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Mini-review

Aiming at the sweet side of cancer: Aberrant glycosylation as possible target for personalized-medicine

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ABSTRACT

One of the frontiers in cancer personalized-medicine aims at glycosylation. Cells are covered with a dense sugar coat of glycolipids, glycoproteins and free glycans. In cancer, the characteristic cell surface glycosylation is frequently transformed due to altered expression of glycan-modifying enzymes. This often leads to aberrant expression of sialic acids (Sia) that cap glycan-chains. Additionally, dietary intake of the non-human Sia *N*-glycolylneuraminic acid (Neu5Gc) leads to natural metabolic-glycoengineering of human carcinomas that accumulate and express Neu5Gc. This Sia provokes a polyclonal anti-Neu5Gc xeno-autoantibodies response that can exacerbate cancer. This review highlights cancer-associated changes in Sia expression and their potential for personalized-theranostics.

1. Introduction

Cancer is a complex heterogeneous disease and the leading cause of death worldwide. Selective biological therapies have emerged to effectively treat certain types of cancers or to target specific determinants that are expressed by many different tumor types [1,2]. Yet patients do not respond uniformly to a given therapy reflecting their inherent heterogeneity. Technological advances in genomics paved the way towards matching a subset of patients with unique genetic signatures that are most likely to benefit from a certain therapy [3–6], thus leading to individually tailored treatments [6–8]. Other high-throughput technologies have also emerged to expand personalized-medicine beyond genomics including proteomics, pharmacogenomics, nutrigenomics [6,8,9] and more recently glycomics [10,11].

Carbohydrates play a major role in cancer and circulating or cell surface tumor-associated carbohydrate antigens (TACA) serve as diagnostics markers [12,13]. TACA represent a modified version of the carbohydrates normal expression, which frequently involve altered expression of sialic acids. While this has been extensively described in the literature, recent research suggests a novel group of TACA that arise from the consumption of the dietary non-human sialic acid, *N*-glycolylneuraminic acid (Neu5Gc). This sugar metabolically incorporates into cells like a 'Trojan horse' replacing the human sialic acid thereby generating neo-TACA that become immunogenic. Since Neu5Gc is a consumed dietary sugar it may provide a unique opportunity for personalized-medicine that likely relates to the individual's dietary habits. To fully appreciate its potential, this assay will first review current literature of glycosylation and its changes in cancer focusing on aberrant sialic acid expression (Sections 2–4). Subsequently, current knowledge on the role of Neu5Gc and the related anti-Neu5Gc antibodies in cancer will be described (Section 5), followed by discussion of their potential as novel personalized-cancer theranostics (Section 6).

2. Cell-surface glycosylation

Cell surface glycosylation is universal to all living cells reflecting their physiological state, and perfectly positioned to mediate adhesion and motility, as well as intracellular signaling events [14,15]. Monosaccharide units serve as building blocks that are synthesized via covalent glycosidic-linkages into chains termed glycans (oligosaccharides and polysaccharides) [16]. Each monosaccharide is transferred from activated sugar-nucleotide donor to the acceptor molecule in a stepwise fashion. The combined action of various enzymes (i.e., glycosyltransferases and glycosidases) leads to diverse glycan structures [17]. These can exist either as free forms or conjugated to proteins and lipids (Fig. 1) and include: (1) glycoproteins with complex and branched *N*-linked glycans (conjugated to Asparagine) and/or with *O*-linked glycans (conjugated to Serine or Threonine) that are abundant on mucins; (2) glycosylphosphatidylinositol (GPI)-anchored proteins; (3) glycosaminoglycans (GAGs) either as linear free polysaccharides (such as hyaluronan) or attached to Serine residues of proteoglycans (such as heparan

Abbreviations: Neu5Ac, *N*-acetylneuraminic acid; Neu5Gc, *N*-glycolylneuraminic acid; Gal, galactose; GalNAc, *N*-acetylgalactosamine; GlcNAc, *N*-acetylglucosamine; Man, mannose; Fuc, fucose; GlcA, glucoronic acid; IdoA, iduronic acid; Xyl, xylose.

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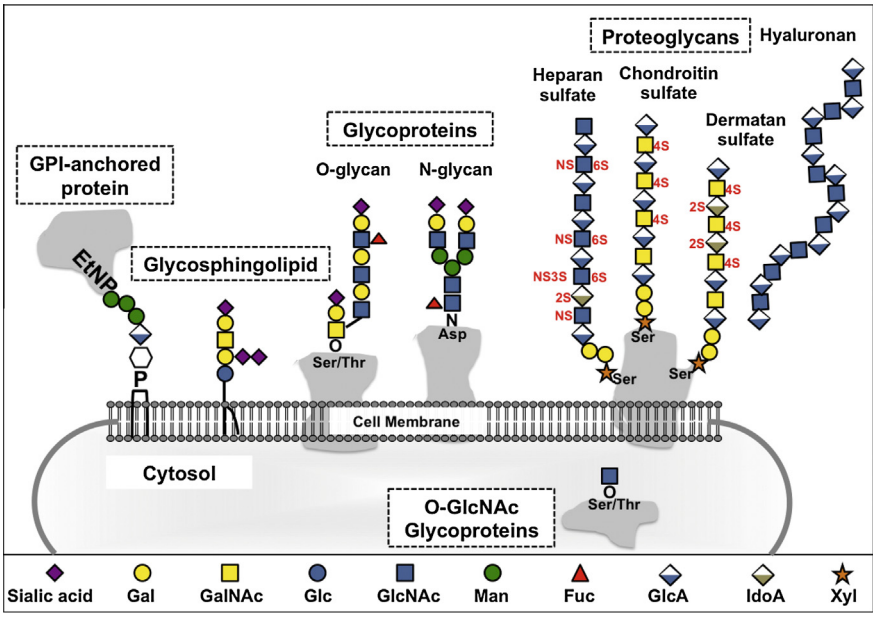

