Biochimica et Biophysica Acta 1840 (2014) 2752–2764

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen

Review

Sialosignaling: Sialyltransferases as engines of self-fueling loops in cancer progression

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ARTICLE INFO

Article history:
Received 4 April 2014
Received in revised form 13 May 2014
Accepted 10 June 2014
Available online 17 June 2014

Keywords:
Glycosylation
Sialylation
Gangliosides
Neural cell adhesion molecule
Integrins
Chemoresistance

ABSTRACT

Background: Glycosylation is increasingly recognized as one of the most relevant postranslational modifications. Sialic acids are negatively charged sugars which frequently terminate the carbohydrate chains of glycoproteins and glycolipids. The addition of sialic acids is mediated by sialyltransferases, a family of glycosyltransferases with a crucial role in cancer progression.
Scope of the review: To describe the phenotypic and clinical implications of altered expression of sialyltransferases and of their cognate sialylated structures in cancer. To propose a unifying model of the role of sialyltransferases and sialylated structures on cancer progression.
Major conclusions: We first discuss the biosynthesis and the role played by the major cancer-associated sialylated structures, including Thomsen–Friedenreich-associated antigens, sialyl Lewis antigens, α2,6-sialylated lactosamine, polysialic acid and gangliosides. Then, we show that altered sialyltransferase expression in cancer, consequence of genetic and epigenetic alterations, generates a flow of information toward the membrane through the biosynthesis of aberrantly sialylated molecules (inside-out signaling). In turn, the presence of aberrantly sialylated structures on cell membrane receptors generates a flow of information toward the nucleus, which can exacerbate the neoplastic phenotype (outside-in signaling). We provide examples of self-fueling loops generated by these flows of information.
General significance: Sialyltransferases have a wide impact on the biology of cancer and can be the target of innovative therapies. Our unified view provides a conceptual framework to understand the impact of altered glycosylation in cancer.

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1. Introduction

The sugar portions of glycoproteins and glycolipids are often terminated by sialic acids (Sia): sugars which, owing to their negative electric charge, are crucial in regulating molecular and cellular interactions [1–3]. Sialic acids can be linked to subterminal sugars through an α2-6-bond to N-acetylgalactosamine (GalNAc) or N-acetylglucosamine (GlcNAc); an α2,3 or α2,6 bond to galactose (Gal) or through a α2-8-bond to another sialic acid, forming polysialic acids. Sialyltransferases are a class of glycosyltransferases which catalyze the transfer of sialic acid from a common donor substrate (CMP-sialic acid) to a carbohydrate chain. Sialyltransferases show a certain degree of redundancy, in that the same glycosidic linkage can often be elaborated by different gene products [4] and are crucially involved in cancer progression [5,6]. In this review we have summarized the studies showing the intimate relationship between sialyltransferases and their products with the mechanisms of cell transformation and cancer progression. In particular, we provide examples of how the signaling generated by sialylated molecules at the cell membrane can activate self-amplification loops fueling cancer growth.

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloblastic leukemia; 5-AZA, 5′-azacytidine; BCG, Bacillus Calmette–Guerin; CIN, chromosome instability; DP, degree of polymerization; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMT, epithelial to mesenchymal transition; ER, estrogen receptors; ERE, estrogen responsive element; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; Gal, Galactose; GalNAc, N-acetylgalactosamine; GlcNAc, N-acetylglucosamine; MAPK, mitogen-activated protein kinase; MSI, microsatellite instability; MSS, microsatellite stability; MUC1, mucin-1; N-CAM, neural cell adhesion molecule; PCR, polymerase chain reaction; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PSA, polysialic acid; PST, polysialyltransferase ST8SIA4; Sia, sialic acid; sT, sialyl-T; sTn, sialyl-Tn; Sia6LacNAc, α2,6-sialylated lactosamine; SNA, *Sambucus nigra* agglutinin; STX, polysialyltransferase ST8SIA2; TF, Thomsen–Friedenreich; sLe^a, sialyl-Lewis^a; sLe^x, sialyl-Lewis^x; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor

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http://dx.doi.org/10.1016/j.bbagen.2014.06.006
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2. Overall effect of sialylation in cancer

Early studies indicated that the level of sialyltransferase activity is often increased in plasma of cancer patients [7–10] and that the extent of sialylation of cancer cells is associated with their invasive properties [9,11–18]. Former functional studies on the overall effect of sialic acids in cancer biology, using sialidases or sialyltransferase inhibitors sometimes provided contradictory results [19]. For example, the effect of sialidase treatment on collagen IV adhesion was the opposite in murine and human cancer cells [13,14], while sialic acid depletion by the sialyltransferase inhibitor KI-8110 reduced metastasis formation [20] without affecting cell adhesion to extracellular matrix glycoproteins but rather decreasing platelet aggregation [16]. According to other studies, the inhibition of sialic acid incorporation by different compounds impaired adhesion, migration, *in vivo* tumor growth and metastasis formation [21–25].

3. Sialylated structures involved in cancer progression

In this section we describe the structure and biosynthesis of specific sialylated structures and discuss their contribution to cancer biology and progression.

3.1. Thomsen–Friedenreich (TF)-related antigens

Antigens T, Tn and their sialylated variants sialyl-T (sT) and sialyl-Tn (sTn) are small cancer-associated O-linked structures, often referred to as Thomsen–Friedenreich (TF)-related antigens [26], whose structure and biosynthesis are depicted in Fig. 1.

