Targeting GPX4 to enhance ferroptosis in supraphysiologic androgen-treated prostate cancer

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Background:

While androgen-signaling–directed strategies and other chemotherapies extend survival, at large, outcomes in metastatic castration-resistant PCa (mCRPC) remain poor. Treatment with Supraphysiological Androgen (SPA), which is clinically known as Bipolar Androgen Therapy (BAT), has been shown to inhibit the growth of certain prostate cancer types while also inducing oxidative stress. Ferroptosis, a regulated and iron-dependent form of cell death, has emerged as a promising vulnerability in androgen receptor-positive prostate cancer, especially in the context of the metabolic changes induced by SPA treatment.

Methods:

AR-positive CRPC cell lines (LNCaP, VCaP, LAPC4, 22Rv1) were treated with SPA to assess changes in ferroptosis sensitivity. Transcriptomic profiling, lipid peroxidation assays, and cellular ultrastructural analyses were used to evaluate ferroptosis hallmarks. Pharmacologic inhibition of GPX4 using RSL3 was employed to induce ferroptosis, and synergy with SPA was quantified through cell viability, ROS accumulation, and other related assays.

Results:

SPA treatment downregulated key ferroptosis defense proteins, including GPX4 and xCt, increased labile iron pools, and promoted mitochondrial ROS, lipid peroxidation, and mitochondrial changes consistent with ferroptosis. These changes sensitized CRPC cells to ferroptotic death. Combined treatment with SPA and RSL3 produced synergistic suppression of cell viability, elevated mitochondrial ROS, and growth suppression.

Conclusion:

SPA primes AR-positive prostate cancer cells for ferroptosis by disrupting redox homeostasis and suppressing protective antioxidant pathways. GPX4 inhibition synergizes with SPA to induce ferroptotic cell death, offering a mechanistically focused strategy to enhance therapeutic efficacy in CRPC. This combination warrants further investigation as a potential approach to overcome treatment resistance.

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