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Platinum Priority – Editorial

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The Microbiome: Another Dimension in the Pathophysiology of Urogenital Disease

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1. Introduction

The human body interacts with approximately 10^{16} bacteria that live in the human microbiome. Besides a large degree of commonality, each individual's microbiome is unique and adapts during life as a result of environmental and genetic influences [1–4]. As a result, the microbiome is mostly species-, community-, and organ-specific [1]. Microbiome-host interactions are far more profound than previously considered and go beyond the organ where the bacteria are present [5]. The depths of these interactions are still largely undetermined. For example, many bacterial metabolites cross the blood barrier and can be detected in serum, but we can only speculate on the degree to which these metabolites impact human physiological processes [6].

Rapidly evolving epigenetic techniques to facilitate whole-genome and transcriptome sequencing have progressed to microbiome research and its role in health and disease. 16S rDNA sequencing is currently the technique most frequently applied to obtain complete genetic data on the species and quantity of bacteria present in a microbiome [7]. This so-called metagenome has been investigated in large research collaborations in the USA and Europe to obtain a complete reference of the varying metagenomes of different organ systems in healthy humans [1,3]. Analyses of the microbiome can be used to study population-wide effects and to detect alterations during disease, environmental changes, and therapeutic interventions.

2. Urogenital microbiome in health and disease

The urinary tract has long been considered a rather sterile environment. Any bacterial growth was considered invasive and therefore treated as a culprit. This mindset comes predominantly from the interpretation of bacterial culturing for diagnosis of urinary tract infections (UTIs). However, the urogenital tract contains a normal bacterial flora that is partly gender- and age-specific [8,9]. Moreover, many species do not grow using standard culturing techniques [8]. Females have predominantly *Lactobacillus* and *Gardnerella* species, while males carry *Corynebacterium*, *Staphylococcus*, and *Streptococcus* as dominant species, which probably have, similar to the intestines and vagina, a role in regulating homeostasis in the organ system [9]. As a result, the question of whether a disease could be primarily caused by a pathologic microorganism that was able to invade or because of a benign microorganism that had vanished may be equally important. The genitourinary microbiome is currently investigated for multiple conditions such as overactive bladder syndrome (OAB) and UTIs [5,8].

In this issue of *European Urology*, Markowski et al. [9] review the evidence on distinct microbiome variations in urogenital cancers. The focus is on kidney, bladder, and prostate cancers. The article provides evident clues that there is more to the urogenital microbiome than preventing UTIs. The main causative oncogenic hypothesis is that dysfunction of the microbiome activates inflammatory pathways that can secondarily induce carcinogenesis. This corresponds with the results from different studies that

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show that the microbiome can modulate immune responses [1,2,9].

A comparison of results from investigations on microbiome changes in bladder cancer reveal variations between studies in terms of the species detected and their relative quantities. One very interesting study describes different bacterial strains in patients with schistosomiasis infections who developed urothelial cancer compared to individuals who did not [9]. Further evidence of potential correlations or causative relations between the microbiome and prostate or kidney cancer is rather limited [9]. One study reported detection of a variety of known infectious bacteria species in prostate cancer biopsies, but no single pathogen significantly stood out [9]. This not only warrants more research but also forces us to think about the potential far-reaching importance of local environmental and genetic variations in the set-up of our studies and how to interpret the results.

The summarized evidence from the review by Markowski et al. [9] is correlative because current sequencing techniques are often limited in proving true causality [7]. Are diseases caused by a specific microbiome or vice versa? Solving this chicken-or-egg dilemma would require large population-based studies involving healthy individuals with long follow-up. Nonetheless, Markowski et al. do reveal real insight into potentially causative microbiome dynamics in urogenital malignancies and explore potential adaptations as a result of oncologic treatment. For the latter point, Markowsi et al. review evidence from other organ systems and animal models to describe potential microbiome effects on treatment efficacy and therapeutic side effects of cancer treatments. Of interest are preclinical studies investigating how some intratumor bacterial strains can modify the efficacy of specific chemo- or immunotherapies such as gemcitabine, anti-PD-L1, and BCG [9].

3. Future goals for genitourinary microbiome research

Beside infectious and malignant diseases, other conditions such as urolithiasis, OAB, and bladder pain syndrome (BPS)/interstitial cystitis (IC) are of interest for microbiome research [5]. In particular, the BPS/IC subtype with Hunner's lesions deserves attention considering its clear inflammatory characteristics and unresolved pathophysiology. Focus should also include the gut and vaginal microbiome, since there is evidence that implies that there is a degree of cross-talk between the bacterial flora of these organs [5,8,10]. Biologic sampling is also important and bacterial culturing of tissues should always be considered, since gut microbiome research demonstrates that the microbiome is multilayered and composition changes depend on depth within the layer [4].

One of the most promising applications for microbiome knowledge in clinical practice is the development of diagnostic tests based on microbiome profiles. A good real-life example of this is the ReceptIVFity test, which can determine success rates for in vitro fertilization and intracytoplasmic sperm injection on the basis of genitourinary microbiome profiling [10]. Microbiome profiling can be used in addition to or integrated in molecular/genetic profiling to predict treatment responses for fine-tuning future personalized medicine protocols. This would also be the primary tool for investigating ways in which we could modify the microbiome to increase treatment efficacy.

Finally, further epidemiology studies should be performed to obtain a better understanding of what role the microbiome plays in regional variations in disease prevalence.

4. Summary

Overall, microbiome research has radically changed the way we think about the requirements of a healthy body to function and how the microbiome influences normal and pathophysiological processes. Understanding these roles could revolutionize health care for genitourinary diseases.

Conflicts of interest: The author has nothing to disclose.

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