Characterization of a Novel IQGAP1-ADRα2 axis as a Target of Norepinephrine in Lung Cancer

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Background: Lung cancer is a leading cause of cancer death worldwide with few personalized treatment options. IQGAP1 is a signaling oncoprotein implicated in lung cancer, but its mechanism is poorly defined. In a yeast screen, the neurotransmitter/hormone norepinephrine (NE) was identified as an inhibitor of IQGAP1 in cell proliferation. As the GPCR Adrenergic Receptor α-2a (ADRα-2a) is a known NE target, its link to IQGAP1 and NE utility in lung cancer therapy was investigated.

Objectives: Decipher the NE-IQGAP1-ADRα2 interplay in human lung cancer.

Methods: Western Blot was used to quantify ADRα-2a and IQGAP1 protein levels in several lung cancer cell lines. MTT assay was used to determine proliferation inhibition of lung cancer cell line and identify the NE IC50 dose. qRT-PCR was employed to measure NE effects on IQGAP1 and ADRα-2a mRNA levels in human cancer cell lines and WT and iqgap1-/- mouse embryonic fibroblasts (MEFs). Wound healing assays were used to measure the NE effects on cell migration capacity of lung cancer cells.

Results: ADRα-2 and IQGAP1 were differentially expressed in the different lung cancer cell lines. NE significantly reduced the ADRα-2 mRNA in normal but not lung cancer cells and insignificantly affected its level in WT MEFs. By contrast, in iqgap1-1- MEFs, NE appeared to increase ADRα-2 mRNA levels, suggesting that IQGAP1 influences ADRα-2a mRNA expression and that NE effects require IQGAP1. Interestingly, NE significantly reduced IQGAP1 mRNA in WT MEFs explaining the lack of effect on ADRα-2a. NE affected migration differently among lung cancer cell lines, suggesting a more individualized approach to developing future NE-based therapy.

Conclusion: IQGAP1 appears to negatively regulates ADRα-2a expression and can serve as an NE target in lung cancer.

