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INVOLVEMENT OF PHOSPHATIDYLINOSITOL 3-KINASE (PI3K) PATHWAY IN H-RAS-INDUCED INVASION AND MOTILITY OF HUMAN BREAST EPITHELIAL CELLS

Il-Chung Shin and Aree Moon

College of Pharmacy, Duksung Women's University, Seoul 132-714

Many studies have identified the phosphatidylinositol 3-kinase (PI3K) as a key regulator for various cellular functions including cell survival, growth and motility. We have previously shown that H-ras, but not N-ras, induces invasiveness and motility in human breast epithelial cells (MCF10A), while both H-ras and N-ras induce transformed phenotype. In the present study, we wished to investigate the functional role of PI3K pathway in H-ras-induced invasive phenotype and motility of MCF10A cells. Activation of PI3K in the parental, H-ras- and N-ras MCF10A cells was examined by detecting phosphorylation of Akt, a downstream molecule of PI3K, by Western blot analysis. Marked activation of Akt was detected not only in H-ras MCF10A cells but also in non-invasive/non-motile N-ras MCF10A cells at comparable levels. We then further investigated the functional significance of PI3K activation in invasion and motility by using known PI3K inhibitors, LY294002 and wortmannin. Treatment of LY294002 and wortmannin significantly inhibited invasive phenotype and motility of H-ras MCF10A cells, suggesting that the activation of PI3K pathway is not sufficient, but may be required for H-ras-induced invasion and motility. Prominent downregulation of MMP-2 and MMP-9 were observed in H-ras MCF10A cells treated with LY294002 in a dose-dependent manner. The results provide evidence that PI3K pathway is critical for H-ras-mediated upregulation of MMPs in MCF10A cells, resulting in phenotypic conversion of non-invasive MCF10A cells to an invasive phenotype. In order to study the molecular mechanisms under PI3K effects cell invasion and migration, we further investigate activation of ras downstream effector molecules, MAPKs, treated with PI3K inhibitors.

Keyword : PI3K,H-ras,invasion,motility