

Abiraterone metabolism in castration resistant prostate cancer

Zhenfei Li¹, Mohammad Alyamani¹, Jianneng Li¹, Sunil K. Upadhyay⁴, Steven P. Balk⁵, Mary-Ellen Taplin⁶, Richard J. Auchus⁴, Nima Sharifi^{1,2,3,*}

¹Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic, Cleveland, OH

²Department of Urology, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH

³Department of Hematology and Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

⁴Departments of Pharmacology and Internal Medicine, Division of Endocrinology and Metabolism, University of Michigan Medical School, Ann Arbor, MI

⁵Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

⁶Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

*Correspondence: Nima Sharifi

Background

Castration resistant prostate cancer (CRPC) is lethal and abiraterone is an FDA-approved drug for CRPC treatment. However, patients have different response in clinic with one third of the patients showing primary resistance to abiraterone. A predictable biomarker is required to distinguish the primary resistant patients for personalized treatment. The structure of abiraterone is similar to that of androgen precursor, dehydroepiandrosterone (DHEA). We hypothesize that abiraterone could have a similar metabolic pathway like the androgens and the metabolism of abiraterone might correlate with its clinical response.

Methods

To test this hypothesis, we use mass spectrometry (MS) to detect abiraterone metabolites in patients. HPLC is used to test the function of the metabolites on steroidogenic enzymes. Xenograft in mouse model is used to investigate the function of the metabolites *in vivo*.

Results

We found that abiraterone is catalyzed by the steroidogenic enzymes to generate delta 4-Abi (D4A), 5 α -Abi and other 5 other metabolites in abiraterone treated patients. The metabolite, D4A, inhibits multiple steroidogenic enzymes and antagonizes AR directly, thus suppresses AR signaling and xenograft progression more potently than abiraterone. However another metabolite, 5 α -Abi, activates AR directly and promotes xenograft growth. The conversion from D4A to 5 α -Abi relies on steroid-5 α -reductase (SRD5A) which is up-regulated in long term abiraterone treated cell lines. To inhibit the conversion from D4A to 5 α -Abi, we combined dutasteride, an inhibitor of SRD5A, together with abiraterone. We found that the addition of dutasteride significantly increases D4A concentration and decreases 5 α -Abi concentration in both cell lines and patients, which may benefit the patients in clinic.

Conclusions

Together, we unveiled a novel androgen-like metabolic pathway of abiraterone. Steroidogenic enzymes are involved in this metabolic pathway. Dutasteride, the inhibitor of SRD5A could redirect the metabolism of abiraterone and might enhance the clinical response of abiraterone in patients.

Conflict of Interest

There is no conflict of interest.

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