Fig. 1. Common glycans on human cells. Examples of the major glycoconjugates classes are depicted, as described in the main text.

sulphate and chondroitin sulphate); and (4) glycolipids, which consist of glycans linked to ceramide. In addition to cell surface glycans, nuclear and cytoplasmic proteins can be modified with *O*-linked *N*-acetylglucosamine (*O*-GlcNAc; conjugated to Serine). O-GlcNAcylation occurs in the cytoplasm and modifies intracellular proteins, regulating their activity together with phosphorylation [18]. In light of its ubiquitous and versatile nature, glycosylation hold promise for novel personalized-theranostics (therapeutics and diagnostics), assuming one can differentiate between the glyco-patterns of the normal versus the disease state.

3. Aberrant cell-surface glycosylation in cancer

Glycosylation is remarkably dynamic and commonly modified in cancer leading to the expression of cancer-associated antigens [19], sometimes referred to as "onco-fetal antigens" that recapitulate expression normally limited to embryonic tissues [19,20]. The two basic principles that phenotypically guide these changes are *incomplete synthesis* and *neo-synthesis* of cancer-associated cell surface glycans [21–23]. These changes commonly apply to early-stage cancers and to advanced-stage cancers, respectively [24]. In general, a shift from the normal glycosylation pathway leads to altered glycan expression due to one or more of the following changes: (1) under- or overexpression of glycosyltransferases deregulated at the level of epigenetics [25,26], transcription [27–31], post-transcription [32] and/or chaperone [33]; (2) altered glycosidase activity [34–36,36,37]; (3) altered expression of glycoconjugate acceptor together with availability and abundance of the sugar nucleotide donors [38]; (4) altered sugar nucleotide transporter activity [39]; and (5) improper function of the Golgi structure [40] where many of the glycosyltransferases are harbored [41]. Evidence is accumulating that aberrant glycosylation contributes to various aspects of cancer development and progression, including proliferation, invasion, angiogenesis, metastasis and immunity [12,16,42]. Yet, oncogenic glycosylation is not random but rather is limited to a distinct subset of glycans that become modified, enriched or decreased on the tumor cell surface and mediate either promotion or inhibition of tumor progression [12,43,44].

4. Altered sialic acids expression

As early as 1960s there was considerable evidence that the surface properties of cancer cells are different than those of normal cells [45] and that sialic acids largely contribute to that phenotypic change [46–48]. Sialic acids (Sia) are nine-carbon backbone α-keto acidic sugars with their carboxylate group normally negatively charged at physiological pH. They are capping vertebrate glycans and found α-linked to underlying sugars via their second carbon to either galactose (α2−3Gal or α2−6Gal), *N*-acetylgalactosamine (α2−6GalNAc) or to another Sia (α2−8Sia) [49] (but in some cases also to *N*-acetylglucosamine (α2−6GlcNAc) [50]). Changes in Sia level, linkage and distribution are associated with various aspects of malignant transformation [44,51–54].

General increase in cell surface Sia was shown to promote metastatic potential [19,51,52,55–57] and result from various routes [44]. Changes to the core structures of *N*-glycans are some of the most common aberrant glycosylation in cancer. Increased activity of the β1-6GlcNAc branching enzyme, *N*-acetylglucosaminyltransferase V (GlcNAc-TV or MGAT5), lead to larger and more branched *N*-glycans thus providing additional acceptors for terminal sialylation (Fig. 2) [38,44,58]. Together with increased expression of sialyltransferases [59,60], these changes contribute to increased cell surface sialylation and metastatic potential [38,38]. Similarly, aberrant *O*-linked glycosylation can lead to increased sialylation. Carcinomas (tumors of epithelial origin) overproduce mucins that are heavily glycosylated high molecular weight glycoproteins (e.g., MUC1, MUC4, MAC6, MAC5AC) characterized by dense clusters of *O*-glycans, although *N*-glycans can also be present [61–64]. Cancer-associated mucin-type *O*-glycans tend to be truncated due to a shift in the normal enzymatic machinery and are usually highly sialylated and less sulphated (Fig. 2) [61–63,65,66].

Increased sialylation is also evident by expression of polysialic acid (polySia or PSA) that is an oncofetal antigen associated with various types of cancers (e.g., neuroblastoma, non-small cell lung carcinoma, breast cancer) [12,67], as well as other diseases [67]. PSA is synthesized in the Golgi by the polysialyltransferases ST8SiaII and ST8SiaIV, generating *N*-glycans with a linear homopolymer of α2−8-linked Sia (n = about 8 to over 100; Fig. 2). These are mainly conjugated to the neural cell adhesion molecule (NCAM)

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