Peer Review File

Article information: https://dx.doi.org/10.21037/tau-23-32

Point to point responses to reviewer's comments:

Comment 1: The methods of abstract were too simple. Please supplement.
Reply 1: Many thanks for your suggestion. We have added appropriate content in the methods of abstract.
Changes in the text: (Page 2, line 1-6)

Comment 2: In the introduction, it was proposed to add related reference (DOI: 10.21037/atm-21-6925) about the germline mutations in cancers.
Reply 2: Many thanks for your suggestion. We have added this related reference in the introduction of our manuscript.
Changes in the text: (Page 3, line 2)

Comment 3: The germline mutation was the crucial topic in the study. Please make a brief introduction.
Reply 3: Thank you for your precious comments and advice. We have made a brief introduction of germline mutation in the introduction of our manuscript.
Changes in the text: (Page 3, line 1-2)".

Comment 4: Why to focus on germline mutation in RCC in the study? Please state in the introduction.
Reply 4: We apologize for the confusion caused by our unclear description. Germline mutations, one of genetic alterations, exist in all cells in body and can be inherited. Germline mutations are associated with generation of various tumors and drug resistance. A recent American study found that 16.1% of RCC patients carried germline mutations in a RCC predisposition gene, and some cases of early-onset aggressive RCC without defined pathogenic germline mutations have been observed. It seems highly probable that the prevalence of germline mutations in RCC is underestimated and underlying causative germline mutations exist in RCC. Thus, it is particularly relevant to identify Chinese RCC patients with germline mutations because their clinical implications can differ from those of patients with sporadic RCC. We have made corresponding modifications in the introduction of our manuscript.
Changes in the text: (Page 3, line 1-16)

Comment 5: What were the roles of germline mutation in the tumorigenesis and development of RCC? Please state in the discussion.
Reply 5: Thank you for your precious comments and advice. Pathogenic germline mutations in cancer predisposition genes are associated with tumorigenesis and development of RCC. VHL disease is an autosomal dominant disorder caused by

germline mutations in the VHL gene. Patients with VHL disease are particularly prone to renal tumors when a stochastic secondary inactivation of the other VHL allele occurs. Similar to those with VHL disease, patients with TSC 1/2, FH and SDHB/C/D germline mutations are more likely to have RCC. Germline mutation in MET can promote hereditary papillary RCC initiation and progression. We have made corresponding modifications in the discussion of our manuscript.
Changes in the text: (Page 8, line 6-11)".

Comment 6:It was better to test the effect of FANCI and FANCM on RCC cells.
Reply 6: Thank you very much for your comment. We are now designing experiments to test the effect of FANCI and FANCM on RCC cells. This section may take a relatively long time and we want to show the results of this section separately in the next article.
Changes in the text: (Page 10, line 1-4)

Comment 7: In the discussion, please supplement the roles of FANCI and FANCM in RCC.
Reply 7: Thank you for your valuable comments and suggestions. The roles of FANCI and FANCM in other cancers have been identified. However, fewer studies concerning biological functions of these two genes were conducted. A recent study showed that a patient with four primary cancers including renal cancer has FANCM mutation. Mutations in these two genes are associated with renal ectopic malformations or dysplasia. We suspect that FANCI and FANCM pathogenic germline mutations might play an important role in tumorigenesis and tumor progression in RCC and further studies are needed to confirm this hypothesis. We also made corresponding modifications in the discussion of our manuscript.
Changes in the text: (Page 10, line 1-4)