Targeting the histone demethylome

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The reversible □□-methylation of lysyl side-chains in histones, catalyzed by distinct classes of methyl transferases and demethylases, has emerged as an important mechanism in orchestration of chromatin state, gene regulation and DNA repair. Despite the progress achieved over the past years in understanding regulation and interactions of these enzymes, chemical tools to interrogate their biological functions, especially for the histone demethylases, are lacking. This impasse is addressed in a public-private partnership that aims to develop potent, selective and cell-active chemical probes to investigate chromatin modification.

Covalent modifications of histone tails play essential roles in mediating chromatin structures and epigenetic regulation. JmjD3 and UTX are Jmj-type histone demethylases, belong to the KDM6 subfamily, and catalyze the removal of methyl groups of methylated lysine 27 on histone 3 (H3K27), a critical mark to promote polycomb mediated repression and gene silencing. The importance of these demethylase enzymes in e.g. cancer biology or immunology has been shown by molecular genetic approaches, however it is unclear if their roles are mediated by protein-protein interaction in transcriptional complexes or by their enzymatic function.

Here we report the first highly selective and potent small molecule enzyme inhibitor for the KDM6 histone demethylase subfamily that is used to probe cellular functions of H3K27 demethylases. The inhibitor is active in HeLa cells and promotes a dose-dependent increase of global H3K27 methylation in both JmjD3 transfected or untransfected cells. This presentation will provide insight how the KDM6 enzymes control critical pathways in inflammation, oncology and development.

Our results resolve the ambiguity associated with the H3K27 demethylase function of KDM6 members, demonstrate the relevance and pharmacological tractability of JmjD3 and UTX, and provide a possible path to selective pharmacological intervention across the Jmj family of histone demethylases.