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Cancer Metastasis and Anti-cancer Vaccines

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Abstract

Complex carbohydrates, major constituents of cell membranes, perform important functions in cell-cell and cell-cell matrix interactions and signal transduction. They contain three types of biomolecules: glycoproteins, proteoglycans and glycosphingolipids. Recent studies have also shown that glycan alterations in malignant cells take different forms and mediate important pathophysiological events at different stages of tumor progression. Glycosylation alterations are a ubiquitous feature of malignant transformation and tumor progression in human cancers, occurring in whole cells or in some specific molecules. They are now his prominent candidates for cancer biomarkers. This review focuses primarily on the correlation between glycosylation and the metastatic potential of tumor cells and from a broader perspective to further address the critical role of glycan in tumor genesis. Moreover, using these glycosylation alterations to protect against tumor metastasis using anti-adhesion approaches or to develop anti-cancer vaccines is one of the promising goals of future research.

Keywords: Cancer, Glycan, Tumors, Vaccines.

1. Introduction

Complex carbohydrates, called glycan, form the most complex group of molecules in the body. Glycosylation generates a rich and diverse tightly regulated repertoire of cellular glycans, often attached to proteins and lipids. Glycans are involved in many important biological processes such as cell adhesion, molecular trafficking and clearance, receptor activation, signal transduction and endocytosis, all of great interest to scientists. Glycans exist in the form of glycoproteins, glycolipids, glycosaminoglycans, or other glycoconjugates and have long been known to play important functions in a variety of biological processes. They participate in molecular recognition activities such as cell migration and metastasis. Host-pathogen interactions such as bacterial and viral infections. In the cellular immune system, specific glycoforms are involved in the folding, quality control, and assembly of peptide-loaded major histocompatibility complex (MHC) antigen and T cell receptor complex. Other macronutrients, the main classification of his dietary carbohydrates proposed by the Expert Meeting on Carbohydrates in Humans (FAO 1998) convened in Rome in 1997, were determined by molecular size, degree of polymerization (DP), bond type (α or non-α), and individual monomer characteristics. The chemical approach classifies carbohydrates into three main groups: sugars (DP 1–2), oligosaccharides (short-chain carbohydrates) (DP 3–9), and polysaccharides (DP ≥10). Recent advances in life science have shown that glycans exist in free as well as conjugated states in glycoproteins, proteoglycans, and glycolipids. The weighted Q-gram method is also used to classify glycan structures.

2. Glycosylation Relevant in Carcinogenesis

Oncogenesis is the result of a variety of genetic or epigenetic alterations in malignant cells that result in sustained growth signals, apoptosis evasion, and anti-proliferation insensitivity signals, which are six functional hallmarks of cancer is a multi-step process involving , unlimited replication potential, angiogenesis, invasion and metastasis. Like normal cells, tumor cells are activated during embryogenesis to rapidly proliferate, adhere to a variety of other cell types and cell matrices, and invade tissues.

Embryonic development and vertebrate cell activation are typically accompanied by changes in the glycosylation profile of the cell. It is therefore not surprising that altered glycosylation is a universal feature of malignant transformation and tumor progression. In addition, recent studies have shown that multiple glacans and host elements on the tumor surface mediate key pathophysiological events at different stages of tumor progression.

Glycan alterations in malignant cells take many forms. Examples have been found for the absence or overexpression of specific structures, the persistence of incomplete or truncated structures, the accumulation of progenitor cells, and the infrequent emergence of new structures. In this section, regulates protein maturation via the secretory pathway, a complex biosynthetic process in cancer research structure and function. Branched N-glycans such as bisecting GlcNAc, β1, 6 GlcNAc and core fucose (α-1,6-fucose) are converted into N-acetylglucosaminyltransferase III (GnTIII), N-acetylglucosaminyltransferase V (GnT-V) and α-1,6-fucosyltransferase (α1,6-FucT). These branched structures are strongly associated with various biological functions of cell adhesion molecules, such as cell adhesion and cancer metastasis.

