**The emerging role of deubiquitinating enzyme USP13 in lung cancer plasticity**

The emerging role of deubiquitinating enzymes in lung cancer plasticity Abstract Lung cancer is characterized by a high degree of genetic and molecular heterogeneity. Lineage plasticity has emerged as a source of intratumoral heterogeneity and drug resistance, resulting in poor prognosis and treatment failure. The molecular mechanisms driving lung cancer plasticity remain unclear. Ubiquitin-Specific Peptidase 13 (USP13), a deubiquitinating enzyme, is one of the most amplified genes in lung squamous cell carcinoma (LUSC). We developed a USP13 knockin overexpressing mouse model in KrasLSL-G12D/+; Trp53fl/fl (KP) background (KPU mice). USP13 overexpression resulted in aggressive tumorigenesis and a shortened survival in Kras/Trp53- driven lung cancer. Notably, while KP mice developed lung adenocarcinoma (LUAD), KPU mice developed LUSC and LUAD. LUSC in KPU mice faithfully recapitulated the key pathohistological, molecular features, and cellular pathways of human LUSC. Bulk RNA sequencing analysis showed that KPU tumors were heterogeneous and enriched in lineage reprogramming pathways including basal cell signaling, stem cell pluripotency, and epithelial mesenchymal transition (EMT). Using cell-type-restricted adenoviral Cre to target cells expressing surfactant protein C (SPC) or club cell antigen 10 (CC10), we identified bronchiolar secretory club cells as the predominant cell origin of LUSC. USP13 altered the levels of lineage transcription factors such as TTF-1 and SOX2 in club cells during early tumorigenesis. Altered expression of these factors reinforced the fate of CC10+ club cells to squamous carcinoma development rather than adenocarcinoma. In addition, USP13 directly acted on the K48-linked ubiquitination of cMyc and increased its protein stability, contributing to the elevation of squamous gene expression (SOX2, CK5, P40) in the primary mouse and advanced human lung cancer cells. These results revealed that USP13 promotes lineage plasticity in club cells during the early stage of cancer development and drives reprogramming into LUSC. We also showed a molecular association between USP13 and EMT pathway. Notably, irrespective of cell origin, USP13 overexpression enhanced EMT marker expression including N-cadherin, SNAI1, and ZEB1, promoting cell migration and invasion. USP13 increased tumorigenic and metastatic abilities of lung cancer cells in 3D organoid culture and syngeneic mouse models. Collectively, our research highlights the pivotal significance of USP13 in unleashing lineage plasticity during lung cancer progression, suggesting the potential role of deubiquitinase enzymes in regulating lineage plasticity, which may lead to novel therapeutics for treating lung cancer.