CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP130651

Project Title:
MAPK4 Activates AR and Promotes Castration-Resistant Prostate Cancer

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

Prostate cancer is the most common cancer and the second leading cause of cancer death in American men. Activated Androgen Receptor (AR) is essential for the growth/survival of human prostate cancer. Therefore, androgen-ablation therapy is a standard therapy for advanced and metastatic prostate cancer. However, most initially regressed prostate cancer will relapse and become castration-resistant prostate cancer (CRPC). Interestingly, most CRPCs maintain functional AR; therefore, AR remains a valid therapeutic target for CRPC. However, even with the best available androgen-blockage agents, including the recently FDA-approved Zytiga, there is still no cure for CRPC. Hormone-independent AR activation may account for this. We found a protein (MAPK4) with no previous known function in cancer. We found that MAPK4 strongly induced AR expression and activated AR independent of hormone in prostate cancer cells. In addition, inhibition of MAPK4 greatly inhibited AR expression and activity. We also found that MAPK4 expression is strongly correlated with AR expression and activity in human CRPC tissues. Therefore, we hypothesize that MAPK4 may be a novel therapeutic target for CRPC. In the proposed studies, we will (1) determine how MAPK4 induces androgen-independent AR activation in prostate cancer (2) determine how MAPK4 regulates castration-resistance growth of prostate cancer in xenograft models (3) develop a novel transgenic mouse model to study MAPK4 biology in prostate tissue. These first-in-field studies will provide key experimental data on whether MAPK4 can serve as a novel therapeutic target for CRPC. Therefore, the proposed studies will have direct impact on the understanding and treatment of human prostate cancer.