Peer Review File

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Reviewer Comments

Dr. Nicolaro et al. explored the current understanding and advancements in the field of microbiome research and discuss its intimate association with genitourinary diseases. This is an exhaustive and comprehensive review. However, there are several questions which need to be answered or further explained by the authors.

Comment 1: The authors said that proinflammatory bacteria such as Escherichia coli and Propionibacterium acnes possess the ability to induce dysplasia and hyperplasia of the prostate, potentially contributing to carcinogenesis. So can we say that there may be a correlation between the occurrence of prostate cancer and prostate hyperplasia?

Reply 1: We changed the text to better reflect the idea of inflammation as a predisposing factor to prostate cancer, rather than hyperplasia. We also removed the source from Wagenlehner et al and replaced it with Porter et al.
Changes in the text: We modified a statement as advised (see Page 10, lines 220-223). See reference (39).

Comment 2: For RCC, targeted therapy such as TKI is first-line treatment options for patients with stage IV disease. Unfortunately, these treatments are sometimes associated with harsh toxicity profiles including cardiotoxicity, hypertension, thrombosis, thyroid dysfunction, skin toxicity, and diarrhea. According to the review, recent data suggested that the GI microbiome may play an important role in the development side effects from this therapy, which indicated appropriate antibiotic therapy should be used in targeted therapy process. However, authors also mentioned that antibiotic therapy was associated with a significantly increased risk of progressive disease and shorter PFS and OS. How the author explains this contradiction?

Reply 2: In the text, we assert that the relationship between antibiotic therapy and oncologic outcome is complex (see Pages 14-15, lines 316-318). We modified our text to clarify that our claims are to support further investigation into these relationships, rather than draw conclusions from contradictory data.
Changes in the text: Modified a statement (see Page 15, line 318) and added a statement (see Page 16, lines 339-340) and elaborated further in the text (see Pages 16-17, lines 359-362).

Comment 3: In addition, the above studies of survival analysis are mostly retrospective, and their selection bias is inevitable. Those who use antibiotics during targeted therapy may have risk factors such as heavier infections and accompanying diseases, resulting in their poorer prognosis.
Reply 3: We acknowledged selection bias in retrospective survival analyses as advised and elaborated on the contradiction in comment 2.
Changes in the text: We added statements (see Page 17, lines 365-367).

Reply 4: Last, is there any published research reporting the relationship between human microbiome and other genitourinary malignancies including penile cancer, testicular cancer etc. If yes, please conduct an appropriate review of these articles.
Reply 4: We were unable to find any published research reporting on the relationship between the human microbiome and other genitourinary malignancies. We acknowledged this in our conclusion.
Changes in the text: We added text to the conclusion (see Page 18, lines 395-399).