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ACTIVATION OF p38 MITOGEN-ACTIVATED PROTEIN KINASE IN H-Ras MCF10A CELLS: ROLE IN H-Ras-INDUCED CELL MOTILITY

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One of the most frequent defects in human cancer is the uncontrolled activation of the ras-signaling pathways. We have previously shown that H-ras, but not N-ras, induces an invasiveness and motility in human breast epithelial cells (MCF10A), while both H-ras and N-ras induce transformed phenotype. Since migration plays a crucial role in invasive, we examined motility of MCF10A cells transformed with H-ras or N-ras. We show that cell motility was increased by H-ras, but N-ras suggesting that H-ras-induced invasive phenotype may be mainly due to enhanced cell motility. It has been recently shown that p38, a member of the mitogen activated protein (MAP) kinase family, is important for cell migration. We wished to investigate the functional role of p38 MAP kinase in H-ras-induced invasive phenotype. We show that p38 is prominently activated in H-ras MCF10A cells comparing to the parental MCF10A cells or N-ras MCF10A cells, while no significant difference was found in the activation of stress-activated protein kinase-1/c-Jun N-terminal protein kinase (SAPK-1/JNK). Extracellular signal-regulated protein kinase (ERK)-1,2 were activated in both H-ras and N-ras MCF10A cells. To assess the functional significance of H-ras-activated p38 in invasion and migration, we examined the effect of SB203580 and dominant-negative p38 (DN p38). Treatment of SB203580, an inhibitor of p38, reduced invasive activity and motility of H-ras MCF10A cells. H-ras MCF10A cells were transfection with dominant-negative p38 but not dominant-negative JNK-1 inhibited cell migration. These results suggest a possible involvement of p38 in H-ras-induced invasiveness/motility.