1. No.

   2020G001

2. Title

   Molecular Mechanisms on Small Cell Lung Carcinogenesis

3. Period

   2020-2024

4. Summary

   In this study, we studied molecular mechanisms on neuroendocrine (NE) differentiation of the lung and carcinogenesis of small cell lung cancer (SCLC). As to NE differentiation, we performed single cell RNA sequence analysis to know molecular changes during NE differentiation of Club cells and found novel transcription factors involving in NE differentiation of the lung. We have developed a genetically engineered mouse model (GEMM) for SCLC using *Tp53(-)*; floxed *RB1*; floxed *Hes1* mice, in which many SCLC precursor lesions. We analyzed molecular alterations of club cells associated with loss of each gene using single cell RNAseq. We further developed an organoid lung carcinogenesis model by *in vitro* culture of isolated fetal airway epithelium of the SCLC GEMM. Interestingly, lung cancers arising from the cultured epithelium, the histological type of the induced lung cancer from the explant was often non-small cell carcinoma. We examined the cultured lung cancer cells with various histological types, which are gained by organoid carcinogenesis, by RNA sequence, ATAC sequence and CUT & Tag methods to know the involvement of epigenetics to determine histological types and to clarify molecular motifs regulating histological types. Through these experiments, we focused on the Hippo-Yap pathway and Runx2/3. We applied *Yap1*/*Wwtr1(Taz)* knockdown to squamous cell carcinoma.

   By silencing the Yap pathway, we were able to observe the development of SCLC from squamous cell carcinoma. This research has enabled us to analyze the development mechanism of SCLC from a multidimensional perspective, from genes to epigenetics, and has provided important basic knowledge for elucidating the molecular mechanism of SCLC in the future.