ST3GAL5-catalyzed gangliosides inhibit TGF-β-induced epithelial-mesenchymal transition

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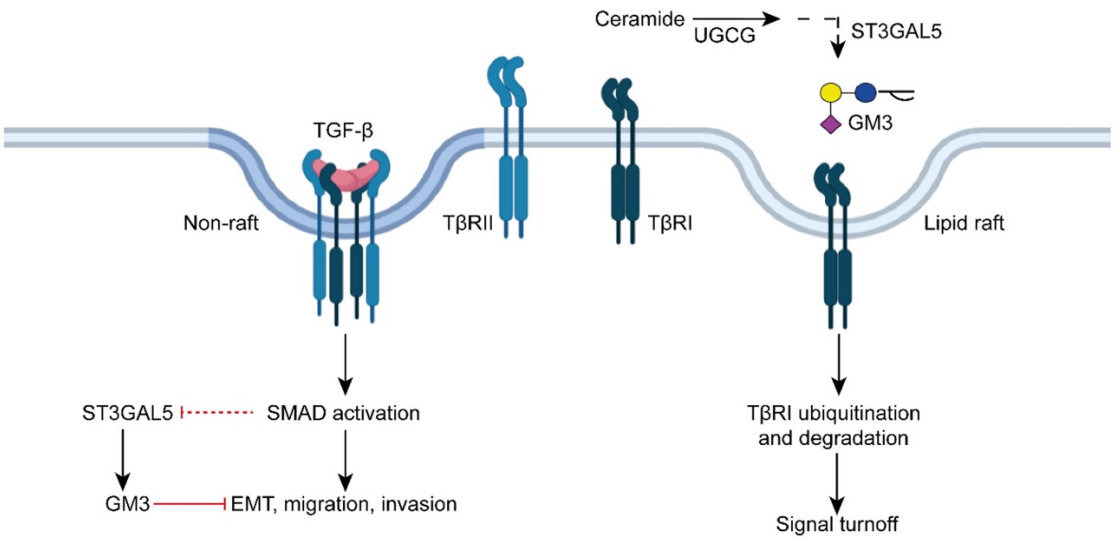
Epithelial-mesenchymal transition (EMT) is of pivotal importance in the development and initiation of cancer cell metastasis. We observed that abundance glycosphingolipids (GSLs), especially the gangliosides subtype, strikingly decreased during the TGF-β-induced EMT of mouse NMuMG cells and human lung A549 adenocarcinoma cells using porous graphitized carbon chromatography coupled to tandem mass spectrometry (PGC nano-LC-MS^2). Transcriptional profiling showed that the TGF-β/SMAD response genes and EMT signatures are strongly enriched in NMuMG cells depleted of UDP-glucose ceramide glucosyltransferase (Ugcg), which catalyses the initial step in GSL biosynthesis. Consistent with this notion, the genetic or pharmacological inhibition of UGCG promoted TGF-β signalling and TGF-β-induced EMT. The inhibition of UGCG stimulated A549 cell migration, extravasation in the zebrafish xenograft model and metastasis in mice. Mechanistically, GSLs inhibited TGF-β signalling by promoting the TGF-β type I receptor (TβRI) localisation into lipid rafts and by increasing TβRI ubiquitination and degradation. Importantly, we identified ST3GAL5-synthesised *a*-series gangliosides as the main branch of GSLs involved in the inhibition of TGF-β signalling and TGF-β-induced EMT in A549 cells. Notably, ST3GAL5 is weakly expressed in lung cancer tissues compared to adjacent normal tissues, and its expression correlated with good prognosis.

This study identifies plasma membrane GSLs composition and related biosynthesis enzymes as key suppressors of dynamic EMT and malignant transformation in human epithelia.



Bibliographic references:

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