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**RAS SIGNALING IN INVASION AND MOTILITY OF MCF10A  
HUMAN BREAST EPITHELIAL CELLS**

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Ras expression has been suggested as a marker for tumor aggressiveness of breast cancer including the degrees of invasion and tumor recurrence. Expression of H-, K-, and N-ras is regulated in a tissue-specific manner and during development, indicating that ras proteins may have different cellular functions. In MCF10A human breast epithelial cells, we show that H-ras, but not N-ras, induces invasive phenotype while both H-ras and N-ras induce transformed phenotype. Matrix metalloproteinase (MMP)-2 is more likely involved rather than MMP-9 in H-ras-induced invasiveness. Since migrative capacity is a prerequisite for cell invasion through the basement membrane, we asked if H-ras also promotes cell motility more effectively than N-ras in MCF10A cells. Here, we show that cell motility was greatly increased by H-ras, but not by N-ras, suggesting that H-ras-induced invasive phenotype involves enhanced cell motility as well as induction of matrix degrading enzyme expression. In this study, we investigated whether H-ras and N-ras differentially regulate ras effector pathways critical for cell motility and invasive phenotype. While neither H-ras nor N-ras activated c-Jun N-terminal protein kinase(JNK)-1, both H-ras and N-ras effectively activated extracellular signal-regulated protein kinase(ERK)-1,2. Importantly, prominent activation of p38 mitogen-activated protein kinase (MAPK) was shown only in H-ras-activated cells but not in N-ras MCF10A cells. Functional significance of H-ras-activated p38 in invasiveness and cell motility was evidenced by studies using a chemical inhibitor of p38, SB203580, and a dominant negative construct of p38. While inhibition of JNK-1 activity had no effect on H-ras-induced MCF10A cell invasion and motility, the inhibition of the ERK pathway using a chemical inhibitor PD98059 or dominant negative mutant of MEK-1, an activator of ERKs, significantly reduced H-ras-induced invasion and migration. We also provide evidence that p38 and,

to a lesser degree, ERKs, are critical for H-ras-mediated upregulation of MMP-2. Taken together, the present study suggests that H-ras-induced activation of both p38 and ERK results in a more invasive and motile phenotypes of human breast epithelial cells, whereas N-ras activation of ERKs is not sufficient for these phenotypic changes.

keyword : invasion, motility, ras, MAPK