A case in point is the N-linked glycosylation of ecadherin involved in the regulation of cadherin-dependent tumor cell-tumor cell adhesion associated with tumor progression. Previously, structural modification of the N-glycan of E-cadherin by GnT-III was shown to cause increased cell-cell adhesion, whereas structural modification of the N-glycan on N-cadherin is accompanied by strengthening of the branched structure by GnT-V. As a result, cell-to-cell adhesion was reduced, contributing to increased motility and invasiveness of cells. Activation of the oncogene stimulates increased expression of Golgi enzymes that generate β1,6-GlcNAc branched tetraantennary N-glycans. These N-glycans are found on proteins, including growth factor receptors and integrins, and have been shown to enhance the growth signal of motile tumor cells. GnT-V activity and levels of the β1,6-GlcNAc branched N-glycan have also been reported to be increased in highly metastatic tumor cell lines, both are elevated in colon, liver and glial tumors. On the other hand, GnT-III suppressed cancer metastasis in high-grade metastatic melanoma cells by decreasing -β1,6-GlcNAc branching of cell surface N-glycans and increasing bisecting N-glycans. Contribute to Enhanced intercellular adhesion by prolonging the turnover of her E-cadherin at the cell surface (Gu et al. 2009). O-glycosylation is another type of glycosylation found on glycoprotein and consists of glycans O-linked to serine or threonine residues. The frequency of O-glycosylation of glycoproteins is high, especially in serine- and threonine-rich secreted or membrane-bound mucins. The O-glycosylation pathway plays an important role in the biological activities of glycoproteins involved in controlling cell differentiation and regulating cell proliferation via the apoptotic and proliferative pathways. Alterations in O-glycosylation, such as Tn and STn expression, are implicated in a variety of processes, including inflammatory responses, angiogenesis, autoimmunity, and cancer.

O-glycans play an important role in cancer cell attachment and invasion, as well as cancer cell survival in the bloodstream. The O-glycan chains of glycoproteins, tissue and blood group antigens (including Lewis antigens) can vary both qualitatively and quantitatively, and are often truncated and highly sialylated in cancer cells. For example, mucin is a large, highly O-glycosylated protein involved in the protection of and regulation of epithelial surface signaling. Mucin itself exerts potent tumor-promoting effects, which are mediated in part through interactions with glycan units. In benign cells of breast, prostate, ovary and pancreas, MUC1 is highly glycosylated, restricted to the apical side of the gland and minimally expressed. Transformation of these cells into malignant cells is associated with overexpression of MUC1, loss of polarity of MUC1 expression, and dysregulation of her O-glycans in MUC1. In addition, cancer cells may contain membrane-bound mucin-like glycoproteins with -O-glycan-rich domains. Gene expression of these glycoproteins is cell-specific and frequently altered in cancer. There has been considerable

knowledge in this area recently. -O-glycosylated glycoprotein is a key factor in the development of -Fi diffuse adenoma. Altered mucin-type O-glycosylation is associated with somatic differentiation and cancer. Other studies have shown that complex O-linked glycans and upregulation of galectin-3 biosynthesis promote breast cancer and brain metastasis progression.

Sialic acids are commonly found as terminal monosaccharides attached to cell surface glycoconjugates. They play important roles in many physiological and pathological processes. Altered expression of certain types of sialic acids or their binding may have prognostic significance in human cancers. Elevated serum sialic acid levels have been observed in various malignancies. Mars et al. (1988) reported differences in sialic acid levels between benign and malignant tumors. Prostate-specific antigen (PSA) and acid phosphatase, which are also sialic acid-containing glycoproteins normally present in the bloodstream, promote the growth of both benign and malignant prostates. There are also reports that sialic acid is overexpressed in colon cancer tissue and skin tumor metastasis. Results of Wang et al. proposed that a high content of α2,3-linked sialic acid residues is associated with the metastatic potential of gastric cancer cells.