In breast cancer, mucin glycosylation undergoes a characteristic switch from the expression of core 2 structures to the accumulation of T [27] and sTn structures [28,29]. This change is accompanied by a concomitant and apparently paradoxical up-regulation of sialyltransferase ST3GAL1 [30], which converts T in sialyl-T (sT) antigen [31], inhibiting the synthesis of core-2 based structures [32]. ST3GAL1 over-expression in breast cancer is associated with conditions characterizing tumor growth, such as the presence of the inflammatory enzyme cicloxygenase-2 (COX-2) and of its product prostaglandin E2 (PGE2) [33] and hypoxia [34]. On the other hand, the expression of the cell membrane mucin 1 (MUC1), which is frequently altered in cancer [35], down-regulates ST3GAL1 expression in mouse mammary carcinoma cells [36]. Constitutive ST3GAL1 expression by murine mammary epithelium contributes to breast cancer progression. In fact, in PyMT mice, which spontaneously develop breast cancer, the concomitant over-expression of ST3GAL1 in mammary glands results in the development of mammary tumors with shorter latency, although no accumulation of sT antigen was observed [37]. Altogether, these data suggest that the biological effect of ST3GAL1 on cancer progression might not be dependent on the synthesis of its cognate carbohydrate antigen, but rather on its proposed tumor promoter activity [37]. A paradoxical over-expression of both T antigen [38] and sialyltransferases ST3GAL1 and ST3GAL2 [39] has also been reported in colon cancer, with the former associated with lymph node metastasis [39]. In bladder cancer tissues ST3GAL1 mRNA was also elevated, particularly in patients with tendency to recurrence [40].

sTn, a pan-carcinoma antigen expressed by many malignancies [41–45], is usually associated with a worse prognosis [46]. The biosynthesis of sTn largely depends on sialyltransferase ST6GALNAC1, while the contribution of ST6GALNAC2 appears to be negligible [47,48], being more specific for s6T biosynthesis. However, the reduced O-acetylation of sialic acid [49] and the down-regulation of the competing core 1 galactosyltransferase [50,51] also contribute to increased sTn expression in cancer [52]. In bladder cancer, sTn is expressed by 75% of high-grade tumors and correlates with ST6GALNAC1 expression [45]. Moreover, the expression of this carbohydrate antigen, associated with s6T, is a marker of disease-free survival and predicts response to immunotherapy with bacillus Calmette–Guerin (BCG) [45]. In different cancer cell lines, the phenotypic effects of sTn over-expression obtained by forcing ST6GALNAC1 expression, are multiple and only partially overlapping. These include: morphological changes and reduced ability to migrate on extracellular matrix (ECM) components [53], reduced cell adhesion and increased cell migration [54–56], increased metastatic ability [57], decreased intercellular aggregation and increased ECM adhesion, migration and invasion [58], increased cell motility and invasion

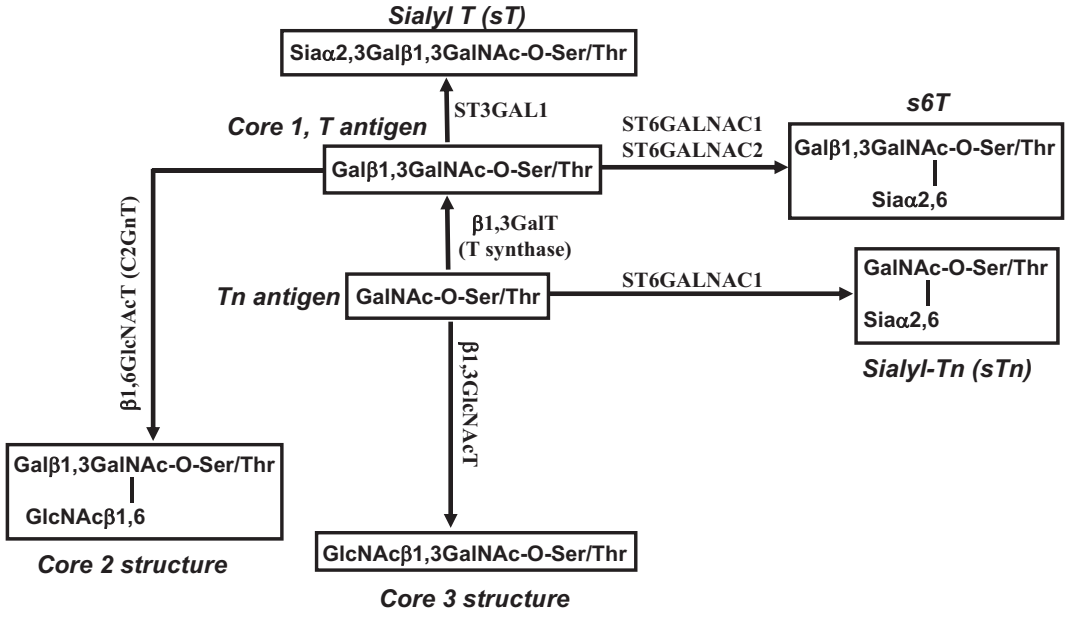

Fig. 1. Structure and biosynthesis of Thomsen–Friedenreich-related antigens. The Tn antigen, originated by the addition of GalNAc to serine or threonine residues of the polypeptide chain, can be transformed in sialyl-Tn antigen by the action of ST6GALNAC1 or can be elongated by the addition of a β1-3-linked galactose, yielding the core 1 structure (T-antigen) or by the addition of a β1-3GlcNAc, yielding the core 3 structure. The T antigen can be further processed by the addition of a GlcNAc β1-6-linked to GalNAc, generating the core 2 structure, or by the addition of sialic acid in α2-3-linkage to Gal, mainly by ST3GAL1, yielding the sialyl-T antigen. Core 1 structure can also be directly sialylated on the GalNAc residue by ST6GALNAC1 or ST6GALNAC2, yielding s6T antigen.

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