Snail mediates Rab25-induced gastric cancer cell EMT and invasiveness

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Introduction: Rab25 is a member of the Rab11 subfamily and exclusively expressed in epithelial cells. As a small GTP-binding protein, Rab25 has been known to mediate recycling of proteins from the endosome to the plasma membrane. Cancer metastasis is a multi-step events including epithelial-to-mesenchymal transition (EMT). Various transcription factors mediate EMT through downregulation of E-cadherin. In the present study, we investigate whether Rab25 induces EMT transcription factors, thereby increasing stomach cancer invasiveness.

Methods: Immunoblotting, quantitative RT-PCR and immunofluorescence assay were used to examine the expression of Rab25 and EMT factors. siRNAs of Rab25, Slug and Snail were transfected to determine their role in Rab25-induced stomach cancer cell EMT and invasiveness. Transwell invasion assay were used to determine cancer cell invasiveness.

Results: Ectopic expression of Rab25 marked reduced E-cadherin expression, while Snail expression was upregulated. In addition, Rab25 significantly aggravated cancer cell invasiveness. However, silencing Snail expression by utilizing specific siRNA significantly attenuated cancer cell invasion. In addition, Rab35 induced phosphorylation of Akt and GSK-3beta. However, pharmacological inhibition of Akt and GSK-3beta marked attenuated Rab25-induced Snail expression. Further, we observed that an integrin beta1 located upstream of an Akt/GSK-3beta signaling is important for Rab25-induced Snail expression and stomach cancer cell invasion.

Conclusion: Our results show for the first time that Snail mediates Rab25-induced stomach cancer cell EMT and invasiveness through an integrin beta1/Akt/GSK-3beta signaling cascade, providing novel biomarkers, and potential therapeutic targets for gastric cancer.