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LETTER

Reciprocal Modulation of Terminal Sialylation and Bisecting *N*-Glycans: A New Axis of Cancer-Cell Glycome Regulation?

Lu *et al.* (1) have investigated the influence of cellular sialylation on the GnT-III-mediated regulation of cancer cell metastatic potential. The authors demonstrated that GnT-III (GlcNAc-bisecting glycosyltransferase) overexpression results in a significant reduction of α2,3-sialylation, with no major alteration of α2,6-sialylation (1). Interestingly, a reciprocal correlation between terminal α2,3-sialylation and bisected *N*-glycans has also been recently reported (2). Glycomic analysis of cancer cells overexpressing the α2,3-sialyltransferase ST3GAL4 showed that increased terminal α2,3-sialylation is accompanied by a substantial loss of bisected *N*-glycans (2).

This coordinated regulation of α2,3-sialylation by bisecting *N*-glycans and vice versa adds a new level of complexity to the regulation of the cancer cell glycome and raises new questions about the molecular mechanisms underlying these glycosylation shifts. Noteworthy, the down-regulation of bisected *N*-glycans and α2,3-sialylation by ST3GAL4 and GnT-III, respectively, do not stem from alterations at the glycosyltransferase transcript levels (1, 2). The supramolecular organization of the Golgi glycosylation pathways is plastic and can be altered in cancer cells (3); thus, we can hypothesize that altered localization of the overexpressed glycosyltransferases could functionally impact the sequential glycan biosynthetic pathways and therefore interfere with bisecting *N*-glycans and terminal sialylation.

Increased α2,3-sialylation is associated with malignancy and patients' poorer prognosis, whereas bisected *N*-glycans suppress metastization (4). Moreover, *N*-glycan branching and sialylation patterns determine galectin lattice dynamics with critical impact on tumor cell signaling and definition of aggressiveness features (5). Therefore, deciphering the mechanisms underlying reciprocal regulation of terminal sialylation and bisecting *N*-glycans is fundamental for our understanding of tumor cell biology.

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