Activation of phosphatidylinositol 3-kinase/Akt signaling by EGF downregulates membranous E-cadherin and â-catenin and enhances invasion in nasopharyngeal carcinoma cells.

Abstract

Dysregulation of E-cadherin and β-catenin function in cell-cell adhesion is common in nasopharyngeal carcinoma (NPC) and correlates with metastatic disease. In this study, we examined the role of EGF-activated phosphatidylinositol 3-kinase (PI3K)-Akt signaling in E-cadherin and β-catenin regulation. We found that reduced membranous E-cadherin and β-catenin expression was positively correlated with Akt phosphorylation in NPC tissues. EGF treatment disrupted cell-cell adhesion and resulted in mesenchymal morphological features in NPC cell lines (TW01, TW04, and TW06). Western blot analysis showed that the E-cadherin protein level was partially reduced in TW04 cells only and the β-catenin levels were not considerably affected upon EGF treatment. In contrast, quantitative real-time RT-PCR showed that the E-cadherin, but not β-catenin, mRNA levels were markedly reduced by EGF in all cell lines. Immunofluorescent staining revealed that E-cadherin and β-catenin appeared to be markedly reduced on the cell surface and more localized in the cytoplasm. Inhibition of PI3K by LY294002 did not abolish the EGF-induced downregulation of E-cadherin protein or mRNA in TW04 cells but moderately increased the β-catenin protein level in TW01 cells and mRNA level in TW06 cells. However, LY294002 substantially restored or increased cell surface E-cadherin and β-catenin in all EGF-treated cell lines, in concordance with the inhibition of cell morphological changes. Moreover, LY294002 significantly blocked EGF-driven cell invasion, correlating with the elevation of membranous E-cadherin and β-catenin levels. In conclusion, EGF-induced epithelial-to-mesenchymal transition may not be only dependent on downregulation of E-cadherin protein/mRNA but also on mislocalization of E-cadherin and β-catenin. The mechanisms involved may be related, at least in part, to the PI3K-Akt pathway.

Keyword: Catenin; Mesenchymal epithelial transition.