Award ID:
RP150648

Project Title:
GATA2 and steroid receptor coactivator-2 cooperate with androgen receptor in prostate cancer progression and androgen resistance

Award Mechanism:
Multi-Investigator Research Awards (Version 2)

Principal Investigator:
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Entity:
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Lay Summary:

Prostate Cancer (PC) is typically dependent upon androgen hormones such as testosterone that interact with the androgen receptor (AR) expressed in PC cells. Drugs designed to block AR function or block androgen synthesis in the body are currently being used in the clinic to treat PC. However, PC frequently becomes resistant to these therapeutic interventions, leading to castration-resistant prostate cancer (CRPC), a very aggressive cancer that leads to death. Importantly, CRPCs still express AR regulated genes, suggesting that the AR axis remains active. CRPC achieve resistance by promoting persistent AR axis activation in several ways such as by: 1) overexpressing cell fate-determining transcription factors (e.g., GATA2) that promote AR overexpression and facilitate the formation of AR-coactivator transcriptional complexes; 2) expression of alternatively spliced and constitutively active AR variants (e.g., AR-V7/AR3) that lack the ligand-binding domain (LBD); 3) overexpression of steroid receptor coactivators (SRCs) that drive an AR target gene expression program while concomitantly promoting growth factor signaling pathways and metabolic reprogramming of CRPC tumor cells. It is of critical importance to point out that these ligand-independent mechanisms of AR activation cannot be inhibited by LBD-targeting or ligand-depleting approaches, such as treatment with enzalutamide or abiraterone, respectively. Instead, new approaches designed to attack the mechanisms enumerated above will be required to achieve more durable and effective treatments. We have found that GATA2, a member of the GATA family and already well-known as a pioneer factor for AR binding to chromatin, can directly drive AR expression. In a panel of AR-expressing PC cell lines, either disruption of GATA2 expression or inhibition of GATA2 with a small molecule inhibitor (SMI), abolished the expression of AR and blocked AR-dependent target gene expression. GATA2 disruption inhibited PC cell growth both in vitro and in vivo. Based on these results, we propose that GATA2 is a key regulator of AR expression in CRPC, and, therefore, of CRPC growth and progression. Our GATA2 SMI can suppress the transcriptional function of AR and exerted potent anticancer activity against PC in vitro and in vivo. We have found that depletion of any one of the three SRCs in hormone-dependent PC, impedes cell proliferation and AR transcriptional activity, including the AR-dependent induction of the TMPRSS2-ERG fusion gene, and enhances sensitivity to ionizing radiation. Gene amplification, point mutations, and widespread overexpression of SRC-2 have been reported in PC and are associated with increased AR transcriptional activity, metastases, and inferior clinical prognosis. CRPC cells are more sensitive,

compared to androgen-dependent cells, to the loss of SRC-2 and SRC-3 expression, and also to inhibition with SRC SMIs developed by our laboratory. These data suggest that overexpression of SRCs is a mechanism by which PC progresses to a castration-resistant state, and that targeting of SRCs can be a highly effective therapeutic approach for patients with CRPC. Here, we plan to characterize mechanisms of action of SRC-2 and/or SRC-3 SMIs in conjunction with existing GATA2 SMIs to devise a strategy to disrupt the AR signaling axis in CRPC in a distinct way. Also, because of our recent discovery of a characteristic SRC-2 dependent metabolic reprogramming that occurs in CRPC, therapeutic strategies designed to target fatty acid metabolism in these tumors will be pursued. AR-mediated transcription hinges on its ability to recruit primary and secondary coactivators and to interact with the GATA2 pioneer factor. Because no prior structural information exists for the intact AR-coactivator complex, we propose to use cryo-electron microscopy (cryo-EM) to determine the structure of an active complex of DNA-bound AR complexed with SRC-2, GATA2 and a secondary coactivator (p300). We will employ this cryo-EM based approach to resolve the structure of full length AR and AR-V7 variant in a complex with ARE-DNA, GATA2 and CoAs. These data are expected to reveal, for the first time, fundamental insights into the structure of the whole AR protein and the receptor's interactions with GATA2 and its primary CoAs – and 'direct interacting' SMIs of coactivators. In summary, AR is a key driver of prostate cancer, even in the CRPC state, and even after the acquisition of resistance to second-line hormonal therapies. The persistence of AR activity via both ligand-dependent and ligand-independent (particularly, in constitutively active AR splice variants) mechanisms highlights the unmet need for alternative approaches to block AR signaling in CRPC. We propose two 'first-in-field' approaches to target the AR axis beyond the AR LBD, at the level of 1) the SRC-AR coactivators and 2) by disrupting AR expression and function through the inhibition of GATA2.