Commentary

Directing abiraterone metabolism: balancing the scales between clinical relevance and experimental observation

Jon K. Obst, Marianne D. Sadar

Department of Genome Sciences Centre, BC Cancer Research Centre, BC V5Z 1L3, Canada

Correspondence to: Marianne D. Sadar. Department of Genome Sciences Centre, BC Cancer Research Centre, 675 W 10th Ave, Vancouver, BC V5Z 1L3, Canada. Email: msadar@bcgsc.ca.

Comment on: Li Z, Alyamani M, Li J, *et al*. Redirecting abiraterone metabolism to fine-tune prostate cancer anti-androgen therapy. Nature 2016;533:547-51.

Submitted Jul 16, 2016. Accepted for publication Jul 22, 2016.
doi: 10.21037/tcr.2016.07.35
View this article at: http://dx.doi.org/10.21037/tcr.2016.07.35

In their recent report published in *Nature*, Li and colleagues investigate the feasibility of exploiting drug metabolism pathways to improve abiraterone treatment for castration resistant prostate cancer (CRPC). Abiraterone is a 17α-hydroxylase/17,20-lyase (CYP17A1) inhibitor, and is used in the context of androgen deprivation therapy to prevent the *de novo* generation of androgens by the tumor from cholesterol or adrenal precursor molecules. While abiraterone initially blocks androgen synthesis and prolongs survival, the disease will ultimately progress despite treatment (1,2).

Dr. Sharifi's group has previously demonstrated that one of the initial metabolites of abiraterone—Δ^4-abiraterone (D4A)—shows improved anti-tumor efficacy with respect to inhibiting androgen synthesis, as well as direct androgen receptor (AR) inhibition compared to the parental compound itself (3). The focus of their current report was to examine other downstream metabolites and determine whether they provide a positive or negative role in the context of disease progression. Additionally, the authors explored the approach of "fine-tuning" abiraterone metabolism in an effort to select for metabolites of interest, specifically D4A.

D4A is generated by metabolism of abiraterone by 3β-hydroxysteroid dehydrogenase (3βHSD) and, based upon its structure, is predicted to be a substrate for steroidal 5α-reductase (SRD5A). Using LC-MS/MS Li *et al*. confirmed when LAPC5, C4-2 and VCaP cell lines were treated with abiraterone or its metabolite D4A, that D4A was first irreversibly reduced to 3-keto-5α-abiraterone (5α-abi) or 3-keto-5β-abiraterone (5β-abi). These in turn are further metabolized by 3βHSD into their respective 3α-OH and 3β-OH congeners (4). Indeed, the authors were able to detect all six 5α- and 5β-reduced metabolites in the serum from 12 patients undergoing abiraterone treatment. 5α-reduction of steroids preserves the planar structure of biologically active androgens, while 5β-reduction renders them inactive and promotes their clearance (4-6). Therefore the authors focused primarily on characterizing the three 5α-reduced metabolites of D4A.

While D4A was able to inhibit the activities of CYP17A1, 3βHSD and SRD5A (as indicated by HPLC analysis of enzyme substrates), its 5α-reduced metabolites demonstrated a significant reduction in activity. Interestingly, while the affinity of 5α-Abi to the AR^{T877A} and AR^{WT} was comparable to D4A, the former acted as an agonist rather than exhibiting the antagonistic properties of the latter. This was confirmed by measuring mRNA transcript levels of the AR regulated gene *PSA* in both LNCaP (AR^{T877A}) and LAPC4 (AR^{WT}) cells. Additionally, 5α-Abi treatment significantly shortened progression-free survival of castrated hosts compared to controls bearing VCaP (AR^{WT}) xenografts. In light of these data, the authors postulated that resistance to abiraterone could occur through selective metabolism of its more potent metabolite D4A by SRD5A to the 5α-reduced metabolites—at least one of which demonstrated statistically significant tumor promoting activity. To test this hypothesis, abiraterone- and D4A-resistant cell lines were generated by chronically treating VCaP and LNCaP cells with respective compounds

© Translational Cancer Research. All rights reserved.

over the course of 6 months. It was shown that the resistant cell lines displayed increased SRD5A1 mRNA, protein levels, and a compensatory increase in consumption of SRD5A1 substrates compared to a control cell line. In agreement with this hypothesis, enzalutamide-resistant VCaP and LAPC4 lines did not show any difference in SRD5A1 protein or mRNA levels over the course of their generation.

