Small molecule- and siRNA-based targeting of scavenger receptor BI in castration resistant prostate cancer

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ABSTRACT

Background: Despite clinical benefits of existing castration-resistant prostate cancer (CRPC) treatments, patients continue to develop therapeutic resistance. Persistence of androgen receptor (AR) pathway activity is attributed to several mechanisms, including intratumoral AR agonist synthesis from the precursor, cholesterol. The high-density lipoprotein (HDL)-cholesterol receptor, scavenger receptor BI (SR-BI), is upregulated in PC and metastatic CRPC. We hypothesize targeting SR-BI can reduce cellular cholesterol availability resulting in suppressed extragonadal androgen synthesis, and induction of metabolic stress in actively dividing CRPC.

Methods: We targeted SR-BI with RNAi duplexes (SR-BI-KD) or the small molecule SR-BI antagonist, Blocker of Lipid Transport-1 (BLT-1), in steroidogenic C4-2, and AR-negative PC-3 PC models.

Results: In C4-2 cells, HDL-derived cholesterol uptake was reduced by SR-BI-KD- and BLT-1-treatment. This correlated with a 2-fold decrease in intracellular testosterone (LC-MS), and an induction of G_1/S cell cycle arrest (propidium iodide FACS analysis). SR-BI-KD-treated cells also exhibited increased cell stress assessed by an induction of autophagy (suppressed TORC activation and signaling, increased LC3-I/II conversion and increased clusterin expression), alongside induction of senescence (morphology, SA-β-Gal activity). Addition of an exogenous steroid, DHEA, did not reverse these responses, indicating that restoring steroid-mediated androgen signaling is insufficient to overcome treatment-induced cell stress. Co-treatment of SR-B1 antagonized cells with chloroquine to block autopahgasome acidification resulted in cytotoxicity. SR-BI-KD or BLT-1 treatment alone induced robust cell death in PC-3 cells (Live/Dead FACS analysis).

Conclusions: These results indicate that targeting SR-BI and depriving PC cells of HDL-derived cholesterol impacted more than androgen availability and suggests that SR-BI is important for cholesterol uptake needed for cellular homeostasis. The ability to impede the growth of both androgen-responsive and -independent PC growth highlights SR-BI as a potential novel therapeutic target in CRPC.

Conflict of Interest: Authors have no conflicts of interest to declare.

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