Friday, December 15, 2023, 12:00 p.m.
Venue

Genetic Analysis of *Kmt2d* Loss in Tumorigenesis Using Genetically Engineered Mouse Models

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The Cancer Genome Atlas Program (TCGA) has discovered multiple tumor suppressors that are commonly mutated across a variety of human cancers, such as chromatin regulators in COMPASS and SWI/SNF complexes. *KMT2D*, a histone H3K4 methyltransferase in the COMPASS complex, is frequently mutated in human lymphoma, melanoma, and epithelial carcinoma. Biochemically, KMT2D shapes the cellular enhancer landscape as the major writer of the putative enhancer mark H3K4me1. Given the critical role of cellular enhancer landscape in determining cellular lineage in embryonic development, it is unknown whether enhancer dysregulation caused by *KMT2D* loss leads lineage switch of tumor cells, which has been associated with tumor progression and therapeutic resistance in human cancers. To address these questions, we utilized genetically engineered mouse models (GEMMs) to study the impact of *Kmt2d* loss during melanoma, lung, and urothelial carcinoma development.

In a mutant *Braf*-driven melanoma, *Kmt2d* loss accelerated tumor development and caused tumor de-dedifferentiation towards a neural crest like state through the upregulation of AP-2 family transcriptional factors.

In a mutant *Kras*-driven lung adenocarcinoma model, *Kmt2d* loss accelerated lung adenocarcinoma development and caused transdifferentiation of adenocarcinoma into squamous carcinoma. Single cell multiome analysis revealed that squamous carcinoma evolved from a highly plastic cluster, which expresses both lung and gastric markers. It is inferred that squamous carcinoma evolved from adenocarcinoma because of the inability to maintain transcriptional networks critical for gastrointestinal gene expression. In a novel mutant *Pik3ca*-drive lung cancer model, *Kmt2d* loss caused lung squamous carcinoma with full penetrance from multiple cells of origin.

Phenotypic results from the GEMMs clearly demonstrate the critical role of *Kmt2d* loss in driving tumor cell lineage plasticity. This will contribute to our fundamental understanding of cancer as a disease of progressive loss of cell identity and gain of plasticity at the epigenetic level. It will also lay down solid foundation for targeting cancer from a cell identity loss perspective.

Advisory Committee:
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