学位論文の要旨

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主論文の題名

CD44v9 Induces Stem Cell-Like Phenotypes in Human Cholangiocarcinoma

主論文の要旨

Our previous study revealed an overexpression of CD44 variant 9 (CD44v9) in human cholangiocarcinoma (CCA) tissues. To clarify carcinogenic mechanism, we examined the potential roles of CD44v9 in CCA. Immunofluorescence (IF) staining confirmed higher protein expression of CD44v9 in CCA cells (KKU213) than normal cholangiocytes (MMNK1). RT-qPCR analysis revealed that the mRNA expression level of CD44v9 was predominantly elevated in CCA cells along with its neighboring exons such as variant 8 and 10, minimally affecting the standard form of CD44. CD44v9 silencing suppressed the CCA cell proliferation by induction of apoptosis and cell cycle arrest. Migration and invasion were decreased in CD44v9 siRNA-treated CCA cells. CD44v9 downregulation inhibited CCA tumor growth in mouse xenografts. IF analysis demonstrated the histological changes in xenograft tissues such as an increase in connective tissues through collagen deposition and reduction of hyaluronic acid synthesis through CD44v9 silencing. CD44v9 knockdown in vitro and in vivo increased E-cadherin and reduced vimentin expression levels, resulting in reduction of epithelial-mesenchymal transition process. Moreover, CD44v9 modulated Wnt10a and ß-catenin in tumorigenesis. Our results indicate that CD44v9 silencing may suppress tumor growth, migration and invasion. It could potentially be applied in the development of targeted cancer therapy.