TARGETING THE PI3K/Akt/mTOR/SREBP1 SIGNALING AXIS IN CASTRATION RESISTANT PROSTATE CANCER

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Despite therapeutic advances with docetaxel, abiraterone, and enzalutamide, prostate cancer progression to lethal castration-resistant PC (CRPC) remains a major clinical problem. High-fat diet (HFD) and obesity are strongly associated with PC incidence and progression, while increased lipogenesis and uptake of exogenous lipids are linked to PC aggressiveness. Interestingly, emerging studies suggest that in African American (AA) PC patients who already have 1.6 times higher PC incidence and 2.6 times higher mortality from PC than Caucasian males - the AR and PI3K/Akt signaling pathways are even more active, frequently resulting in even greater increase in lipid metabolism. The p160 steroid receptor coactivators (SRCs) are potent oncogenic drivers that are overexpressed/overactivated in PC and mediate the transcriptional activity of several PC-promoting transcription factors (TFs). Previously, we reported that SRC-2, which is overexpressed in metastatic PC, can drive glutamine-dependent de novo lipogenesis via activating SREBP1. Furthermore, transcriptomic profiling of BCM PC patients identified SREBP1 and MNX1, an androgen-induced TF, as selectively upregulated in AA PC. Androgen and the PI3K/Akt signaling pathway can positively stimulate MNX1 to activate of SREBP1 and result in upregulation of FASN and other lipogenic genes and overall increase in lipid metabolism in PC cells. We are currently exploring inhibition of PI3K/Akt/mTOR/p160 SRC/SREBP1 axis via direct inhibition of p160 SRCs and via inhibition of activation of SREBPs. We demonstrate that two classes of compounds (p160 SRC inhibitors and SREBP activation inhibitors) are exciting new classes of drugs that suppress the oncogenic transcriptional and metabolic programs of CRPC cells, potently inhibit CRPC cell proliferation and migration, and ultimately inhibited PC xenograft and PDX tumor growth in vivo. Given strong rationale and preliminary data, we believe the impact of these new classes of inhibitors will extend to other tumors that are dependent on the PI3K/Akt/mTOR signaling axis.

Conflicts of Interest: Salma Kaochar is a consultant for FGH BioTech Inc.

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