J-1

A novel gene DRG9 positively regulates NF-κB activity through the interaction with NIK and TRAF2

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The transcription factor NF-κB is a crucial mediator of linking inflammation and immunity to cancer development and progression by regulating cell proliferation, apoptosis, angiogenesis and metastasis. Sustained NF-κB activation has been described in various human malignant tumors. We previously identified a novel zinc finger protein DRG9, whose expression is regulated by NF-κB activity, using genomics and proteomics approaches. Here, we described that DRG9 activates NF-κB activity by direct interaction with TRAF2 and NIK. The expression of DRG9 was induced by various stimuli such as TNF-α, IL-1α, PMA and hydrogen peroxide in several human cancer cell lines, Furthermore, DRG9 is up-regulated in several human tumor tissues including human gastric tumors. The forced expression of DRG9 into several cancer cells induced the NF-κB activity and increased phosphorylation of p65/RelA, p38, IKKα and induced p100 processing, but not IκB degradation. Furthermore, coimmunoprecipitation experiments revealed that DRG9 directly interacted with TRAF2 and NIK, and overexpression of dominant-negative form of NIK or TRAF2 significantly suppressed the DRG9-induced NF-κB activity. These findings suggest that DRG9 could be a potential target in NF-κB signaling pathway.

J-2

A role of p-AKT on epithelial-mesenchymal transition (EMT) in oral cancer

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Epithelial-mesenchymal transition (EMT) is an important process during development and oncogenesis by which epithelial cells acquire fibroblast-like properties and show reduced intercellular adhesion and increased motility. Also, the process of EMT plays a pivotal role in the conversion of early stage tumors into invasive malignancies, and has been shown to be regulated by the transcriptional factor, Snail. Recently, activation of the phosphatidylinositol 3' kinase (PI3K)/AKT axis is emerging as a central feature of EMT. However, it is unclear whether the phosphorylation of AKT regulate the expression of snail in oral cancer cell underwent EMT. To investigate a role of p-AKT in EMT, we assessed the effects of inhibiting p-AKT activity in oral squamous cancer cells (KOSCC-25B) using PIAs, structurally modified phosphatidylinositol ether lipid analogues (PIAs). PIAs decreased phosphorylation of a number of downstream targets of AKT, such as extracellular signal regulated kinase (ERK), glycogen synthase kinase 3beta (GSK-3beta) and NF-kB. These findings suggest that future therapies based on p-AKT inhibition may provide more effective strategy to control tumor cell invasion and metastasis.

J-3

Aberrant expression of the FGFR2 gene associated with epigenetic modification in human gastric carcinomas

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Aberrant DNA hypermethylation of gene promoters is a major mechanism associated with inactivation of tumor-suppressor genes in cancer. In a previous report, we have identified identical somatic mutations in FGFR2 that cause carniosynostosis syndromes in gastric carcinomas (Cancer Res. Jang et al. 2001). Here we have found that FGFR2 is frequently down-regulated (>50%) in gastric carcinoma cells. We also found that CpG islands at FGFR2 was extensively hypermethylated in gastric carcinoma cells. Our results indicate that FGFR2 in addition to their potential role in skeletal dysplasias, play an important role in tumorigenesis.

J-4

Activating HIF-1alpha is critical for LPA-induced VEGF expression in ovarian cancer cells

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Lysophosphatidic acid (LPA) plays an important role in mediating cell proliferation, survival and tumor invasion and angiogenesis. This bioactive phospholipid at the concentration in ascitic fluid stimulates the growth of malignant ovarian tumors by increasing the expression of vascular endothelial growth factor (VEGF). In the present study, we investigated whether LPA activates hypoxia inducible factor-1 (HIF-1), a key transcriptional complex in tumor progression and metastasis, thereby increasing the expression of VEGF. LPA induced expressions of VEGF and HIF-1alpha in OVCAR-3 cells. Importantly, we found that siRNA-induced reduction of HIF-1alpha expression significantly attenuated VEGF expression by LPA. Taken together, our results demonstrate for the first time that LPA induces VEGF via HIF-1alpha activation, and reveal a critical role of HIF-1alpha in LPA-induced cancer cell proliferation and angiogenesis [This study was supported by the Korea Science and Engineering Fund through the Cancer Metastasis Research Center (CMRC) at Yonsei University]