Four-and-a-half LIM protein 2 promotes invasive potential and epithelial-mesenchymal transition in colon cancer

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Introduction: Cancer invasion and metastasis may be associated with the phenotype transition called epithelial-mesenchymal transition (EMT). As an adaptor for protein interactions, the four-and-a-half LIM protein 2 (FHL2) has oncogenic potential in gastrointestinal cancers. The aim of this study was to evaluate the role of FHL2 on EMT and invasion of colon cancer.

Methods: FHL2 over-expression in stable transfectants or suppression by siRNA was used. Expression of vimentin, MMP9 and E-cadherin was detected by RT-PCR, real-time PCR and western blot. The trans-activity of beta-catenin was determined by luciferase-reporter system and the detection of its downstream genes. The composition of E-cadherin/beta-catenin complex was visualised under fluorescence microscopy.

Results: FHL2 was overexpressed in colon cancer penetrating through basement membrane. FHL2 siRNA inhibited while FHL2 over-expression promoted invasion capacity of cancer cells. FHL2 expression was inducible by TGF-beta and FHL2 mediated TGF-beta induced vimentin expression. Over-expression of FHL2 increased while FHL2 siRNA suppressed the expressions of vimentin and MMP-9. Furthermore, FHL2 siRNA suppressed the trans-activity of beta-catenin and inhibited the expressions of its downstream genes survivin and cyclin D1 through modulating the phosphorylation of beta-catenin. FHL2 siRNA increased E-cadherin expression and the presentation of membrane-associated E-cadherin/beta-catenin complexes.

Conclusion: We conclude that FHL2 promotes EMT of colon cancer through modulating the organisation of E-cadherin/beta-catenin complex and may facilitate the invasion or metastasis of colon cancer.

Human cardiac Kv4.3 channels are regulated by protein tyrosine kinases

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Introduction: The transient outward K^+ current I_{to} (encoded by Kv4.3) plays an important role in the phase 1 rapid repolarisation of cardiac action potentials in the heart. Modulation of I_{to} by intracellular signal transduction is largely unknown.

Methods: The present study was designed to determine whether hKv4.3 channel (α-subunit of human cardiac I_{to}) is regulated by protein tyrosine kinases (PTKs) in HEK 293 cells stably expressing human Kv4.3 gene using a whole-cell patch-clamp technique, immunoprecipitation and western blot.

Results: It was found that human cardiac Kv4.3 current amplitude was remarkably inhibited by the broad-spectrum PTK inhibitor genistein (10 μM), and the inhibition was partially antagonised by the protein tyrosine phosphoatases inhibitor orthovandate (1 mM). It is interesting that the selective EGFR (epidermal growth factor receptor) kinase inhibitor AG556 (10 μM) reversibly reduced Kv4.3 current, and the inhibitory effect was almost fully countered by orthovandate. In addition, the Src-family kinase inhibitor PP2 (10 μM) also decreased hKv4.3 current and the effect was partially antagonised by orthoavanadate. Immunoprecipitation and western blot analysis revealed that tyrosine phosphorylation level of hKv4.3 channel was reduced by genistein, AG556 or PP2. Their reduction of hKv4.3 channel phosphorylation level was reversed by orthovanadate.

Conclusion: These results demonstrate that hKv4.3 channel is regulated by both EGFR kinase and Src-family kinases. EGFR and Src-family kinases favour tyrosine phosphorylation of the channel, and therefore may affect the cardiac repolarisation.