

Dear Editors and Reviewers:

Thank you for giving us the opportunity to submit a revised draft of the manuscript “**TM9SF1 promotes bladder cancer cell growth and infiltration**” for publication in *World Journal of Clinical Oncology*. We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments on and valuable improvements to our paper.

We have carefully considered all the suggestions of the reviewer. We have tried our best to revise the manuscript, and in the latest manuscript, the revision is highlighted in yellow. Please see below, for a point-by-point response to the reviewers’ comments and concerns.

Responses to reviewer’s comments:

Reviewer #1:

1.

Some of the more advanced findings published in journals over the past 12 years should be provided to clarify the role of members of the transmembrane 9 superfamily in the possible treatment of bladder cancer. I therefore recommend that the report be significantly revised before further consideration

Response: We are grateful for the suggestion. We carefully read the journal requirements for the word. We supplemented and improved the content, so as to clarify more clearly the role of transmembrane 9 superfamily in the possible treatment of bladder cancer and then revised it in the most recent manuscript and marked it in yellow.

Core tip

The biological function of the TM9SF family has not yet been explored. Only a few studies have reported that its expression may be related to the occurrence and development of tumors. In this paper, different experimental methods and results of

CCK8, wound healing test, transwell test, flow cytometry was used to study the influence of transmembrane 9 superfamily member 1 (TM9SF1) on the biological behavior of bladder cancer (BC), aiming to provide a new perspective for the treatment of BC.

Bladder cancer has a high recurrence rate and is resistant to chemotherapy(1-4). The most prominent symptom of BC is microscopic or visually visible hematuria, and 75% of bladder tumors are uroepithelial carcinomas limited to mucous membranes, i.e., non-muscular aggressive BC(NMIBC)(5-8). Approximately 80% of bladder cancers are superficial papillary lesions caused by urothelial hyperplasia, which are of low grade and may recur, but rarely invade the bladder wall or metastasize. The remaining 15-20% are high-grade solid non-papillary bc, which is caused by high-grade intraepithelial urothelial neoplasia, which has a high tendency to spread far. Most bladder cancers (75-80%) do not involve the bladder muscle wall and are usually treated with TURBT, however, many BC patients have poor prognosis and poor long-term survival (9, 10). So, the treatment of bladder cancer needs to go further

TM9SF1 has been linked to a number of cancers. In the experiment to determine the prognostic markers of esophageal squamous cell carcinoma (ESCC), two marker genes directly related to cancer 4-year overall survival (os) were found through the establishment of an effective ESCC prognostic nomogram model, one of which was TM9SF1, and the expression value of TM9SF1 gene was high in cancer, which was significantly different from that of normal people(11). These results indicate that the role of TM9SF1 in cancer is worthy of further investigation. ApostolosZaravinos' study employs enome-wide microarray analysis, grouping samples according to histology and identifying the differentially expressed (DE) gene in each sample and in the BC tumor group. A total of 17 DE genes were identified, of which TM9SF1 was one and increases the necessity and feasibility of the effects and mechanisms of TM9SF1 on bladder cancer cells(12) Transmembrane 9 superfamily member 1(TM9SF1) has been identified as an estrogen receptor binding fragment-associated antigen 9 (EBAG9) interaction factor. TM9SF1 and EBAG9 work synergistically to regulate the migration of prostate cancer cells by affecting genes associated with EMT This conclusion is consistent with the study in this paper that TM9SF1 overexpression can promote the migration of BC cells(13). However, in Wei et al.'s study, TM9SF1 (transmembrane 9 superfamily member 1) is a functional mRNA target of phosphorylated CTD interaction factor 1 (PCIF1), and acts as a tumor suppressor gene in cancer. PCIF1 uses m6Am to modify TM9SF1mRNA, resulting in reduced TM9SF1 translation. TM9SF1 reverses the effect of PCIF1 on the aggressiveness of cancer cells. These results indicate that TM9SF1 plays different functions and roles in different tumor types(14). Wei Long et al further investigated the role of TM9SF1 overexpression and silencing in three cell lines (5637, T24, and UMUC-3), which opens the door to new strategies for BC therapy. Through CCK8, wound healing test, cross-well migration test and separation of high - and low-nutrient protein sets, TM9SF1 was identified as an oncogene in BC. When TM9SF1 was silenced, it inhibited the proliferation of BC cells in vitro, and inhibited the migration and invasion of BC cells. When TM9SF1 was overexpressed, the proliferation of BC

cell When TM9SF1 was overexpressed, the proliferation of BC cells was determined. The ability of migration and invasion was significantly improved.

2.

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

Response: Thank you for your input. We have implemented the recommended alterations pertaining to the abbreviations within the article, aligning them with the prescribed abbreviation conventions. These modifications have been distinctly highlighted in yellow within the latest manuscript.

We sincerely hope that this revised manuscript has addressed all your comments and suggestions. We appreciated for reviewer's warm work earnestly, and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions.