

Trop2 as a Novel Driver and Therapeutic Target for Metastatic Castration-Resistant Prostate Cancer with Neuroendocrine Phenotype

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Background:

Advanced prostate cancer, whether present at the time of diagnosis or arising after treatment of localized disease, responds to androgen deprivation, but invariably fails and recurs as castration resistant prostate cancer (CRPC). Heavily treated tumors, particularly those treated with secondary hormone therapies, frequently acquire a neuroendocrine phenotype (NEPC), which currently accounts for 10-20% of CRPC. NEPC is commonly characterized by downregulation or loss of androgen receptor (AR) and is thus not responsive to androgen deprivation therapies, expression of neuroendocrine markers, and an aggressive clinical course, making it the most lethal and currently untreatable subset of prostate cancer.

Methods:

We used tissue microarrays to assess the correlation of Trop2 levels with clinical outcomes. CRISPR/Cas9 technology and lentiviral infection were used to achieve Trop2 gene deletion and Trop2 overexpression in prostate cancer cells. To evaluate the role of Trop2 in prostate tumorigenesis, we utilized in vitro functional assays such as colony formation, tumorsphere formation, and cell migration assays. In vivo tumor growth and metastasis were assessed by subcutaneous xenograft, intracardiac injection and spontaneous subcutaneous metastasis tumor models. Whole proteomic profiling was utilized to identify Trop2 downstream targets and mediators. To target Trop2, we utilized antibody-based strategies and small molecule inhibitors of downstream mediators.

Results:

Here, we identify that cell surface glycoprotein Trop2 is significantly elevated in CRPC and NEPC and represents a novel driver of metastatic CRPC with neuroendocrine features. Trop2 overexpression increases tumor growth and drives prostate cancer metastasis to diverse organs including bone and liver. Furthermore, inhibition of Trop2 or deletion of the *TROP-2* gene significantly slows prostate cancer growth and metastasis of prostate cancer cells.

Conclusions: Our findings establish Trop2 as a novel driver and therapeutic target for metastatic CRPC with neuroendocrine phenotype and suggest that inhibition of Trop2 may represent a new therapeutic strategy for CRPC and NEPC.

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