Secondary-Type Carbohydrate Modification as a Driver of Epithelial-Mesenchymal Transition and Features of Cancer Stem Cells

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Tumor glycosylation not only provides the molecular foundation for a broad range of diagnostic tumor markers [1], but specific patterns of glycosylation have also been shown to influence the biological behavior of tumors and their clinical outcome [2]. Recent evidence highlights a role of expressed glycans to escape cellular [3–5] or humoral [6, 7] immune responses, eventually as self-associated molecular patterns [8, 9]. However, it has long been known that tumor glycosylation has an impact on other aspects of tumor progression, such as tumor growth and proliferation, invasion, or metastasis [10]. The biosynthesis of tumor-specific glycans involves primary-type biosynthesis of glycans by elongation, branching, and tailoring of the glycans by glycosyltransferases and glycosidases [2]. Secondary-type carbohydrate modification is here defined as the transfer of a noncarbohydrate moiety to a carbohydrate structure by enzymes, such as by distinct sulfotransferases.

In this issue of *Pharmacology*, Behrens et al. [11] provide evidence for a role of carbohydrate (chondroitin 4) sulfotransferase-11 (CHST11) in the induction of epithelial-mesenchymal transition and stem cell-like properties, at least partially involving the Wnt pathway [11]. While it is known that sulfation by CHST11 alters the function of chondroitin sulfate glycosaminoglycans, the authors found that transfection of the breast cancer cell line MCF-7 with the human *CHST11* gene resulted not

only in the expression of chondroitin sulfate A but also in the transition from a cobblestone-like to a spindle-like shape. These morphological changes were associated with downregulation of cell surface E-cadherin and the accumulation of cytoplasmic and nuclear β -catenin proteins, as well as altered gene expression such as decreased E-cadherin (*CDH1*) and increased N-cadherin (*CDH2*), fibronectin, and vimentin mRNA levels. Furthermore, *CHST11* gene transfection of MCF-7 cells (MCF-7-CHST11) resulted in the expression of major genes involved in self-renewal and pluripotency. MCF-7-CHST11 cells exhibited a higher proliferation rate, stronger anchorage-independent growth, and higher migratory capacity, indicating the enhanced aggressive behavior of these cells. Indeed, using a publicly available database, the authors found that elevated expression of CHST11 predicts poor survival of breast cancer patients.

The observations by Behrens et al. [11] not only reveal the potential of CHST11 as a potential drug target, but also support the view that public databases may play an increasingly important role for reverse translational research approaches in pharmacology [12]. While such databases often do not offer direct information on the expression of biologically relevant glycans, they can provide useful information on molecules involved in glycan biosynthesis [13]. From the data published by Behrens et al. [11] in this issue, it can be inferred that examination of

glycopatterns in tumors should also include glycan-modifying enzymes involved in secondary-type carbohydrate modifications, which may also be relevant for personalized medicine approaches for the therapy of cancer.

Disclosure Statement

The author declares no conflicts of interest.

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