Effects of Inhibition of the Catalytic Domain of Histone Lysine Demethylase KDM5

John R. Horton[1,2], Qin Chen[1], Xu Liu[2], Clayton B. Woodcock[1] Xing Zhang[1,2], and Xiaodong Cheng[1,2]

Department of Molecular and Cellular Oncology, University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA (jrhorton@mdanderson.org)

[2]Department of Biochemistry, Emory University School of Medicine, Atlanta, Georgia, USA

Accumulating evidence indicates a crucial role for KDM5 family members of histone demethylases (A, B, C, and D) either as oncogenic drivers or tumor repressors (1–4). For instance, in ER+ breast cancer cells, KDM5B is overexpressed and knockdown of KDM5B in MCF7 (ER+) cells induces growth arrest through increased activity of the TGF-β signaling pathway (3). KDM5 enzymatic activities are specific for removing methyl groups from trimethylated and dimethylated histone 3 lysine 4 (H3K4me3/me2) – a chromatin mark that is associated with regions of accessible chromatin, including gene promoters and enhancers. Our laboratory's recent studies, as well as that of others, on the development of KDM5 inhibitors have shown that inactivation of KDM5 enzymatic activity by small molecule inhibitors suppresses the growth of subtypes of human cancer cells, suggesting that KDM5 inhibition could be exploited for cancer treatment.

Our laboratory has made some interesting observations with the examination of crystal structures of the catalytic domain of KDM5A with over twenty small molecule inhibitors (5,6) in combination with *in vivo* experiments. The KDM demethylases belong to a larger family of dioxygenases that contain Fe(II) and α-ketoglutarate as cofactors in their active site. Thus far, we have looked at inhibitors that displace α-ketoglutarate and partially utilize the metal for their binding to the enzyme. The lessons learned give potential strategies which hopefully can be utilized in the successful design of selective and potent epigenetic inhibitors of KDM5. We hope that in the long term such an inhibitor could be developed into a new cancer therapeutic.

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