Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Metabolic rewiring and HIF1α accumulation upon Rnf20 loss result in lung cancer progression

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During my PhD research, I investigated the role of RNF20 loss in the initiation, development, and progression of lung cancer. Rnf20 haploinsufficiency in mice led to a marked increase in tumor incidence, which was accompanied by elevated DNA damage and a reduction in the tumor suppressors p53 and Rb1. These findings were further corroborated in vitro using control and Rnf20+/- lung epithelial cells, where transcriptomic analysis revealed significant upregulation of genes involved in cell migration, extracellular matrix organization, metabolic pathways, and the HIF-1 signaling pathway following RNF20 loss.

To explore the impact of RNF20 on cellular metabolism, I conducted metabolomic assays, which showed that Rnf20 deficiency enhances glycolytic capacity and increases TCA cycle metabolite levels. Integrating RNA-seq with metabolomic profiling, I found that the genes upregulated in Rnf20+/- cells were closely associated with glycolytic metabolism. Importantly, through Hif1α knockdown and glycolysis inhibition, I demonstrated that HIF1α mediates both metabolic reprogramming and tumor-promoting effects in the context of RNF20 loss. Mechanistically, Pol II ChIP-seq revealed that RNF20 loss promotes RNA polymerase release at HIF1α target genes and EMT markers, contributing to transcriptional activation. In contrast, ChIP-seq for H2Bub1 and H3K4me3 showed that genes downregulated upon RNF20 loss were more closely associated with loss of histone ubiquitination rather than changes in Pol II dynamics, suggesting distinct regulatory mechanisms. Further analysis uncovered that the accumulation of HIF1α upon RNF20 loss is likely due to the downregulation of RBX1, a key component of the E3 ubiquitin ligase complex responsible for HIF1α degradation. Additionally, I observed functional divergence between RNF20 and RNF40, despite their role in the same ubiquitin ligase complex, indicating distinct roles in lung cancer progression.

In summary, my study demonstrated that RNF20 acts as a tumor suppressor in lung cancer, and its expression is significantly reduced in patient samples, correlating with poor clinical outcomes. RNF20 loss drives lung tumorigenesis through epigenetic deregulation of metabolic genes, particularly via HIF1α-mediated transcriptional and metabolic reprogramming. However, the key question remains: what causes RNF20 downregulation in lung cancer? Given the strong link between environmental exposures such as smoking and air pollution and lung cancer risk, these factors may contribute to RNF20 suppression. Future studies aimed at understanding the regulatory mechanisms governing RNF20 expression could provide valuable insights into early detection, risk assessment, and targeted therapeutic strategies for lung cancer.