In addition, α2,6-sialic acid has important functions in retention of platelet endothelial cell adhesion molecule (PECAM) on the cell surface, cell adhesion, detection of mechanical stress, anti-apoptosis, and angiogenesis. It is necessary for. Thus, enhanced expression of terminal 2-6-linked Sia on cell surface N-linked glycan and sialyl-LewisX on O-linked glycan often correlates with poor prognosis in many human malignancies. In some solid tumors, incomplete synthesis of carbohydrates at the cell surface results in ABH precursors such as Lewisa, sialyl-Lewisa and their isomers (Lewisx and sLewisx). Structural expression is increased. Antigenic epitopes of the sialyl Lewisa antigen are used clinically as tumor markers for pancreatic cancer, colon cancer, and other selected malignancies. Sialyl Lewisa antigen expression is associated with tumor progression. Several lines of evidence suggest that sialyl-Lewis oligosaccharides are involved in the adhesion of several types of cancer cells to E-selectin presented on the surface of endothelial cells.

On the other hand, Lewisx is involved in selectin-mediated adhesion of cancer cells to vascular endothelium, and is probably closely related to hematogenous metastasis and thus to the malignant behavior of cancer cells. For example, colon cancer cells strongly express sialyl-Lewisx, , but have significantly reduced expression of sialyl-6-sulfo-Lewisx- compared to normal colonic epithelial cells. Sialyl Lewis x in cancer cells plays an important role in E-selectin-mediated adhesion of cancer cells to vascular endothelial cells during tumor angiogenesis and distant metastasis. Selectins are expressed by leukocytes, endothelial cells, and platelets, interact with cell surface glycoconjugates , and mediate attachment, rolling, and adhesion of multiple cell types . There are three subgroups of selectins. L-selectin is constitutively expressed by leukocytes, E-selectin by -activated endothelial cells, and P-selectin by platelets and -activated endothelial cells. It has been known for a relatively long time that cancer cells, especially epithelial cancer cells, express high levels of sialylated fucosylated selectin ligands. Microvasculature and its potential to promote metastasis Laubli et al. On the other hand, the endothelial adhesion molecule E-selectin has been implicated in colon and breast cancer metastasis by promoting tumor cell adhesion to the endothelium. Furthermore, P-selectin plays an important role in mediating interactions between cancer cells, platelets, and endothelial cells by interacting with its counterpart ligand. Alternatively, P-selectin has been reported to bind to several human cancers and cell lines derived from human cancers, including colon cancer, lung cancer, breast cancer, malignant melanoma, gastric cancer, and squamous cell carcinoma of the tongue. masu, and neuroblastoma. Numerous reports have shown that tumor cells form multicellular complexes with platelets (via P-selectin) and leukocytes (via an L-selectin-

dependent mechanism) and target the microvasculature of distant organs. It shows that they remain and eventually extravasate and become established Metastatic colonies.

Glycosphingolipids (GSLs) are lipid components of eukaryotic cell membranes that are critical for proper vertebrate development, including cell type-specific adhesion, cell-cell interactions, embryonic development, and neuronal development and differentiation involved in multiple processes cells and leukocytes, and tumor progression in vivo. Functions of GSL in 'Defining Carcinogenesis and Its Reversion' is closely associated with the hypoxic/epithelial-mesenchymal transition process (EMT), a fundamental molecular alteration associated with development and cancer progression. Predominant expression of a specific ganglioside, GD3, GM2 or GD2, has been observed in several types of tumor cells, including melanoma, neuroblastoma, lymphoma, and ovarian cancer cells. GSL-GM3 is highly expressed in human bladder benign non-invasive KK47 tumor cells, whereas levels are very low in highly malignant invasive bladder cancer YTS1 cells. Toshio Ariga et al. have shown that certain His GSL antigens, particularly His SGGL, GD3 and OAc-GD3, are expressed in neuronal tumor cells. Glycophosphatidylinositol (GPI) moieties are distributed in the membrane of all eukaryotes and are part of a long list of surface proteins involved in signaling, cell-cell interactions, and interactions with extracellular molecules in the blood. It serves to fix the terminal or connective tissue. In addition, GPI-anchored membrane cytokines have been shown to play important roles in the host immune response against tumor cells. A previous study showed amplification and overexpression of GPI transamidase subunits in head and neck squamous cell carcinoma. Similarly, -GPI-PLD mRNA expression increases with tumor progression in human ovarian cancer cell lines, skin epithelial cells, and high-grade H-ras-transfected mouse bladder cancer cells (He et al. 2002). Recently, some investigators found that GPI-anchored CD55 and CD59 are expressed in almost all primary tumors and cancer cell lines examined. Some studies have also suggested that GPI anchor attachment protein 1 (GPAA1) is upregulated in HCC (hepatocellular carcinoma).

