Characterization of the Novel IQGAP1-Adrenergic Receptor Pathway in Lung Cancer

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Lung cancer is the leading cause of cancer death for both men and women making up almost a quarter of all cancer-related death in the United States. The IQ-motif containing Ras GTPase-activating-like (IQGAP1) protein is a ubiquitously expressed protein in humans. IQGAP1 is a signaling scaffold involved in regulating various cellular functions ranging from organization of the actin cytoskeleton, transcription, and cellular adhesion to regulating the cell cycle and secretion. Chronic activation or inhibition of IQGAP1 both leads to a myriad of diseases, including cancer and diabetes. We employ a pharmacogenetic approach to define mechanisms of IQGAP1 in such diseases and identify potential therapeutics. Our studies revealed that yeast cells lacking IQGAP1, the homolog of human IQGAP1, had diminished cell growth when treated with norepinephrine (NE), suggesting that NE works through IQGAP1. The Alpha-2A-Adrenergic receptor (α-2ADR) is a known target of NE that we recently found differentially expressed in various lung cancer cell lines and interacts with IQGAP1. To begin characterizing this pathway, we determined dose effect of NE on proliferation of human lung cancer cells and identified an optimal dose (IC50) of NE. Next, we evaluated the effect of that dose on the gene expression levels of the two proteins and a downstream transcription factor, Nuclear Respiratory Factor 1 (NRF1), comparing response of lung cancer cells with normal lung epithelia by qRT-PCR. Our results showed that while NE significantly downregulated the α -2ADR mRNA in normal cells, it caused a slight increase in some cancer cells. Our ongoing research will examine the effect of NE on protein levels and localizations in lung cancer and IQGAP1 mutant cells, as well as on the activity of signaling components downstream of IQGAP1. Our findings have significance in precision medicine.

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