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Nsd2 is an actionable mechanism in metastatic CRPC progression

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INTRODUCTION: Metastasis is a complex process that culminates progressive molecular alterations of cancer cells, which allow them to escape the confines of the tumor, survive during dissemination, and ultimately reside at distant sites, wherein requisite adaptive changes ensue in the new microenvironment. Therefore, it would be most informative to study the biological processes and molecular mechanisms underlying metastatic progression as they occur in the context of the whole organism *in vivo*. However, inherent challenges in accessing primary tumors and their metastases from cancer patients make it difficult to study *de novo* metastasis formation. Moreover, most *in vivo* studies of metastasis have utilized transplantation models wherein cells or tumors are implanted into host organisms, usually immune-deficient ones. While such investigations have advanced our understanding of mechanisms of metastasis and have elucidated factors that promote organ tropism, they may not ideally model the cell-intrinsic mechanisms of *de novo* metastatic progression. Analyses of genetically engineered mouse models (GEMMs) can overcome these obstacles, since they enable access to tumors and their resultant metastases as they arise *de novo* during cancer progression in the whole organism.
OBJECTIVES: In the current study we aimed at identifying actionable, cancer cell intrinsic mechanisms of metastatic progression in prostate cancer
METHODOLOGY: We have exploited genetic lineage tracing of prostate cancer cells in a mouse model of fully penetrant metastatic CRPC. We have performed transcriptomic profiling and computational cross-species interrogation of regulatory networks to identify driver of the metastatic phenotype, which have then been functionally validated and targeted using small molecule inhibitors in preclinical trials. The potential value of the candidate drivers has been assessed in human prostate cancer specimens and publicly available datasets.
RESULTS: Transcriptome analysis from primary tumors of non-metastatic, pre-metastatic and post-metastatic prostate primary tumors and distant metastasis to lungs, livers and lymph nodes reveal that a metastatic signature capturing the most dramatic changes in gene expression is present in advanced primary tumors that have already spread to distant organs. Interrogation of prostate cancer regulatory networks with this mouse derived metastatic signature as well as with a human metastatic signature publicly available reveal an striking enrichment for epigenetic master regulators, including DNA methyltransferases, histone modifying enzymes and chromatin remodelers. An 8-gene signature is able to stratify patients based on clinical endpoints like time to biochemical recurrence and prostate cancer survival. Functional validation of these 8-genes demonstrates the nuclear hormone interacting protein NSD2 is a prostate cancer vulnerability. In particular, silencing of NSD2 reduces viability and clonogenicity of prostate cancer cells and increases survival of tumor bearing mice. Further, NSD2 is significantly overexpressed in the most aggressive prostate cancer phenotypes, including lethal NeuroEndocrine Prostate Cancer (NEPC). Finally, preclinical assays with a potent and selective NSD2 inhibitor MCTP39 results in significant reduction of tumor growth *in vivo* and viability and clonogenicity *in vitro*.
CONCLUSIONS: Our study shows that *NSD2* is an actionable target for treatment of advanced prostate cancer, as well a functional driver of prostate cancer metastasis. Notably, the role of *NSD2* in cancer has been shown to be dependent on its activity as a histone methyltransferase for the histone H3 di-methyl K36 (H3K36me2), which supports targeting *NSD2* activity in cancer. Furthermore, the activity of *NSD2* as a histone methyltransferase has been shown to be coordinately regulated by EZH2, a major component of the histone methyltransferase polycomb repressive complex 2 (PRC2), which is also dysregulated in prostate cancer. Additionally, in

multiple myeloma, *NSD2* has been shown to be a regulator of DNA damage response that impacts resistance to chemotherapy. These previous studies combined with our current preclinical evidence showing that inhibition of *NSD2* activity inhibits prostate tumor growth *in vivo* suggests that combination therapy targeting *NSD2* together with inhibition of PI-3 Kinase, AR, EZH2, and/or DNA repair mechanisms, all of which are themselves targetable and highly relevant for prostate cancer, may prove to be efficacious for treatment of metastatic prostate cancer. We further proposed that these combination treatments could be evaluated in co-clinical assays using the *NPK* mouse model described herein.

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