Uncovering the role of KDM6A in epigenetic regulation of subtype plasticity in small cell lung cancer

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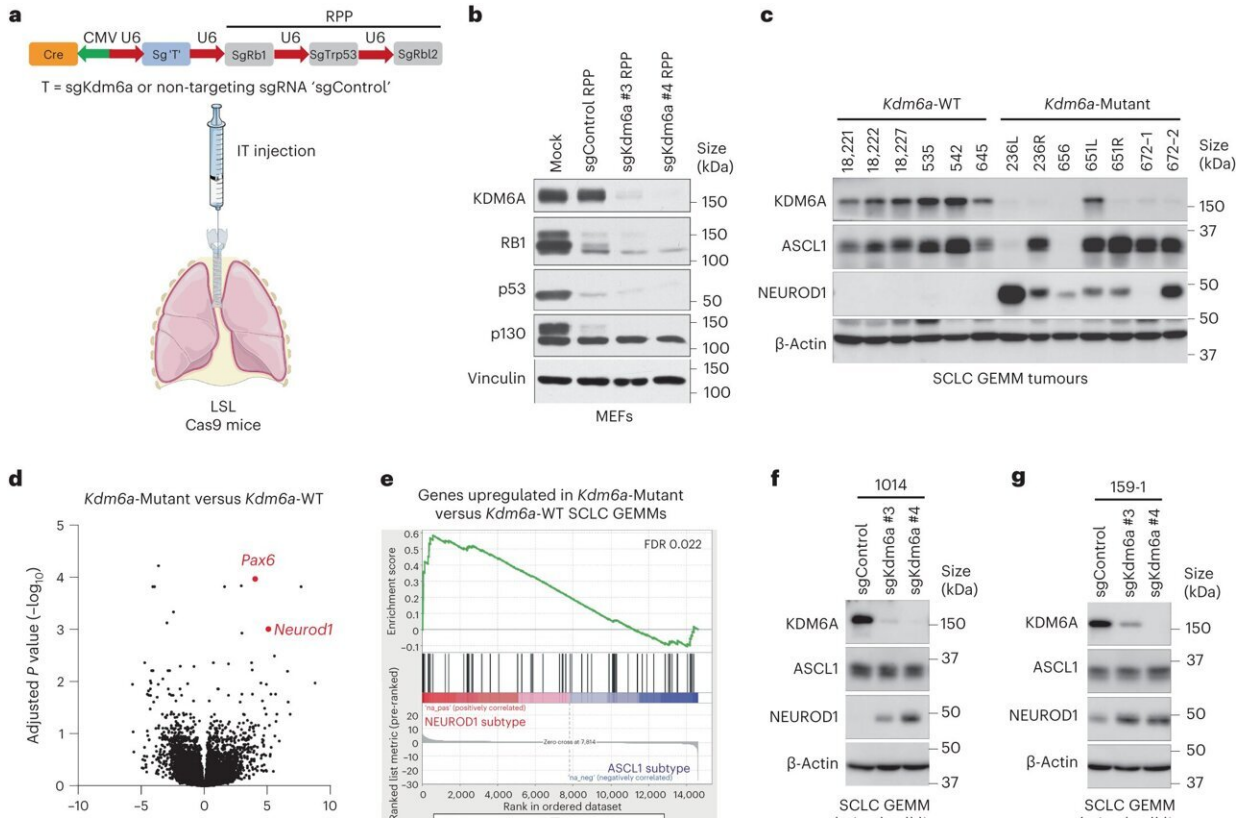

KDM6A inactivation in an autochthonous SCLC mouse model promotes NEUROD1 expression leading to SCLC tumors that express both ASCL1 and NEUROD1. a, Schematic of the adenovirus used for IT injection into the lungs of LSL-Cas9 mice to generate autochthonous SCLC tumors that are Kdm6a inactivated or Kdm6a WT. RPP: sgRb1, sgTrp53, sgRbl2; sg "T": sgKdm6a or sgControl (non-targeting sgRNA). b, Immunoblot analysis of MEFs expressing

Cas9 infected with the sgControl RPP, sgKdm6a #3 RPP or sgKdm6a #4 RPP adenoviruses as indicated. c, Immunoblot analysis of SCLC lung tumors formed in LSL-Cas9 mice injected with sgControl RPP (Kdm6a-WT) or sgKdm6a RPP (Kdm6a-Mutant) adenoviruses. d, Volcano plot of differential expression analysis from RNA-seq data comparing Kdm6a-Mutant versus Kdm6a-WT from tumors in c. n = 7 Kdm6a-Mutant tumors, n = 6 Kdm6a-WT tumors. FDR P values adjusted for multiple comparisons after log transformation are shown. Neurod1 and one of its target genes Pax6 are highlighted in red. e, Gene set enrichment analysis (GSEA) of RNA-seq data from ASCL1 and NEUROD1 human SCLC tumors of the upregulated genes in Kdm6a-Mutant versus Kdm6a-WT GEMMs (Supplementary Table 2). FDR q value adjusted for multiple comparisons is indicated. f,g, Immunoblot analysis of two mouse SCLC cell lines derived from Kdm6a-WT mice 1014 (f) and 159-1 (g) transduced with two independent Kdm6a sgRNAs or a non-targeting control (sgControl) and maintained in culture for 30 days post-transduction. h,i, Immunoblot analysis of two human ASCL1-positive SCLC cell lines, NCI-H69 (h) and DMS79 (i), nucleofected with Cas9 RNP containing a Kdm6a sgRNA or a non-targeting control (sgControl). Cells were then treated with cisplatin (1 μM) or DMSO for 3 days. j, Multiplexed IF for ASCL1 and NEUROD1 from three Kdm6a-WT and three Kdm6a-Mutant mouse SCLC lung tumors indicated. Scale bars, 50 μm. Credit: *Nature Cell Biology* (2023). DOI: 10.1038/s41556-023-01210-z

In a new study published in *Nature Cell Biology*, researchers used CRISPR/Cas9 in vivo somatic engineering to make mouse models of small cell lung cancer (SCLC) that either expressed KDM6A (KDM6A-WT) or were inactivated for KDM6A (KDM6A-Mutant). KDM6A is an epigenetic modifier that is mutated in human SCLC.

Researchers discovered a link between mutations in the KDM6A gene and the development of diverse subtypes within SCLCs. The loss or alteration of the KDM6A gene seems to play a role in promoting this diversity within the tumors.

Researchers found a mechanism involving KDM6A, which directly interacts with neuroendocrine genes. This interaction leads to the maintenance of a chromatin state that promotes the activation of these neuroendocrine genes, potentially playing a role in regulating processes related to the nervous and endocrine systems.

Mutations in epigenetic drivers like KDM6A can lead to plasticity in different subtypes of SCLC. A surprising observation is that a single mutation can have a profound impact on these subtypes.

Although KDM6A is likely not a good drug target directly, as its loss promotes intra-tumoral heterogeneity, this work suggests that identifying epigenetic drivers that when inhibited promote SCLC subtype plasticity toward more homogenous molecular subtypes may be effective strategies to combine with other therapeutic approaches that selectively target a subtype vulnerability.

Future studies will focus on identifying other druggable epigenetic drivers that may oppose the function of KDM6A or when inhibited block intra-tumoral subtype heterogeneity.

More information: Leslie Duplaquet et al, KDM6A epigenetically regulates subtype plasticity in small cell lung cancer, *Nature Cell Biology* (2023). DOI: 10.1038/s41556-023-01210-z

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