Targeting histone lysine demethylase KDM4A in Aggressive Variant Prostate Cancer
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ABSTRACT
Background: Despite advancement in treatment, prostate cancer remains the second leading cause of death among men. Prostate cancer patients treated with androgen deprivation therapy (ADT) develop with potent second-generation anti-androgen inhibitors such as enzalutamide and abiraterone inevitably develop therapeutic resistance and progress to castration-resistant prostate cancer (CRPC). Neuroendocrine prostate cancer (NEPC), which has a median survival of 7 months after initial diagnosis, represents one of the most lethal forms of CRPC. In contrast, castration-resistant prostate adenocarcinoma, the more common subtype of CRPC, has a median survival of 13 to 31 months depending on the organ sites of metastasis. NEPC is characterized by attenuated androgen receptor (AR) signaling, the expression of neuroendocrine lineage markers (e.g., synaptophysin), uncontrolled hyperproliferation, and widespread metastasis (e.g., bone, liver, and lung). De novo NEPCs are rare (2%-5%); the majority arises as a mechanism of resistance from prostate adenocarcinoma treated with potent AR pathway inhibitors (ARPIs). The widespread use of ARPIs in non-metastatic CRPC and hormone-sensitive metastatic tumors has led to an increase in the incidence NEPC. Due to the lack of life-prolonging systemic therapies, there is an urgent need to better understand the mechanisms underlying the pathogenesis of NEPC.

Recent evidence suggests that epigenetic dysregulation is a hallmark of NEPC. Among the various epigenetic regulatory mechanisms, histone lysine methylation, which is balanced by histone lysine demethylase (KDM) enzymes, is an important role in development and cancer, including prostate. However, whether KDMs play any role in NEPC progression is unknown.

METHODS: By perturbation of KDM4A expression (overexpression, knockdown and knockout) and inhibition of KDM4A functions with small-molecule inhibitors in multiple model systems in vitro and in vivo, we will determine the function of KDM4A and the potential regulatory pathway of KDM4A in NEPC.

RESULTS
KDM4A is overexpressed in NEPC

Figure 1. KDM4A is overexpressed in NEPC

Figure 2. Loss of function of KDM4A hinders growth of NEPC cells in vitro and reduces tumor burden and delay NEPC appearance in vivo

Figure 3. KDM inhibitor suppresses NEPC progression in vivo

Figure 4. (Continued). GC3552 suppressed progression in vivo

CONCLUSIONS

Our findings demonstrated that histone lysine demethylase KDM4A plays an undeniable role in the progression of NEPC in prostate cancer through regulating MYC and the downstream pathways. Targeting KDM4A could potentially be an effective therapeutic option for combating NEPC. In the future, we will further delineate and confirm the detailed mechanism of which KDM4A regulates MYC, be it by directly binding to the MYC promoter or its function in a transcriptional co-activator (or both). It will also examine the potential to leverage the combination of silencing KDM4A by either RNAi or QC3552 treatment with chemotherapy, with the aim to reduce side effects of chemotherapeutic drugs.

REFERENCES