We greatly appreciate the reviewers' constructive comments and suggestions. These comments identified important areas that require further clarification and improvement. Below are our point-by-point responses to reviewers' comments/suggestions (reviewers' comments are in black and our responses in blue). We believe that the quality of this manuscript will be greatly enhanced after completion of those experiments and revision.

Reviewers' comments:

Reviewer #1:

General Comment.

Authors have conducted a remarkably comprehensive and in depth review on the area of the brain cancer stem-like cells interacting with the tumor cell microenvironment. Their knowledge and work for this manuscript is commendable.

Not only they currently carry out the investigations but also present several areas of future research for the improved management of the currently near fatal brain cancer.

Minor comments

There are too many abbreviations.

This is an excellent educational paper. Healthcare workers and scientists in other field may read and learn a great deal.

There seems no need to abbreviate glioblastoma and medulloblastoma to GB and MB.

If used only a few times, please, write it out.

HSPGs (for haparan sulfate proteoglycans) and HA (for hyaluronic acid) appeared only once under Matrix section.

Or illustrate all the abbreviations on the front page. This will certainly help the readers

Thanks for the reviewer's positive comments and insightful suggestions. We agree with the reviewer that it really makes the manuscript well-understood by more healthcare workers and scientists in other fields after revision. The abbreviations, such as GBM, MB and HSPGs, have been revised as the whole names. The others, such as scRNA-seq, have been illustrated on the front page because they are used a few times or they have been widely used in the publications, such as central nervous system for CNS.

Reviewer #2:

The authors present a well-written review article concerning interaction of cancer stem-like cells with the microenvironment. The following points are suggested for further consideration.

1. The authors emphasize the use of valuable scRNA-seq technology in the cancer research such as application in the brain tumor in the last sentence of the introduction. I would suggest the authors to consider to describe the issue (underlying concept) of scRNA-seq technology in more detail in a separate subsection first before subsequent description for its application (i.e. may be describe before the subsection 4. Glioma and medulloblastoma).

2. Is the word 'depictes' correct (the last line of p. 8)? Perphaps 'depicts' is more adequate. Another area of typo error (?): 'Chongsathidkiet'

1. Thanks for the reviewer's constructive suggestion. The issue about scRNA-seq technology has been separated and described before the subsection "Glioma and medulloblastoma" in more details. The Reviewer#3 also mentioned this question and the key points have been highlighted in the Introduction part.
2. We thank the reviewer for pointing these typos out. We really feel sorry for not being explicit with these statements. In the resubmission, the manuscript has been carefully re-edited one sentence by one sentence. The typos have been corrected and highlighted by red words.

Reviewer #3:

This study demonstrates the importance of CSCs and microenvironment in brain cancer treatment. Introduction may be revised to explain more in detail how single-cell RNA sequence revealed the cancer and immune cell characterization. The organization of the sections may be revised to have different numbers for subsections. Figure 2 may be revised to be more suitable for the text citation.

1. Thanks for the reviewer's positive comments and valuable suggestion. In the introduction section, the important role of scRNA-seq and the advances of this new technology have been highlighted. Because of the word limitation, the detailed information regarding the application and key role of scRNA-seq in brain tumor research has been provided in the "2 tumor microenvironment" section. The Reviewer#1 also mentioned this issue and the scRNA-seq associated part has been separated based on his suggestion.
2. We apologize for the confusion about the numbers for subsections. The sections have been re-organized and re-numbered in the resubmission, which has been highlighted by blue words.

3. Figure 2 and the figure legends have been revised. The confused HE staining have been deleted (Figure 2A and 2C_version 1). As shown in the revised Figure 2, the H.&E. analysis displayed the pathological vessels distributed in medulloblastoma. The representative IHC images showed the expression of CD34 (vascular endothelial cell marker) in glioblatoma, CD38 (T cell marker) in anaplastic diffuse astrocytoma, CD68 (macrophage marker) in medulloblastoma, IBA1 (microglia marker) in glioblastoma and GFAP (astrocyte marker) in medulloblastoma. The corresponding statements have been revised in the resubmission and highlighted by red words.