contribute to the clinical diagnosis for each kind of cancer. In the case of gastrointestinal cancers, sialyl Lewis-related antigens such as sialyl Lewis x (sialyl Le^x) and sialyl Lewis a (sialyl Le^a) antigens are the most often investigated tumor markers as sialylated carbohydrate antigens (11). Sialyl-Le^a antigen is also known as CA 19-9 and frequently used in clinical diagnosis combined with Carcinoembryonic antigen (CEA) (12-14). The combined evaluation of CEA and CA19-9 is recommended for better sensitivity in diagnosing the prognosis of gastrointestinal cancer patients. Another cancer-associated sialo-oligosaccharide antigen is sialyl Tn antigen. This antigen is barely expressed in normal epithelial tissue and is carried on cancer-associated proteins such as CD44 and mucins (15,16). Those antigens are considered to have an important biological role in cancer invasion and metastasis. Serological levels of CA72-4, related to sialyl Tn antigen, are elevated in patients with gastric cancer and ovarian cancer (17-19). DUPAN-2, which is identical with sialyl Le^c antigen, can be used for supportive diagnosis or monitoring behavior of pancreatic cancer (20-22). This antigen is also elevated in patients with hepato-biliary diseases but not with gastrointestinal cancers. Those sialylated carbohydrate antigens have been suggested to be related to induction of worse cancer behavior such as cancer cell invasion and metastasis while the detailed mechanism is still under investigation.

Mechanisms of overexpression of cancer-associated carbohydrate antigens are very complex. Up-regulation of glycosyltransferases was suggested to induce the aberrant structure of carbohydrate chains. There are many kinds of glycosyltransferases expressed in cancer cells, and therefore differences in up-regulated mechanisms caused by the different kinds of tumor markers for each cancer. In the case of sialic acid-containing carbohydrate antigens, down-regulation of ST6GalNAc VI, which transfers α 2,6-linked sialic acid to GlcNAc to synthesize a disialyl Lewis structure, is

**Figure 1. Current effectiveness and limitation of cancer-associated glycoconjugate antigens.**

suggested to induce the elevated levels of sialyl Lewis-related antigens (23,24). Biochemical and pathological studies performed by Marcos NT *et al.* suggested the main regulator of sialyl Tn antigen expression was ST6GalNAc-I activity (25,26). Investigating the change of expression and activity of glycosyltransferases is considered to contribute to the elucidation of cancer biology including the expression of tumor markers.

Serological tumor markers have been used for monitoring the effect of surgical treatment or chemotherapy for cancer. If the level of tumor marker is elevated before the patient received the cancer therapy, an altered level of tumor marker is suggested to mean a change of cancer behavior. However, as described above, multiple tumor markers should be evaluated simultaneously to increase the sensitivity of diagnosis. Carbohydrate antigens which have different structures and specificity were identified. Therefore, effective use of those current tumor markers can contribute to a powerful diagnostic method while other imaging techniques are necessary for definitive diagnosis (Figure 1). In addition, new cancer-associated glycoconjugates can also be investigated for specific detection of cancers. Further investigation is expected to develop more sensitive and specific tools to screen cancer patients at an early stage.

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