44 Xenobiotic metabolism of abiraterone acetate and glucocorticoids by the gut microbiota

Eur Urol Suppl 2019; 18(1);e60

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Introduction & Objectives: Testosterone and dihydrotestosterone (DHT) stimulate the growth of prostate cancer by activating androgen receptors. Androgen deprivation therapy (ADT), the first line of systemic treatment, aims to decrease circulating androgens to castrate levels; however, castration resistant prostate cancer (CRPC) can develop. Abiraterone acetate (AA), an inhibitor of androgen synthesis, in combination with supportive glucocorticoids are used to treat CRPC. Many drugs are orally ingested and pass through the gastrointestinal tract, however, the dense bacterial population in the gut is often overlooked. We hypothesize that AA can modify the composition of the gut microbiota and gut bacteria can transform glucocorticoids into compounds that can activate androgen receptors.

Materials & Methods: A chemostat gut model was inoculated with human feces and exposed to physiological doses of AA. Samples were analyzed by culture-dependent and -independent methodologies. Bacterial isolates that increased in abundance upon exposure to AA were tested on agar containing AA. Secondly, *Clostridium scindens*, a corticosteroid-utilizing gut bacterium with known androgenic-producing abilities, were exposed to various clinically relevant glucocorticoids (prednisone, prednisolone and dexamethasone). The metabolic products were measured by liquid chromatography–mass spectrometry and bacterial gene expression by quantitative PCR. A yeast-based human androgen receptor assay was also used to detect the biotransformation of glucocorticoids for potential activation by bacterial metabolites.

Results: The bacterial composition of the gut model changed when exposed to AA. Select bacterial isolates were also able to utilize AA as a sole carbon source. *C. scindens* was found to metabolize prednisone, prednisolone and dexamethasone, possibly using machinery encoded on the *des*ABCD operon. Gene expression analysis revealed increased expression of: *desA* by 8-fold; *desB* by 5.2-fold; *desC* by 4.8-fold; and *desD* by 2.6-fold. DHT-like activity on human androgen receptor assay increased significantly with *C. scindens* incubation with prednisone ($3.6 \pm 0.8 \times 10^{-9}$M) but not with prednisolone (no detectable activation) or dexamethasone (no detectable activation).

Conclusions: These results suggest that we may need to consider the role of the gut microbiota in the treatment of CRPC. Bacterial interactions may change the pharmaceutical properties of drugs such as AA. Prednisone, co-administered with AA, can also be metabolized into androgenic compounds, which may play a part in CRPC treatment failure.