Hee Jun Cho, Arch Can Res 2017, 5:4
DOI: 10.21767/2254-6081-C1-003

EphrinB1 promotes cancer cell migration and invasion through the interaction with RhoGDI1

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Eph receptors and their corresponding ephrin ligands have been associated with regulating cell-cell adhesion and motility and thus play a critical role in various biological processes including tissue morphogenesis and homeostasis, as well as pathogenesis of several diseases. Aberrant regulation of Epinephrin signaling pathways is implicated in tumor progression of various human cancers. Here, we show that a Rho family GTPase regulator, Rho guanine nucleotide dissociation inhibitor-1 (RhoGDI1), can interact with ephrinB1 and this interaction is enhanced upon binding the extracellular domain of the cognate EphB2 receptor. Deletion mutagenesis revealed that amino acids 327~334 of the ephrinB1 intracellular domain are critical for the interaction with RhoGDI1. Stimulation with an EphB2 extracellular domain-Fc fusion protein (EphB2-Fc) induces RhoA activation and enhances the motility as well as invasiveness of wildtype-ephrinB1 expressing cells. These Eph-Fc-induced effects were markedly diminished in cells expressing the mutant ephrinB1 construct (Δ327-334) that is ineffective at interacting with RhoGDI1. Furthermore, ephrinB1 depletion by siRNA suppresses EphB2-Fc-induced RhoA activation and reduces motility and invasiveness of the SW480 and Hs578T human cancer cell lines. Our study connects the interaction between RhoGDI1 and ephrinB1 to the promotion of cancer cell behavior associated with tumor progression. This interaction may represent a therapeutic target in cancers that express ephrinB1.

Biography

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