dose-dependent manner and significantly extended survival of the mice.

**Conclusions:** These results provide comprehensive evidence for the oncogenic functions of L-Myc and further support the concept of targeting the gene and its related molecular pathways to intervene in SCLC. Additionally, the new approaches demonstrated in this study will facilitate functional analysis of numerous candidate genes, increasing the likelihood of determining cancer-relevant genes and pathways.

**E2F8 and its target genes as novel therapeutic targets for lung cancer**

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Lung cancer remains a major cause of cancer mortality in the world. There is a significant need to develop new strategies that provide effective treatment for lung cancer. Current study reports that targeting oncogenic transcription factors could be a potential treatment method for lung cancer. The E2F transcription factor family members have been shown to be involved in cancer development. The E2F members have been divided into transcription activators (E2F1-E2F3) and repressors (E2F4-E2F8). E2F8 with E2F7 has been known to play an important physiologic role in embryonic development and cell cycle regulation by repressing E2F1. We found that E2F8, an E2F transcription factor family member, is overexpressed in lung cancer cell lines and tumors from lung cancer patients compared with normal lung cells and tissues, as determined by immunoblotting or immunofluorescence staining in human lung cancer cells and tissues from lung cancer patients. Kaplan-Meier survival analysis showed that aberrantly overexpressed E2F8 in patients with lung cancer is associated with worse prognosis. Depletion of E2F8 inhibited cell proliferation, colony formation, invasion and tumor growth in vitro and in vivo, while growth of normal cells was not affected by the loss of E2F8. In addition, depletion of E2F8 induced substantial DNA damage in cancer cells but not in normal cells. Moreover, targeting E2F8 using its specific siRNAs and morpholino-modified antisense dramatically suppressed tumor growth in vivo studies using mouse models, including s.c. xenograft in nude mice, syngeneic mouse lung cancer model, and a transgenic lung cancer mouse model. To identify genes regulated by E2F8, we performed microarray analyses using human lung cancer cell lines (NCI-H1975, H441, and H520) and Affymetrix Human Genome Arrays. Bioinformatical analyses revealed that knockdown of E2F8 deregulated gene sets involved in regulation of transcription, cancer progression, chromatin organization, regulation of immune system, glutamate receptor signaling, and cell surface receptor signaling. Further analysis of E2F8 binding motif using chromatin immunoprecipitation (ChIP) assays combined with sequencing (ChIP-Seq) method, we identified genome-wide distribution of 204 E2F8 binding sites. From the microarray analysis and ChIP-Seq assay, we identified the UHRF1 (ubiquitin-like PHD and RING domain-containing 1), critical for DNA replication of cancer cells, as one of the E2F8 target genes. In conclusion, we report that E2F8 is overexpressed in lung cancer and is required for the growth of lung cancer cells. The E2F8 knockdown significantly perturbed genes involved in the DNA replication pathway in cancer cells. These findings provide evidence that E2F8 is a novel therapeutic target for lung cancer treatment.

**Rare but poor prognosis of TERT promoter mutation in non-small cell lung cancer patients**

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The mutation in the promoter region of telomerase reverse transcriptase (TERT) and telomere length have been focused in various cancers. In present study, the frequency and clinical characteristics of TERT promoter mutation and telomere length were studied in non-small cell lung cancers (NSCLC). TERT promoter mutation and telomere length were analyzed in 188 patients by using sequencing and real-time PCR, respectively. The TERT promoter mutation rate was 2.2% (4/188) of NSCLC and it was associated with regional lymph node invasion (p < 0.001) and poor differentiation (p = 0.060). Telomere length was not associated with TERT promoter mutation and it divided into high and low groups by median value (3.04). Telomere length was shorter in males (p = 0.058) and smokers (p = 0.008). Survival analyses showed a poor prognosis of NSCLC with TERT promoter mutation (p < 0.001). Multivariate survival analyses demonstrated that TERT promoter mutation was associated with poor overall survival (p = 0.045). These data demonstrated TERT promoter mutation was not frequent in NSCLC, however, it might have a potential value for prognostic factor in NSCLC.
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**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 stage 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.

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**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...