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A Role of Phosphatidylinositol 3-Kinase(PI3K)pathway in H-ras-induced Invasive Phenotype and Motility

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We have previously shown that H-ras, but N-ras, induces an invasiveness and cell motility in human breast epithelial cells (MCF10A), while both H-ras and N-ras induce transformed phenotype. It has been recently shown that phosphatidylinositol 3-kinase (PI3K) plays an important role on cell migration. In the present study, we wished to investigate the functional role of PI3K in H-ras-induced invasive phenotype in MCF10A cells. The activation of PI3K was examined by detecting phosphorylation of Akt, a downstream molecule of PI3K, by Western blot analysis. We show that phosphorylated Akt level was upregulated both in H-ras MCF10A cells and N-ras MCF10A cells comparing to the parental MCF10A cells while the amount of Akt was equal in the parental, H-ras- and N-ras MCF10A cells. The data indicate that activation of PI3K is not sufficient for invasiveness and motility since PI3K is also activated in the non-invasive and non-motile N-ras MCF10A cells. We investigated the functional significance of PI3K activation in invasion and motility by using PI3K inhibitors, LY294002 and wortmannin. Treatment of LY294002 and wortmannin significantly reduced invasive phenotype and motility of H-ras MCF10A cells, suggesting the requirement of PI3K activation for H-ras-induced invasion and motility. We then examined the effect of the PI3K inhibitors on matrix metalloproteinase(MMP) expression. Treatment of LY294002 inhibited secretion of MMP-2 and MMP-9 in a dose-dependent manner in H-ras MCF10A cells. The possible role of Rac1 in H-ras-induced invasive phenotype in MCF10A cells are currently under investigation.