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N6-adenosine methyltransferase complex regulator ZC3H13 deletion as malignant prognosis factor in prostate cancer

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Prostate Cancer (PCa) stands as the most prevalent malignant condition in men and the primary cause of death in developed nations. Despite advancements in diagnostic techniques and treatments, more than 20% of patients still advance to an aggressive form of the disease with limited treatment options. This underscores the imperative need to discover new molecular pathways involved in PCa development.

Our objective was to identify the function of novel m^6A regulators in PCa and develop innovative therapeutic approaches through a combination of in silico screening, utilizing various genomic and expression datasets, CRISPR-ko and CRISPRa technology, pre-clinical models replicating metastatic PCa, and patient samples. Substantial evidence suggests that the epitranscriptome plays a pivotal role in tumorigenesis. The m^6A deposition process is overseen by a methyltransferase complex consisting of METTL3/METTL14 as the catalytic units, with additional non-catalytic components continuously emerging. Additionally, m^6A can be removed by FTO and ALKBH5 demethylases.

Our research reveals that the epitranscriptomic regulator ZC3H13 is deleted in 15% of PCa and 12% of metastatic Castration-Resistant Prostate Cancer (mCRPC) patients, a pattern correlated with recurrence, progression, and unfavorable prognosis. Through gain- and loss-of-function assessments, we have demonstrated that ZC3H13 governs the proliferation, migration, and invasiveness of PCa cells in vitro, impacting vital cellular processes such as adhesion and EMT (Epithelial-Mesenchymal Transition). This observed phenotype can be ameliorated by the pharmacological inhibition of FTO demethylase. Furthermore, the knockout of ZC3H13 increases the metastatic potential of PCa cells in pre-clinical models, and this phenotype can be rescued both, by FTO inhibition and by METTL3 overexpression. Mechanistically, our findings indicate that ZC3H13 stabilizes the core methylation complex both in vitro and in patient samples, resulting in reduced m^6A deposition levels upon the deletion of ZC3H13.

In summary, our study identifies ZC3H13 as a significant prognostic factor in PCa. Our data suggests that targeting m^6A deposition levels in PCa by inhibiting m^6A mRNA demethylases, either alone or in conjunction with other therapeutic agents, presents a promising strategy for inhibiting tumor growth and curtailing metastatic invasion.