Commentary

Novel lipid mediators contributing to androgen receptor therapy resistance in prostate cancer

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In this article of EBioMedicine, Lin M-H et al. [1], used lipidomics analysis on prostate cancer (PCa) patients undergoing androgen/androgen receptor targeting therapies to show that ceramide and its downstream signaling lipid, Sphingosine 1P (S1P) contribute to Androgen receptor signaling inhibitor (ARSI) resistance and implicating the role of sphingosine kinase (SPHK) inhibitors for breaking ARSI resistance in patients. Clinical data have previously shown elevated ceramide levels are associated with reduction in progression free survival and overall survival in patients undergoing second-generation androgen receptor targeting therapies in PCa patients with advanced metastatic disease. The study also suggests that ceramide signaling pathway genes are elevated in castrate resistant metastatic prostate cancer (CRPC) patients and may mediate ARSI resistance.

CRPC is a lethal disease, which often develops in patients undergoing androgen ablation therapies. Two classes of drugs are currently used in clinic: one against androgen synthesis, abaterone and another class directly targeting androgen receptor, enzalutamide, apalutamide and darolutamide. These two classes of drugs are highly efficacious for treating advanced and metastatic disease, and provide considerable therapeutic benefit for patients with both castrate naïve and resistant phases of prostate cancer[2,3]. Despite their efficacy in containing disease progression, failure of these therapies is inevitable leading to ARSI resistance. Understanding the molecular mediators contributing to ARSI resistance predominantly focused on tumor genetic alterations and transcriptome analysis, which identified several pathways contributing to resistance development. AR genetic alterations are common in ARSI resistant tumors, where it is often overexpressed leading to persistent activation. Additionally, a truncated AR which lacks the ligand binding domain has also been enriched in ARSI resistant tumors [4], AR mutations which often lead to agonistic activity of enzalutamide and AR bypass pathway involving aberrant regulation of glucocorticoid receptor (GR) in resistant cells [5]. Modelling enzalutamide resistance with prostate cancer cells identified a noncanonical AR binding site to CpG islands and upregulation of CpG dinucleotide protein CXXC5 and its binding partners suggesting novel mediators of ARSI resistance [6]. Additional pathways activated in ARSI include PI3K-AKT-mTOR, DNA damage repair pathway, Wnt-b-catenin and neuroendocrine differentiation pathways [7,8] which contribute to epithelial-mesenchymal transition, angiogenesis and DNA repair, leading to multiple metastases.

The current study, by Lin M-H et al., identifies ceramide and its downstream lipid S1P contributing to ARSI resistance. Ceramide is a sphingolipid, which is converted into sphingosine 1-phosphate through sphingosine kinase (SPHK), which induces cellular signals through cell surface S1P receptor [9]. S1P-S1P receptor axis mediates cancer cell proliferation, migration and metastases [10]. Interestingly, the enzymes involved in the ceramide-S1P axis are upregulated in metastatic PCa contributing to elevated ceramide synthesis and enhanced S1PR signaling in tumors. These events along with tumoral AR gene aberrations contributed to shorter duration of ARSI resistance. To explain the relationship between Ceramide-S1P axis and enzalutamide action, authors conducted several in vitro investigations. These studies show that blocking ceramide conversion to S1P through SPHK1 inhibitors enhanced enzalutamide action on cancer cells through ER stress and lipogenesis. Lipidomic analysis shows that combined SPHK1 and enzalutamide treatment caused accumulation of lipids through the activation sterol regulatory-element binding protein 1 leading to lipotoxicity-induced cell death, suggesting that SPHK1 inhibitors can sensitize tumor cell death through AR inhibiting therapies.

Several unanswered questions remain. The study is based on one cohort from prostate cancer patients comprised mainly of Caucasians in Australia and independent studies with cohorts from other countries and ethnicities are needed to validate the findings. Lipidomic analysis of patient serum samples were complemented with LC-MS quantitation for different ceramide lipids but a more precise quantitation is required for precise quantitation of ceramides in samples. The functional significance of ceramide species on tumor cells is not addressed, which will unravel the biological significance of elevated ceramides observed in patients. SPHK1 inhibitors are currently in clinical use and testing these inhibitors in animal models of bone metastases and relevant PDX models with enzalutamide combination.
will provide biological significance of altered ceramide-S1P axis on ARSI resistance in tumors. Since the sphingolipid pathway involves several members, including cell surface S1P receptor, a comprehensive analysis of other enzymes/receptors involved in the regulation may provide further insights into significance of the sphingolipid pathway on ARSI resistance.

The findings presented in this article identifies elevated ceramides in plasma samples associate with ARSI resistance in prostate cancer patients. These patients have poor prognosis when androgen receptor aberrations present alongside elevated Ceramide levels. Inhibiting ceramide signaling through its downstream modulator SPHK1 sensitizes prostate cancer cells for enzalutamide. These data support the idea that SPHK1 inhibitors may sensitize prostate cancer cells to enzalutamide function by abrogating or delaying the enzalutamide resistance. Nevertheless, the study is preliminary in unraveling the sphingolipids’ role in ARSI resistance, and further studies will increase our understanding of sphingolipid function on metastatic prostate cancer progression during anti-AR therapies.

Contributors
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Declaration of Competing Interest
The author declares no conflict of interest.

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References
[1] Lin HM, Mak B, Yeung N, Huynh K, Meikle TG, Mellett NA, et al. Overcoming enzalutamide resistance in metastatic prostate cancer by targeting sphingosine kinase. EBioMedicine 2021;72:103625.
[2] de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364 (21):1995–2005.
[3] Tran C, Ouik S, Ciegg NJ, Chen Y, Watson PA, Arora V, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009;324(5928):787–90.
[4] Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Roesser JC, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014;371(11):1028–38.
[5] Arora VK, Schenlein E, Murali R, Subudhi SK, Wongvipat J, Balbas MD, et al. Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. Cell 2013;155(6):1309–22.
[6] He Y, Wei T, Ye Z, Orme JJ, Lin D, Sheng H, et al. A noncanonical AR addiction drives enzalutamide resistance in prostate cancer. Nat Commun 2021;12 (1):1521.
[7] Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161(5):1215–28.
[8] Beltran H, Prandi D, Mosquera JM, Benelli M, Puca L, Cyota J, et al. Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer. Nat Med 2016;22(3):298–305.
[9] Ogretmen B. Sphingolipid metabolism in cancer signalling and therapy. Nat Rev Cancer 2018;18(1):33–50.
[10] Pyne NJ, Pyne S. Sphingosine 1-phosphate and cancer. Nat Rev Cancer 2010;10 (7):489–503.