

Dear reviewer,

I am very grateful for your comments on the manuscript. These comments are valuable and helpful for revising and improving our paper, as well as providing important guidance for our research. According to your advice, we have changed the relevant part in the manuscript and highlighted the revised/added content with yellow colour in the revised manuscript. The responds to your comments are as flowing:

Comments 1: The manuscript requires a minor editing. Please take attention about the abbreviations. Please define the abbreviations when they first appear in the abstract and main text.

Answer: Abbreviations in the abstract and main text have been corrected according to the standard formatting corrections. The English language has been re-checked by a language editing service. Many grammatical and typographical errors have been corrected.

Comments 2: The images should be improved. Some of the words are too small in the images.

Answer: The symbols in Figures 3B, 4A, 4B, 4C and 6A have been enlarged to make them easier to recognise when consulting the images.

Comments 3: The reference list should be updated, and edited.

Answer: Following the standard format of the journal, the list of references has been corrected.

We appreciate your feedback and hope that the revised manuscript meets your expectations. Should you have any questions, please contact us without hesitate.

Best regards,

Fei Liu

Dear Editor,

I am very grateful for your comments on the manuscript. According to your advice, we have changed the relevant part in the manuscript and highlighted the revised/added content with yellow colour in the revised manuscript. The responds to your comments are as flowing:

Comments 1: Fig 2 A: Human dental pulp stem cell surface marker identification. Bar graphs should be used to show the right shift from isotype controls, which is a standardized representation of FACS data.

Answer: As peak plots may be more indicative of gene expression intensity, scale plots may be the most appropriate method for determining the expression of stem cell surface markers.

Comments 2: Fig 2B. Scale bars should be added to all the imaging panels.

Answer: The Fig 2B diagram has been modified to include a scale bar.

Comments 3, 4: Fig 3. The cell compositions of prevascularized dental pulp organoids (Vorganoids) in vitro cultured should be compared with the in vivo counterpart to be functional. The authors needed to straighten such a point for the readers. Organoids differ from the in vivo counterpart of tightly controlled structures. The limitations of organoids are that they are not highly representative of the in vivo counterpart regarding cell composition and structure; thus, organoids are not highly reproducible. Refer to Fig 4 for the mathematics of in vivo structure. Refer to Q3 to Fig 5: How much such organoids represent the in vivo counterpart of tightly controlled structures?

Answer: Thank you for your suggestions. Our team is currently investigating this issue and has attempted various methods to compare the simulation effect of the organoid-real pulp structure in multiple dimensions. The 3D group has been verified to exhibit significant structural similarity, including pathological sections, immunofluorescence staining of major markers, and electron microscopy. We attempted to compare the gene expression aspects of scRNA-seq single-cell genomics and RNA-seq. However, a precise comparison between the two histological sequencing technologies was not possible due to differences in gene fluxes and expression levels. The team has summarised their work and proposed a potential solution: a comparison of the high-throughput spatial transcriptomes of 3D organoid and real dental pulp tissues. The team is currently engaged in an experimental

implementation, and new findings may follow. Advanced technologies are recognized as necessary for multidimensional comparison to ensure that the function and structure of 3D organoids closely resemble real dental pulp tissues. This will provide a more reliable foundation for future research.

Comments 5: Fig 7: Not only did the structure of organoids but also the structure affect the function of the in vitro assembly: Both are essential. Neither is a minus. The integration should be focused on building a functional unit.

Answer: Thank you for your suggestion. Current organoid models do not fully replicate all cell types, levels of cell maturation, and physiological functions of their respective organs. They only exhibit some of the organ's functions. Future studies will investigate whether the structure of organoid assembly in vitro affects its functional impact. This will help to understand the mechanisms by which organoids interact between structure and function.

We appreciate your feedback and hope that the revised manuscript meets your expectations. Should you have any questions, please contact us without hesitate.

Best regards,

Fei Liu