In addition, MMP25 (MT6-MMP) is one of two GPI-anchored matrix metalloproteinases (MMPs) suggested to increase mRNA expression in colon cancer (Sun et al. 2007; Radichev et al. 2010). Correlations between Galectins and Cancer Galectins are members of the soluble lectins that bind to β-galactoside-containing glycans and are defined by a conserved carbohydrate recognition domain (CRD) and a consensus structural fold. Among the various types of lectins, the galectins are perhaps the well-conserved and ubiquitous family, whose members have been identified in most animal taxa studied to date. Up to 15 galectins have been identified in mammals and have been proposed to mediate various biological processes involved in regulating innate and adaptive immune responses.

3. Role of Glycans in Cancer Diagnosis

The lack of specific and sensitive tumor markers for early detection of cancer drives the search for new approaches to biomarker identification. Glycoconjugate modifications are a ubiquitous feature of cancer, making them important cancer biomarkers. Many of the current biomarkers in clinical use in both tissue and serum assays are based on these carbohydrate modifications. Despite intensive research efforts, the number of serum markers useful for monitoring patient response to therapy or predicting recurrence after cancer therapy is very limited. Alpha-fetoprotein (AFP) is a known glycoprotein that is produced in developing embryos and fetuses, and healthy adults have very low levels off. In particular, AFP was detected in his patient with HCC. will be However, elevated AFP is only a predictor of HCC, as it provides limited clinical information about HCC and its low specificity (~50%), the isoform AFP-L3 is for early detection of advanced tumors. is particularly useful for Associated with HCC with a specificity of 96%. Currently known serological assays detect carbohydrate antigens such as SLea (CA19-9) and STn (CA72-4) or mucin glycoproteins such as MUC1 (CA15-3) and MUC16 (CA125) (Reis et al. 2010).

Many studies have used SLex levels in diagnosing cancer. SLex is a weak marker in some small cell lung cancers (24% in all stages). However, this increases with progressive progression, reaching .71% in terminal cancer. Glycan alterations of two serum glycoproteins, PSA and pancreatic ribonuclease, are currently used separately as tumor markers for prostate cancer and pancreatic adenocarcinoma. mAb F77 as is also a unique prostate cancer marker.

In addition, Yi et al. (2009) and Rose et al. (2010) suggested that α2-HS glycoprotein (AHSG), anti-AHSG autoantibody and non-metastatic B could be useful biomarkers for breast cancer screening and diagnosis. Alternatively, glycosylated MUC1 and MUC5AC have been considered as potentially useful tumor markers in the diagnosis of gastric cancer. Toshio Ariga and others. I have also shown that certain GSL antigens, especially SGGL, GD3, and OAc-GD3, can be considered tumor-associated antigens that represent important biomarkers for neuronal tumors.

4. The Role of Glycans in Cancer Therapy

Chemotherapy, radiotherapy and surgery are the three main modalities available for cancer treatment, and are well known to be characterized by low therapeutic indices.

However, with improved analytical tools to study glycosylation and the application of molecular techniques to characterize genes encoding glycosyltransferases, it is possible to identify the structure of some of the glycosylation alterations associated with cancer has become possible.

