[PC3-3] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Transforming Growth Factor-β (TGF-β) Induces Invasion and Migration of MCF10A Human Breast Epithelial Cells

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Transforming growth factor (TGF)-β, a hormonally active polypeptide found in normal and transformed tissue, is a potent regulator of cell growth and differentiation. In this study, we examined the effect of TGF-β on invasion and motility of MCF10A human breast epithelial cells. TGF-β induced migration and invasive phenotype of the parental MCF10A cells in a dose-dependent manner. Activity of MMP-2 promoter was increased by TGF-b, suggesting that the TGF-β-induced invasive phenotype may possibly be mediated by MMP-2 rather than MMP-9. TGF-β-stimulated invasive and migratory properties were decreased by inhibition of the p38 MAPK and ERK pathways by SB203580 and PD98059, respectively. We show that TGF-β induces prominent morphological changes of MCF10A cells which was also abolished by SB203580 and PD98059. The present study suggests that TGF-β-induced cell migration and invasion as well as morphological changes involves activation of both p38 MAPK and ERK pathways and is associated more closely with the expression of MMP-2 rather than MMP-9. [Supported by the Korea Food and Drug Administration Grant (KFDA-03092-LIF-000)]

[PC3-4] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Roles of PI3K and Rac pathways in H-ras induced invasion and motility

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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. [Supported by a Korea Health 21 R&D, Ministry of Health and Welfare (02-PJ1-PG10-20801-0001) grant]

[PC3-5] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

The two-tiered activation of JNK1 prolongs cell survival prior to induced apoptosis

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The c-Jun N-terminal kinase (JNK) plays essential roles in apoptosis and cell survival. Because apoptosis is promoted by blocking the MEK kinase1-mediated activation of JNK1, we tested whether JNK1 plays dual roles in apoptosis. We show here that JNK1 activity is differentially up-regulated in a two-tiered fashion by specific mechanisms during taxol- or ginsenoside Rh2-induced apoptosis. The early phase of JNK1 activation, but not