Finally, the authors asked whether the levels of the D4A metabolite could be specifically increased by co-treatment with abiraterone and the dual SRD5A inhibitor dutasteride. An ongoing phase II clinical trial (NCT01393730) exploring dutasteride treatment following abiraterone allowed the investigators to directly measure the effect SRD5A inhibition had on abiraterone metabolism. As predicted, serum D4A levels increased significantly (9.96 to 18.20 nM; P=0.002) and 5α-Abi levels decreased (25.80 to 2.94 nM; P<0.001) following the addition of dutasteride to the treatment regimen. Unfortunately, no levels of any biomarkers of AR transcriptional activity (such as *PSA*) were reported in these patients. Thus the implied benefit of increasing circulating D4A lacks definitive clinical evidence.

The authors concluded that sustained AR signaling through the persistent synthesis of androgens can contribute to both CRPC and abiraterone resistance via upregulation of genes involved with steroidogenesis. Specifically, this may occur through increased SRD5A activity; modulating not only dihydrotestosterone (DHT) synthesis, but also the metabolism of the potent abiraterone metabolite D4A into one with tumor-promoting attributes. Exploiting drug metabolism may prove a powerful therapeutic tool in selectively preventing unwanted metabolites from being created, while retaining only the most potent ones.

This report is the first to examine and describe six previously unknown D4A metabolites and their effect on both androgen metabolism and tumor progression. The authors of this study are also commended on their approach of using this knowledge to specifically fine-tune abiraterone metabolism; and its potential impact on advancing CRPC therapy is recognized. While undeniably valuable as a proof-of-concept study, there is however some concern that the emphasis on D4A and 5α-Abi may be overstated. The concentration ranges of D4A (up to 10 μM) which were used to complete the HPLC experiments were significantly higher than what was reported in patient's serum (~8 nM), bringing into question the clinical relevance of some of these experiments. Specifically, while D4A is indubitably as potent as abiraterone in the context of inhibiting CYP17A1 activity in the low nM range, inhibition of 3βHSD and SRD5A1 required doses of 1 and 10 μM D4A respectively.

Similarly, the 5α-metabolites (5α-Abi and 3α-OH-5α-Abi) that the authors focused on when examining *PSA* and *TMPRSS2* mRNA transcription levels, also employed concentrations in large excess (~3 orders of magnitude) of that measured in the clinical samples (~40 and ~6 nM respectively). Additionally, even at concentrations that were up to 2000× that of 0.5 nM DHT, the potency of 5α-Abi and 3α-OH-5α-Abi on AR transcriptional activity was only fractional to that achieved with DHT. This begs to question whether metabolism of D4A to 5α-Abi is really a major contributor to abiraterone resistance compared to elimination of abiraterone (I.E. through 5β-reduction). Clearance of abiraterone and its non-functional metabolites would allow the restoration of synthesis of androgens from precursor steroids, and may play a more relevant role in clinical abiraterone resistance. This interpretation is supported by the fact that the patient data presented in this report show 5β-Abi and its 3α-OH and 3β-OH congeners are the more prevalent metabolites following abiraterone and D4A metabolism.

The importance of understanding abiraterone metabolism should not be understated, and the data presented here provide a solid foundation for examining this phenomenon. Li *et al.* describe the generation of novel metabolites and offer a validated proof-of-concept for driving selective metabolite production in the clinical setting. Further study is warranted to better combat abiraterone resistance through studying mechanisms of its metabolism. This work will hopefully shed light not only on the functionality of specific metabolites, but also on preventing their inactivation and clearance.

Acknowledgments

Funding: This work was supported by the National Cancer Institute (2R01CA105304 to M.D.S).

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Peng Zhang (Department of Urology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China).

© Translational Cancer Research. All rights reserved.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.07.35). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

Cite this article as: Obst JK, Sadar MD. Directing abiraterone metabolism: balancing the scales between clinical relevance and experimental observation. Transl Cancer Res 2016;5(S3):S529-S531. doi: 10.21037/tcr.2016.07.35

References

1. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995-2005.
2. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138-48.
3. Li Z, Bishop AC, Alyamani M, et al. Conversion of abiraterone to D4A drives anti-tumour activity in prostate cancer. Nature 2015;523:347-51.
4. Li Z, Alyamani M, Li J, et al. Redirecting abiraterone metabolism to fine-tune prostate cancer anti-androgen therapy. Nature 2016;533:547-51.
5. Russell DW, Wilson JD. Steroid 5 alpha-reductase: two genes/two enzymes. Annu Rev Biochem 1994;63:25-61.
6. Di Costanzo L, Drury JE, Penning TM, et al. Crystal structure of human liver Delta4-3-ketosteroid 5beta-reductase (AKR1D1) and implications for substrate binding and catalysis. J Biol Chem 2008;283:16830-9.

© Translational Cancer Research. All rights reserved.