The role of the lysine-specific histone demethylase 5B (KDM5B) in epigenetic regulation in renal tubular cells

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Hypoxia interferes with the activity of histone modifying enzymes such as lysine-specific histone demethylases (KDMs). Some of these enzymes are transcriptionally upregulated by hypoxia-inducible transcription factors (HIF) pointing to a regulatory loop for balancing epigenetic homeostasis under hypoxic conditions. Until now, little is known about HIF-regulated histone demethylases in the kidney. However, hypoxia and HIF play important roles in acute kidney injury (AKI) and renal cancer development. We hypothesize that these pathways are significantly entangled in kidney cell damage and repair.

Exposing human renal primary tubular cells (PTC) to hypoxia or prolyl hydroxylase inhibitors (PHDi) confirmed elevated expression of several KDMs including KDM5B. KDM5B operates on the histone marks histone 3 lysine 4 tri-methylation (H3K4me3) and H3K4me2, which are enriched at active promoters. To gain more insights into a potential regulation, we generated CRISPR/Cas9-mediated KDM5B knock-out clones of cells in immortalized PTC. We observed significant increases in H3K4 methylation upon deletion of KDM5B under ambient oxygen and hypoxic conditions in western blot and genome-wide assays using Cut&Tag. These changes were accompanied by substantial transcriptomic changes. Moreover, 2D-growth of KDM5B-defective cells was changed compared to control cells indicating an important role of this enzyme in cell proliferation.

Here, we report preliminary data on the role of KDMs in controlling epigenetic and transcriptomic homeostasis in primary human tubular cells of the kidney. Future experiments will address the function of KDM5B in the setting of AKI and renal cell repair.