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Roles of PI3K and Rac Pathways in H-ras Induced Invasion and Motility

Ilchung Shin, Seonhoe Kim and Aree Moon
College of Pharmacy, Duksung Women's University, Seoul 132-714, Korea

Phosphatidylinositol 3-kinase (PI3K) and Rac play important roles that regulate cellular functions including cell survival and migration. In the present study, we investigated the functional roles of PI3K and Rac1 pathways in H-ras-induced invasive phenotype and motility of MCF10A cells. Akt, a downstream molecule of PI3K, was effectively activated not only by H-ras but also by N-ras, suggesting that the activation of PI3K pathway is not sufficient to induce metastatic potential of MCF10A cells. Inhibition of PI3K pathway by treatment of LY294002 and wortmannin, known PI3K inhibitors, significantly reduced invasiveness, motility and secretion of MMP-2/-9 in H-ras MCF10A cells. The data suggest that the activation of PI3K pathway may not be sufficient but is required for H-ras-induced invasion and motility. We then asked the functional role of Rac pathway in H-ras-induced invasion and migration. Prominent activation of Rac1 was shown only in H-ras-activated cells but not in N-ras-activated MCF10A cells. Functional significance of H-ras-activated Rac1 pathway in invasiveness and cell migration was evidenced by studies using a dominant-negative (DN) construct of Rac1. Blocking Rac1 pathway significantly inhibited the H-ras-induced invasiveness and motility. We also show that the activation of downstream effector molecules, p38 MAPK and ERKs, were inhibited in DN Rac1 transfectants. This study reveals the Rac as a key-signaling molecule differently regulated by H-ras and N-ras, leading to H-ras-specific cell invasive and migratory phenotypes.
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