**Mechanisms of epigenetic sensitization to lung cancer risk**

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Epigenetic perturbations in cancer are commonly encountered but poorly understood. We sought to understand how latent epigenetic information contributes to tumorigenesis in lung adenocarcinoma. We developed a mouse model of epigenetic sensitization in which loss of the epigenetic regulator KDM6A (UTX) in the paternal germ line in mice result in elevated lung tumor burden in offspring even when the mutant *Kdm6a* allele itself is not inherited. We hypothesized that these ‘epigenetically sensitized’ offspring carry silent epigenetic perturbations that predispose them to cancer and can interact with specific driver mutations to enhance lung tumorigenesis. Preliminary data suggests that epigenetic sensitization induced by paternal KDM6A loss enhanced overall lung tumor burden in mice carrying an activated KRAS allele (*KrasLA1*). Further, exome sequencing of epigenetically sensitized tumors revealed frequent mutations in the histone methyltransferase KMT2D (MLL4), a functional interactor of KDM6A. Correspondingly, disruptions in H3K4me1, the histone modification deposited by KMT2D, occur in the KDM6A mutant germline in regulatory regions of lung oncogenes. Ongoing work is aimed at determining if these epigenetic lesions are present in normal lung tissue and tumors of epigenetically sensitized offspring and may lower the threshold to malignant transformation. Future work will evaluate if similar signatures of epigenetic sensitization can be detected in tumors from patients with a history of familial cancer.