Investigating *SSTR1* as an Actionable Drug Target in Prostate Cancer Resistant to Androgen Receptor Signaling Inhibitors

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Background: Resistance to androgen receptor signaling inhibitors (ARSIs), such as abiraterone or enzalutamide, is a major obstacle to improving outcomes for patients with prostate cancer. We previously analyzed paired RNA-seq data generated from metastatic biopsies before and after ARSI therapy in patients with metastatic castration-resistant prostate cancer (mCRPC) and identified *SSTR1* as the most significantly downregulated gene in ARSI-resistant tumors. *SSTR1* encodes somatostatin receptor type 1, one of the five somatostatin receptors, which, as a class, mediate anti-proliferative, anti-invasive, and anti-angiogenic effects when binding to the endogenous hormone, somatostatin, or exogenous somatostatin analogues. We were motivated to study the biology of *SSTR1* in prostate cancer, particularly its relationship with ARSI-resistance and therapeutic potential. We hypothesized that *SSTR1* has anti-tumor effects in prostate cancer, and its downregulation after ARSI treatment may promote tumor growth and ARSI resistance. We further assessed *SSTR1* as a potential drug target for overcoming ARSI resistance.

Method: To assess *SSTR1* expression in mCRPC, we selected the enzalutamide-resistant 22Rv1 cells as a model for ARSI-resistant prostate cancer. To assess the effects of genetic manipulation of *SSTR1*, we generated a stable knockdown cell line using CRISPR interference and a stable lentiviral overexpression cell line and then conducted proliferation assays. We also performed RNA-seq experiments on these cell lines to understand the transcriptomic impact of modulating *SSTR1*. To assess the impact of AR signaling on *SSTR1* expression, we treated 22Rv1 cells with dihydrotestosterone (DHT) for 48 hours and measured *SSTR1* mRNA. To evaluate the therapeutic potential of targeting SSTR1, we tested pasireotide, the only FDA-approved somatostatin analogue with SSTR1 agonist activity.

Results: Incucyte experiments confirmed the anti-proliferative effects of *SSTR1* overexpression and the growth-promoting effects of *SSTR1* knockdown. RNA-seq analysis showed that EGFR signaling was the most significantly upregulated pathway after *SSTR1* knockdown, with an upregulation of *SSTR5,* potentially as a compensatory mechanism. *SSTR1* overexpression induced no significant change in *AR* mRNA but a remarkable decrease in canonical AR target genes such as *KLK3*, *STEAP1*, and *TMPRSS2*, as well as significantly downregulated FGFR signaling. DHT treatment for 48 hours did not significantly change *SSTR1* mRNA expression. Pasireotide treatment significantly suppressed the proliferation of 22Rv1 cells.

Conclusions: *SSTR1* is anti-proliferative in enzalutamide-resistant 22Rv1 cells. SSTR1 signaling impacts the expression of AR target genes and EGFR and FGFR signaling pathways. Pasireotide treatment suppresses 22Rv1 cell proliferation. Further work using additional cell lines and *in vivo* models is warranted to further investigate SSTR1 in prostate cancer, particularly as a potential drug target for overcoming ARSI resistance.

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