論 文 要 旨

膵臓癌転移においてCD133はERK経路との相互作用を介して上皮間葉移行を促進する

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Background: Pancreatic cancer is a lethal disease due to the high incidence of metastasis at the time of detection. CD133 expression in clinical pancreatic cancer correlates with poor prognosis and metastasis. However, the molecular mechanism of CD133-regulated metastasis remains unclear. In recent years, epithelial-mesenchymal transition (EMT) has been linked to cancer invasion and metastasis. In the present study we investigated the role of CD133 in pancreatic cancer metastasis and its potential regulatory network.

Methods: A highly migratory pancreatic cancer cell line, Capan1M9, was established previously. After shRNA was stable transducted to knock down CD133 in Capan1M9 cells, gene expression was profiled by DNA microarray. Orthotopic, splenic and intravenous transplantation mouse models were set up to examine the tumorigenesis and metastatic capabilities of these cells. In further experiments, real-time RT-PCR, Western blot and co-immunoprecipitate were conducted to evaluate the interactions of CD133, Slug, N-cadherin, ERK1/2 and SRC.

Results: We found that CD133+ human pancreatic cancer cells were prone to generating metastatic nodules in in vivo models using immunodeficient mice. In contrast, CD133 knockdown suppressed cancer invasion and metastasis in vivo.Gene profiling analysis suggested that CD133 modulated mesenchymal characteristics including the expression of EMT-related genes, such as Slug and N-cadherin. These genes were down-regulated following CD133 knockdown.Moreover, CD133 expression could be modulated by the extracellular signal-regulated kinase (ERK)1/2 and SRC signaling pathways. The binding of CD133 to ERK1/2 and SRC acts as an indispensable mediator of N-cadherin expression.

Conclusions: These results demonstrate that CD133 plays a critical role in facilitating the EMT regulatory loop, specifically by upregulating N-cadherin expression, leading to the invasion and metastasis of pancreatic cancer cells. Our study provides a novel insight into the function of CD133 in the EMT program and a better understanding of the mechanism underlying the involvement of CD133 in pancreatic cancer metastasis.

Keywords: Pancreatic cancer, CD133, Epithelial-mesenchymal transition (EMT), ERK1/2, N-cadherin, Cancer metastasis