Loss of somatostatin receptor 2 expression reduces small cell lung cancer growth and alters cellular metabolism

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Small cell lung cancer (SCLC) is a high grade poorly differentiated neuroendocrine carcinoma of the lung responsible for ~15% of diagnosed lung cancers and up to 25% of lung cancer deaths. Treatment paradigms in small cell lung cancer have not changed significantly in the last 20 years. Advances in targeted therapies for SCLC are sorely needed. Somatostatin receptors (SSTR) are neuroendocrine associated G protein-coupled receptors associated with multiple tumor types and which have effects on cell cycling, angiogenesis, apoptosis, and growth factors. They canonically signal by inhibition of adenylate cyclase, calcium influx, and act through downstream MAPK and Akt as well as other downstream kinases. We evaluated SSTR2 expression by IHC staining and western blotting of multiple cell lines and tumor tissues and found high expression in multiple neuroendocrine lung carcinomas including classical and variant SCLC lines. Given the high level of SSTR2 expression found in most SCLC lines, we hypothesized that this signaling pathway stimulates growth and survival of these tumor cells. We followed these preliminary studies with an assessment of 98 SCLC patients whose tumor IHC was subdivided into high or low SSTR2 expressing tumors by continuous IHC scoring. Low SSTR2 tumors had a better prognosis with a median survival in limited disease of 36 months compared to 12 months in the SSTR2 high expressing SCLCs suggesting that SSTR2 expression has clinical relevance in SCLC progression. The hazard ratio was 0.45 with a p<0.05. This led to further experiment to interrogate the mechanism and function of SSTR2 in SCLC. We established multiple stable SSTR2 shRNA knockdown lines including bronchial carcinoid, and multiple adherent SCLC lines. SSTR2 knockdown led to up to 3 fold changes in cell viability in vitro with reduced proliferation in multiple cell culture lines and constructs as well as apoptosis in H1048 cells. Metabolic testing with Seahorse mito stress kits concurred with significant differences in mitochondrial respiration and metabolic activity in the SSTR2 knockdown cell lines with a slightly increased basal metabolic rate and a significant greater than 75% increase in maximal respiration compared to the control scrambled construct cell line. We are actively pursuing metabolic studies in SCLC and will expand this work to evaluate ADP/ATP and AMP/ATP ratios to determine if aberrant energy homeostasis may contribute to the observed cell death in this metabolically active cell population. Collectively, this data brings new interest to SSTR2 signaling as a pathway target for therapy in a subset of SCLC and suggests potential metabolic targets in SCLC.

An epigenetic switch leads to EMT memory in chronic inflammation in non-small cell lung cancer

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Metastases are the major causes of death in cancer patients. Prevention and therapy against metastatic or dormant tumor cells have achieved limited success due to gaps in our knowledge regarding the underlying mechanisms. Dysregulated inflammation is associated with the development and progression of lung cancer. Lung cancer patients with increased levels of inflammatory mediators or inflammatory cells have poorer outcomes. It has been shown that inflammatory cytokines in the tumor microenvironment can promote cancer metastasis and facilitate formation of stem-like malignant cells. However, the mechanisms of these effects in lung cancer have not been fully understood. Recently, we have found that a subset of NSCLC cells undergo epithelial-to-mesenchymal transition (EMT) in the presence of cytokines including IL-1β, TNF-α and TGF-β (within 7 days). This occurs concomitantly with increased cell migration and invasion. Surprisingly, chronic exposure to these inflammatory cytokines leads to EMT memory, referring to the phenomenon that cells are able to maintain EMT despite withdrawal of the original stimulus. Intriguingly, EMT memory cannot be induced by acute cytokine exposure and the signaling pathways (JNK/ERK) and transcription factors (fra-1/slug) mediating the acute EMT are necessary to establish but not required to maintain EMT memory. Further studies demonstrated that EMT memory is due to a dynamic alteration of histone modifications and subsequent DNA methylation during chronic IL-1β exposure. Importantly, EMT memory also allows cells to irreversibly become migratory and invasive. In a pilot study, we