

Peer Review File

Article information: <https://dx.doi.org/10.21037/tcr-24-1660>

Reviewer A

This review of membrane-spanning proteins (TMEM) is complete but exclusively descriptive, with no new information or ideas. The same topic has been debated recently (refs:2, 24 and others). This other review provides a good survey of the literature in the field but it does not more than the quality and originality of the illustrations are relatively weak (two trivial figures).

Comment 1: It would be very useful to better illustrate the review, to make it more attractive.

Reply: Thanks for your comments. According to your suggestion, we have added the section of '2.7 Metastasis', and '3 TMEMs in immunity'. Besides the summarization of the functions and mechanisms of how TMEMs is involved in the regulation of immune response for human cancers, a new illustration, Figure 3, was included in this revised manuscript. Indeed, several TMEMs-related reviews have been published, but they reported that TMEMs were difficult to purify, hydrophobic and lipophilic, thus therapeutic strategies for targeting TMEMs remain a major challenge. In this review, we summarized and emphasized several strategies to target TMEMs, such as TMEM173, TMEM16A and TMEM63A. We believe that these revisions make the manuscript more attractive than the previous version for the audience.

Changes in the text: We have modified our text as advised (see 12-16, line244-322).

Comment 2: The role of TMEM in immunity and immune regulation of cancer should be discussed further.

Reply 2: Thanks for your suggestion. A new section on 'TMEMs in immunity' and relative figure have been included in the revised manuscript.

Changes in the text: We have modified our text as advised (see Page14-16, line279-322).

Comment 3: The role of TMEM in metastasis is superficially addressed. A specific subsection (2.7) could be added.

Reply 3: Thanks for your suggestion. The role of TMEMs in metastasis has been discussed in the revised content as a new section of '2.7 Metastasis'.

Changes in the text: We have modified our text as advised (see Page12-14, line244-277).

Reviewer B

It is very clearly written and there are no corrections required. It is a manuscript worthy of acceptance.

Reply: Thanks a lot for your positive comments to our work.