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EDITORIAL

# The interplay of microbiota and hormone regulation in men with prostate cancer

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The interplay between the gastrointestinal (GI) microbiota and drug metabolism and/or efficacy is an emergent area of interest in clinical oncology. In men with prostate cancer, the GI microbiota may specifically influence hormonal therapies, and vice versa. A study by Li et al. published in this issue of *Prostate Cancer and Prostatic Diseases* examined the GI microbiota of men undergoing treatment with androgen deprivation therapy (ADT) versus radical prostatectomy. Compared to the radical prostatectomy group, men undergoing treatment with ADT had (1) lower GI microbial diversity and Firmicutes-to-Bacteroidetes ratio (used as an indicator of GI health) and (2) enriched predicted prevalence of the biosynthesis of lipopolysaccharide (endotoxin) and propanoate. The authors hypothesize that the compositional and functional differences observed in men undergoing ADT may contribute to the known development of metabolic complications from ADT, but caution that longitudinal studies to both confirm that GI microbiota profiles change upon ADT treatment as well as explore their relationship to the development of metabolic complications are needed [1].

The study by Li et al. [1] builds on previous work demonstrating that commonly used nonantibiotic drugs, including proton pump inhibitors (PPIs), metformin, antidepressants, and oral steroids impact the composition and metabolic function of the GI microbiota [2]. In some instances, these changes in microbial composition had unexpected implications for overall health. For example, the authors quantified carriage of antibiotic resistance genes in participants using PPIs and report consistent increases in antibiotic resistance gene markers in PPI users compared to nonusers. In regards to use of oral steroids, the authors noted an increase in the prevalence of *Methanobrevibacter smithii* in users of glucocorticoids including prednisolone, prednisone, hydrocortisone, and cortisone. Interestingly, *M. smithii* is a methanogen implicated in the development of obesity via its capacity to increase caloric harvest [3]. The authors hypothesize that an increased abundance of *M. smithii* in participants taking oral steroids could potentially explain the weight gain associated with oral steroid use.

Previous studies in animal models also demonstrate that the GI microbiota can influence circulating hormone levels [4] and be altered by castration [5]. Likewise, a study in men with prostate cancer reported measurable compositional differences in the GI microbiota of men taking oral antiandrogens compared to men with and without prostate cancer who were not undergoing treatment with these therapies [6]. Species overrepresented in men taking oral antiandrogens included species previously linked to response to anti-PD-1 immunotherapy such as *Akkermansia muciniphila* [7] and *Ruminococcaceae* spp [8], and functional analyses indicated an enriched representation of bacterial gene pathways involved in steroid biosynthesis and steroid hormone biosynthesis. We speculate that alterations to the GI microbiota by oral hormonal therapies for prostate cancer may influence clinical response to oral antiandrogens or future therapies including immunotherapy. This notion is supported in a study by Daisley et al. who demonstrated the depletion of *Corynebacterium* spp. in men on ADT alone and an increase in the health-associated *Akkermansia muciniphila* upon treatment with ADT and abiraterone acetate [9]. These authors further report a coinciding predicted increase in bacterial biosynthesis of vitamin K2 in correlation to increases in *A. muciniphila*, which may affect the efficacy of abiraterone acetate.

Collectively, the studies in prostate cancer to date demonstrate an impact of hormonal therapies on the

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composition of the GI microbiota, and suggest that these compositional changes may impact response to therapy and/or mediate therapy-related comorbidities.

## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.

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