

**Divergent Roles of SPOP and CHD1 in ACSL4 Regulation Reveal Context-dependent
Vulnerabilities for Targeting Ferroptosis**

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Running Title: Targeting ferroptosis in SPOP/CHD1-deficient prostate cancer

Background

Although therapeutic options for prostate cancer (PCa) have expanded over the past decade, durable clinical responses remain limited, and therapeutic resistance frequently emerges, underscoring the need for new therapeutic strategies. Ferroptosis has emerged as a promising therapeutic approach for advanced PCa; however, the genetic determinants governing ferroptosis sensitivity remain poorly understood. Recurrent SPOP mutations and CHD1 loss define a clinically distinct molecular subtype of PCa; however, how these genetic alterations cooperatively drive disease progression and inform therapeutic strategies remains incompletely understood.

Methods

Genetically engineered human and murine PCa models, organoids, and patient-derived xenografts were used to investigate the functional interaction between SPOP mutations and CHD1 loss. Integrated multiomic and functional analyses were performed to define the mechanisms underlying tumor progression and therapeutic response across preclinical models of SPOP/CHD1-altered PCa.

Results

SPOP mutations and CHD1 loss cooperatively promoted prostate tumorigenesis. CHD1 loss enhanced cholesterol biosynthesis, resulting in increased intratumoral androgen production, sustained androgen receptor signaling, and resistance to androgen deprivation in SPOP-mutant tumors. Furthermore, SPOP mutations increased sensitivity to GPX4-targeting ferroptosis inducers, whereas concurrent CHD1 loss attenuated this vulnerability through suppression of the MYC-ACSL4 axis. Importantly, pharmacological inhibition of cholesterol metabolism restored ACSL4 expression, thereby re-sensitizing SPOP/CHD1-altered tumors to GPX4-targeting ferroptosis inducers and significantly enhanced antitumor efficacy in multiple preclinical models.

Conclusions

Our findings demonstrate that SPOP mutations and CHD1 loss cooperatively shape therapeutic responses in prostate cancer through distinct metabolic mechanisms. These findings support biomarker-guided combination strategies integrating cholesterol-lowering agents with GPX4-targeting ferroptosis inducers for SPOP/CHD1-altered advanced PCa.

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Conflicts of Interest Disclosure Statement

The authors declare no potential conflicts of interest.