【P-57】

Activation of Rac-MKK3/6-p38 Pathway is Critical for H-Ras-Induced Invasion and Migration of Breast Epithelial Cells

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Human tumors frequently exhibit constitutively activated Ras signaling which contributes to the malignant phenotype. Mounting evidence suggests unique roles of the ras family members, H-ras, N-ras and K-ras, in normal and pathological conditions. In an effort to dissect distinct ras-isoform-specific functions in malignant phenotypic changes, we previously established H-ras- and N-ras activated MCF10A human breast epithelial cell lines. Using these we showed that p38 kinase is a key signaling molecule differentially regulated between H-ras and N-ras, leading to H-ras-specific induction of invasive and migrative phenotypes (Cancer Res. 63, 5454-5461, 2003). The present study is to further investigate H-ras- and N-ras-mediated signaling pathways and to unveil how these pathways are integrated for regulation of invasive/migrative phenotypic conversion of human breast epithelial cells. Here we report that Rac-MKK (MAP kinase kinase)3/6-p38 pathway is a unique signaling pathway activated by H-ras leading to the invasive/migrative phenotype. In contrast, Raf-MEK (MAPK/ERK kinase)-ERK and PI3K (phosphatidylinositol 3-kinase)-Akt pathways, which are fundamental to proliferation and differentiation, are activated by both H-ras and N-ras. Here, we provide evidence for cross-talk among the Rac, Raf, and PI3K pathways critical for regulation of MMP-2 and MMP-9 expression and invasive phenotype. Taken together, the present study elucidated the role of Rac-MKK3/6-p38 pathway leading to H-ras-specific induction of malignant progression in breast epithelial cells, providing implications for developing therapeutic strategies for mammary carcinoma to target ras downstream signaling molecules required for malignant cancer cell behavior, but less critical for normal cell functions [Supported by a grant for Leading Researchers (041-E00036) from Korea Research Foundation].

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