

The histone demethylase KDM6A in urothelial cancer: A combined matter of activity, interaction and localization?

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Regulating gene activity by post-translational modification of histone tails and DNAs a crucial and tightly controlled matter. Consequently, deregulation of control elements can lead to cancer and other developmental diseases.[1] Numerous epigenetic modifiers and proteins involved in proliferation, differentiation and cell cycle regulation are involved as control elements. Among them, the histone demethylase KDM6A removes the repressive K27me_{2/3} marks on histone 3, thus enhancing chromatin accessibility. Loss and inactivation of KDM6A (often in combination with associated proteins) promotes uncontrolled proliferation and might indirectly affect cell cycle control through a deregulated retinoblastoma protein network. In urothelial tissue, KDM6A appears as one of the most prominent urothelial cancer (UC) genes.[2] Most likely, inactivating mutations which occur predominantly in the catalytically active domain (JmjC) of KDM6A[3] found in UC could either influence the activity, localization and/or interaction of KDM6A. Although being of high medical relevance, lack of structural information and knowledge considering interaction of full-length KDM6A poses a challenge for a comprehensive understanding of the system. In this study, we created point mutations naturally found in UC as well as truncated variants mimicking deletion mutations to further understand the structure-function relationship of KDM6A. An ELISA-based demethylase activity assay was established to assess the activity of KDM6A variants. Their localization was also studied by super-resolution microscopy (SIM and STED). To address interaction of KDM6A with database-predicted binding partners, colocalization analysis based on super-resolution imaging was applied. Additionally, co-IP in combination with Western Blots was used to support the findings. Deeper understanding of the system will eventually benefit medical research on urothelial carcinoma and any other tumor type linked to high mutation rates of KDM6A.

[1]: Schulz, W. A. et al. The Histone Demethylase UTX/KDM6A in Cancer: Progress and Puzzles. *Int J Cancer* **145**, 614-620 (2019).

[2]: Lang, A. et al. Contingencies of UTX/KDM6A Action in Urothelial Carcinoma. *Cancers* **11**, 481 (2019).

[3]: Sengoku, T. et al. Structural basis for histone H3 Lys 27 demethylation by UTX/KDM6A. *Genes Dev* **25**, 2266–2277 (2011).