

POINT-BY-POINT RESPONSES TO REVIEWER'S COMMENTS

Reviewer #1

We thank the reviewer #1 for their positive remarks. We have revised the text according to their specific comments as follows:

1) Since the great importance of metabolism in medulloblastoma CSC, the author needs to summarize the alteration of detailed metabolites examined by LC/MS or NMR.

We have now included more information on this topic in page 9, lines 11-15 as follows:

“Mass spectrometry also detected an increased concentration of glycolysis intermediates (3-phosphoglyceric acid, 2-phosphoglyceric acid, phosphoenolpyruvic acid) and amino acids (arginine, glycine, histidine, leucine, lysine, serine) in rMSLCs, as well as decreased levels of NADH and ATP, and dysregulation of TCA cycle intermediates.”

2) In different subtypes of MB, the markers of CSC is isolated with different markers or not ?

The markers included in the manuscript have been used to isolated CSCs from all the subtypes, except CD272, as detailed in the text (page 6, lines 1-7). To help interpretation, we have now included a new column in table 1 with this information.

3) The author need to add one row to describe the therapeutic strategy (drugs) of MB in table 1 ?

Thank you for this suggestion. A new table (table 2) has been now created and included in the manuscript, detailing the therapeutic strategies used against MB in general and MB-CSCs in particular, for each subgroup.

4) The resolution of Figures are low, needs improvement.
A high resolution version of the figures has been independently sent to the editorial office for further processing.

Reviewer #2

We thank the reviewer #2 for their positive revision. We have revised the text according to their minor issues as follows:

1. Does the metabolism shift in CSCs is unique in MB or totally same as other tumours?

Thank you for your question. In fact, the metabolic differences between differentiated cancer cells and CSCs are reported for all the cancer types studied. However, depending on the tumor type, CSCs can be more or less glycolytic than their differentiated counterparts. For MB-CSCs, they are more glycolytic, similar to the situation in breast CSCs. We have now included a longer explanation in page 8, lines 27-31, and we hope this clarifies the question.

“Thanks to recent advances, we know now that cellular metabolism and stemness are highly interconnected in normal development and cancer. **Indeed, CSCs from different cancer types show distinct metabolic features when compared with their more differentiated progenies, though their dominant metabolic phenotype varies across tumour entities, patients and even subclones within a tumour**”

2. They should summarize the metabolism therapeutic targets in Table 1 or Figure2.

Thank you for this suggestion. A new table (table 2) has been now created and included in the manuscript, detailing the therapeutic strategies used against MB in general and MB-CSCs in particular, for each subgroup.

3. Add some new evidence from FDA approved clinical trial (targeting metabolism) in MB, or AACR reports.

Thank you for this suggestion. We have now included in several sections of the manuscript information of clinical trials related to metabolism in MB. Specifically, see pages 11, 12 and table 2.

4. The interaction between different metabolic pathways should be discussed in CSCs.

A new paragraph discussing how the different metabolic pathways up-regulated in MB-CSCs could be interacting and supporting stemness has now been added in page 9, line 29-page 10, line 2 .

“In general, all these reports suggest that the metabolic phenotype harboured by MB-CSCs is mainly glycolytic, which is favoured by hypoxia. Both glycolysis and hypoxia generate the anti-oxidant redox status needed to maintain their stemness. Moreover, the elevated availability of macromolecules needed to support their enhanced proliferation may be sustained by biosynthesis derived from glycolysis intermediates and an increased autophagy in these cells.”