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CD146 mediates an E-cadherin-to-N-cadherin switch during TGF-β signaling-induced epithelial-mesenchymal transition

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Abstract

Cadherin switch is an initiating factor of epithelial-mesenchymal transition (EMT) and is intimately correlated with cancer metastatic potential; however, its underlying mechanisms remain unclear. Here, using a transforming growth factor-β (TGF-β)-induced EMT model, we provide explicit evidence that CD146, with elevated expression and activity in a variety of cancers, is a key factor involved in the cadherin switch. We show that CD146 can be induced by TGF-β signaling. Moreover, CD146 expression is positively correlated with the activation levels of STAT3/Twist and ERK pathways. Transcriptional response of the CD146/STAT3/Twist cascade inhibits E-cadherin expression, whereas the CD146/ERK cascade enhances N-cadherin expression. CD146 overexpression also significantly promotes EMT in both mouse embryonic fibroblasts (MEFs) and ovarian cancer cells. Clinically, ovarian cancer patients with detectable CD146 expression had a significantly lower survival rate than that of patients without CD146 expression. Furthermore, CD146-deficient MEFs exhibited decreased motility as a result of reversion in this cadherin switch, strongly suggesting that targeting CD146 is a potential strategy for cancer treatment. Therefore, CD146-mediated regulation of the E-cadherin-to-N-cadherin switch provides an insight into the general mechanisms of EMT as well as cancer metastasis.