Several recent reports have shown that chemically or genetically disrupting her N-glycosylation pathway in cancer cells reduces the malignant properties of cancer cells. Targeting defective glycosylation pathways is therefore a novel approach for the treatment of malignancies and a potential strategy for preventing metastasis. Inhibition of N-linked glycosylation is a novel therapeutic strategy for both glioma and other malignancies. Promising results for also suggested that new N-glycoside compounds such as N-(α-D-glucopyranoside) salicyloyl- hydrazine (NGSH) could be useful in cancer therapy. On the other hand, α-tocopherol oglycoside can be considered as a prodrug in the prevention and treatment of colon cancer. In addition, therapy based on the use of anti-ganglioside antibody in neuroblastoma has been proposed. Other studies have shown promising results: Garcea et al. found it to be a potential new target. A long-acting rhIFN-α2b mutein, 4NIFN, was found to have a plasma half-life that was 25-fold longer than the non-glycosylated, demonstrating its in vivo antitumor activity in nude-implanted human prostate cancer showed a significant increase.

In addition, Tietze et al. A new glycoside prodrug was developed to reduce side effects (Tietze et al. 2008). To date, such an approach has failed to eradicate tumors in patients without side effects when a single agent is used. Nevertheless, some drugs that manipulate tumor metabolism in combination with established cancer therapies are potential adjunctive therapies.

5. Glycans used in cancer vaccines Glycosylation expression in malignant tumor cells

Aberrant glycosylation of glycoproteins and glycolipids in cancer cells is correlated with decreased viability and has been exploited for the development of anticancer immunotherapies. In particular, advances in our knowledge of the linkages between innate and adaptive systems provide avenues for the rational design of vaccine candidates. Fully synthetic anti-cancer vaccines that target tumor-associated carbohydrates are an attractive option for cancer therapy, with significant advantages as they can be designed to contain only the elements required for the desired immune response. It should also be mentioned that it is now recognized that glycopeptides can mediate classical MHC-mediated immune responses. Moreover, the use of synthetic glycopeptides as partial or complete building blocks of vaccines

targeting these antigens is a preferred approach for the development of cancer immunotherapy, as they can be produced as homogeneous formulations. As a result, tumor-associated glycan antigens were considered superior for vaccine development, and many of his proceeded to clinical trials.

A good example is MUC1, a high molecular weight glycoprotein that is upregulated in adenocarcinoma and hematological cancers. MUC1-based vaccines have rapidly entered human clinical trials, and numerous clinical trials have shown that MUC1 immunotherapy is beneficial and protects early-stage breast cancer patients from recurrence for up to 8 years (Tang et al. al.2008). A recently reported synthetic vaccine composed of the tumor-associated sialyl-TNMUC1 tandem repeat glycopeptide and tetanus toxoid can induce a potent and highly selective immune response.

In addition, a vaccine based on Tn, TF, sTn, LewisY, polysialic acid, and GloboH is currently in phase I or II clinical trials (Oyelaran and Gildersleeve 2007).

Bettahi's study investigated the self-assisting glycolipopeptide (GLP) as a cancer vaccine platform. Recent advances in peptide-based his breast cancer vaccine strategies with an emphasis on self-adjuvanted polyvalent glycolipopeptide vaccine strategies were developed in the laboratory and showed encouraging his results. Fengshu Zhao et al. prepared a tumor vaccine co-expressing GPI-anchored IL-21 and GMCSF and found it to be effective in anti-tumor immunotherapy. Carbohydrate-sequencing technology is still in its infancy, but has great potential to accelerate the development of carbohydrate-targeted cancer vaccines.

6. Conclusions

Although glycosylation is observed in many human cancer cells, aberrant glycosylation of N- or O-linked glycoproteins is closely associated with tumor growth and metastasis; can be used for early diagnosis and monitoring. It treats a range of cancers in people. Also, several cases of clinical application mentioned above confirmed this novel approach. The use of these glycosylation in anti-tumor metastasis or anti-cancer vaccine research is one of the promising targets and will be a breakthrough for future research. However, since the basic and detailed structures of glycosylation are not well understood, the discovery of highly sensitive and specific cancer sugar biomarkers useful for clinical diagnosis is an important issue that urgently needs to be resolved. In addition, several issues remain unsolved, such as the preparation and design of safe and effective cancer vaccines.

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