Galeterone metabolism in castration resistant prostate cancer

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Background: Steroidal medicine like abiraterone is used for castration resistant prostate cancer (CRPC) treatment. Previously we have reported that abiraterone is recognized by steroidogenic enzymes to generate several new metabolites which would affect the efficacy of abiraterone. It is not clear whether the novel metabolism of abiraterone is unique to abiraterone or common to all other steroidogenic medicines. So we investigated the metabolism of galeterone, a steroidal CYP17A1 inhibitor under evaluation in a clinical trial for CRPC treatment.

Methods: We used LC-MS to detect potential galeterone metabolites in cell medium and mouse serum. To evaluate the function of galeterone metabolites, we used HPLC to detect androgen metabolism and qPCR to investigate AR target gene expression. Xenograft in mouse model is utilized to investigate the function of galeterone metabolites *in vivo*.

Results: We found that galeterone is metabolized by 3βHSD to D4-galeterone (D4G), which is further converted by steroid-5α-reductase (SRD5A) to 3-keto-5α-galeterone (5αG), 3α-OH-5α-galeterone, and 3β-OH-5α-galeterone in prostate cancer cells. *In vivo* galeterone is also converted to other three corresponding 5β-reduced metabolites. D4G inhibits steroidogenesis and suppresses AR protein stability, AR target gene expression, and xenograft growth comparably with galeterone, and further conversion by SRD5A leads to loss of several activities that inhibit the androgen axis that may compromise the clinical efficacy of galeterone.

Conclusions: Together, our findings define a critical metabolic class effect of steroidal drugs with a Δ^5,3β-hydroxyl structure. The function of galeterone metabolites is different from that of abiraterone metabolites.

Conflict of Interest: There is no conflict of interest.

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