In vivo CRISPR Screening Unveils Important Tumor Suppressor Gene in Lung Tumorigenesis

A joint research team led by Dr. JI Hongbin at the Shanghai Institute of Biochemistry and Cell Biology (SIBCB), Chinese Academy of Sciences (CAS) and Dr. CHEN Liang at the Institute of Life and Health Engineering, Jinan University has provided a systematic CRISPR screening of tumor suppressor genes (TSGs) *in vivo* and demonstrated that UTX functions as the important epigenetic regulator in lung tumorigenesis.

Cancer genomic studies have provided a comprehensive spectrum of thousands of potentially important genetic alterations of TSGs. Except for a few well-studied TSGs, most of these genetic aberrations still remain to be functionally validated and characterized. Given the emergence of a tremendous amount of cancer genomic alterations, traditional methods, such as the genetically engineered mouse models (GEMMs), clearly could not meet the demand. The clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 system has been proven to be a powerful genome editing tool in recent years. Thus, this type of somatic gene knockout technique makes it feasible to efficiently and systematically identify potential TSGs *in vivo*.

In this current study, researchers first generated a list of potential TSG candidates based on integrative bioinformatics analyses. Taking advantage of the CRISPR/Cas9-mediated screening *in vivo* technique, multiple TSGs including *Utx*, *Ptip*, *Acp5*, *Acacb*, and *Clu* were identified for their contribution to lung cancer malignant progression. All these genes were frequently down-regulated in human lung cancer specimens and significantly associated with lung cancer patient survival. Importantly, conditional knockout of the histone demethylase *Utx* dramatically accelerated lung tumorigenesis in the $Kras^{LSL\text{-}G12D/+}$ mouse model. Further evidences demonstrated *Utx* knockout increased H3K27me3 level potentially through EZH2 upregulation. Moreover, researchers found a treatment strategy for UTX-deficient lung tumors. The EZH2 inhibitor JQEZ5 preferentially suppresses the growth of *Utx*-knockout lung tumors, providing therapeutic implication for human lung cancer with KRAS mutations exhibiting low UTX level.

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