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

Sin-Aye Park, Jong Woo Lee, James Platt, Joann Sweasy, Peter Glazer, Roy Herbst, Jaseok Peter Koo Yale Cancer Center, Yale School of Medicine, New Haven, CT

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 analysis of data from a public database 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

Jung-Soob Jung,1 Dong-Sun Kim,2 Won-Jin Park,1 Hyunsu Lee,1 In-Jang Choi,1 Jae-Yong Park,2 Jae-Ho Lee1 Keimyung University School of Medicine, Daegu, Korea, 2Kyungsung National University, Daegu, Korea

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.