CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170330

Project Title:
A novel GRK3-EZH2 regulatory pathway in prostate cancer progression

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Health Science Center at Houston

Lay Summary:

Prostate cancer (PCa) is a leading cause of cancer-related deaths for men. Androgen deprivation therapy (ADT) is the treatment of choice for advanced and metastatic PCa. Most patients respond to this treatment initially but the disease invariably recurs and becomes ADT-resistant. Frequently associated with ADT resistance is the emergence of neuroendocrine prostate cancers (NEPC) that have a poor prognosis with no effective treatment. With the recent introduction of potent ADT into clinic, the incidence of NEPC is expected to rise significantly. The objectives of this proposal are to obtain critical new insights in NEPC biology that is poorly understood, to identify new drug targets and to facilitate the development of effective therapy for NEPC. Through our recent studies, we have found a new pathway that is activated by ADT and is critical for ADT-induced development of NEPC. This pathway centers around a druggable enzyme called GRK3 that we have found to be overexpressed in human metastatic PCa and essential for the growth of aggressive PCa cells. Here, we propose to elucidate the mechanisms through which this new GRK3 pathway promotes ADT-induced NEPC development, and to determine the association between the activity of this pathway and patient prognosis. Given the essential role of GRK3 for PCa progression, we will test whether suppressing GRK3 will be an effective approach to inhibit NEPC growth in preclinical mouse models. We will delete GRK3 in PCa genetically engineered mouse models to study its pathophysiological role in PCa progression. We have identified several potent GRK3 inhibitors that kill NEPC cells in culture. We will further test them in xenograft models of human NEPC cells and patient tissues. Results from this study will substantially expand our understanding of NEPC development and therapy resistance. It will also establish GRK3 as a valuable drug target and identify its inhibitors as drug candidates for preventing and treating aggressive PCa.