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β-1,4-galactosyltransferase III enhances invasive phenotypes via β1 integrin and predicts poor prognosis in neuroblastoma

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Abstract

Purpose: Neuroblastoma (NB) is a neural crest-derived tumor that commonly occurrs in childhood. β-1,4-galactosyltransferase III (B4GALT3) is highly expressed in human fetal brain and is responsible for the generation of poly-*N*-acetyllactosamine which plays a critical role in tumor progression. We therefore investigated the expression and role of B4GALT3 in NB.

Experimental design: We examined B4GALT3 expression in tumor specimens from 101 NB patients by immunohistochemistry and analyzed the correlation between B4GALT3 expression and clinicopathologic factors or survival. The functional role of B4GALT3 expression was investigated by overexpression or knockdown of B4GALT3 in NB cells for *in vitro* and *in vivo* studies.

Results: We found that B4GALT3 expression correlated with advanced clinical stages ($P = 0.040$), unfavorable Shimada histology ($P < 0.001$), and lower survival rate ($P < 0.001$). Multivariate analysis showed that B4GALT3 expression is an independent prognostic factor for poor survival of NB patients. B4GALT3 overexpression increased migration, invasion, and tumor growth of NB cells, while B4GALT3 knockdown suppressed the malignant phenotypes of NB cells. Mechanistic investigation showed that B4GALT3-enhanced migration and invasion were significantly suppressed by β1 integrin blocking antibody. Furthermore, B4GALT3 overexpression increased lactosamine glycans on β1 integrin, increased expression of mature β1 integrin via delayed degradation, and enhanced phosphorylation of focal adhesion kinase (FAK). Conversely, these properties were decreased by knockdown of B4GALT3 in NB cells.

Conclusion: Our findings suggest that B4GALT3 predicts an unfavorable prognosis for NB and may regulate invasive phenotypes through modulating glycosylation, degradation, and signaling of β1 integrin in NB cells.

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The molecular chaperone Cosmc enhances malignant behaviors of colon cancer cells via activation of Akt and ERK

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Abstract

Expression of T antigen (Galbeta1,3GalNAc) is associated with enhanced metastatic potential and poor prognosis in colorectal cancer. Cosmc is a molecular chaperone required for the formation of an active T-synthase, which catalyzes the synthesis of T antigen. However, the expression and role of Cosmc in colorectal cancer are still unclear. Here, real-time PCR showed that overexpression of *Cosmc* mRNA in colorectal tumors compared with paired non-tumorous tissues was associated with increased American Joint Committee on Cancer (AJCC) tumor stage. Forced expression of Cosmc in HCT116 cells significantly increased T antigen expression and enhanced cell growth, migration, and invasion, which was associated with increased phosphorylation of focal adhesion kinase (FAK), ERK and Akt. These Cosmc-enhanced malignant phenotypes were significantly suppressed by specific inhibitor of MEK or PI3K. We also found that Cosmc overexpression increased tumor growth and decreased survival of tumor-bearing SCID mice. Conversely, knockdown of Cosmc with siRNA in SW480 cells decreased malignant behaviors and the signaling pathways, which were substantially reversed by constitutively active Akt or MEK. Taken together, these results suggest that Cosmc promotes malignant phenotypes of colon cancer cells mainly via activation of MEK/ERK and PI3K/Akt signaling pathways, and that Cosmc may serve as a potential target for colorectal cancer treatment.

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