The O-GalNAcylating enzyme GALNT5 mediates EGFR-driven progression of CCA

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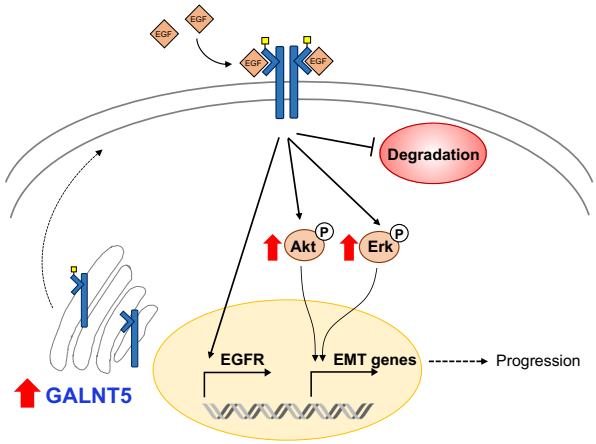
Abstract: Mucin type O-linked glycosylation is a post-translational modification that significantly affects protein conformation, stability and activity. The biosynthesis of O-linked glycosylation is initiated by a polypeptide *N*-acetylgalactosaminyltransferase (GALNT) that adds the first sugar, *N*-acetylgalactosamine, to serine or threonine residue. Our previous study demonstrated that GALNT5 modulated progression of cholangiocarcinoma (CCA) via activation of Akt/Erk signaling and the epithelial to mesenchymal transition (EMT) process. It has been shown previously that function and stability of epidermal growth factor receptor (EGFR) were altered by GALNTs glycosylation. This study was aimed to elucidate the significances of GALNT5 on EGFR expression and function. Analysis of gene expression microarray of CCA tissues from Thai patients revealed the correlation between the expression levels of EGFR and GALNT5. High expression of EGFR and GALNT5 were significantly influenced the survival of CCA patients. The GALNT5 knocked-down and over-expressing CCA cells were established to determine the effects of GALNT5 on EGFR. Correlation of GALNT5 and EGFR expression was also observed in CCA cell lines. Suppression of GALNT5 expression by a specific siRNA significantly reduced expression level, activation and stability of EGFR. In contrary, over-expressing GALNT5 increased expression, activation, and stability of EGFR. GALNT5 modulated EGFR function in CCA cells by increasing the binding affinity of EGF-EGFR which consequently activated the Akt and Erk signaling. In conclusion, this study revealed the significance of GalNAcylation of EGFR by GALNT5 in mediating EGFR expression and function. GALNT5 together with EGFR may be the potential targets for controlling CCA progression.

Graphical abstract:



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