

Author's Response

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We thank the reviewers and editors for their positive votes and valuable comments.

We have made revisions throughout the manuscript according to the reviewer's reports and thereby significantly improved the quality of our review.

Below, we provide point-to-point responses to all comments and suggestions.

We highly appreciate the opportunity to resubmit our edited manuscript and hope that the carefully revised version is now suitable for publication in children.

Sincerely,

Stephanie Sendker, Katharina Waack and Dirk Reinhardt

Point by point response to reviewer's comments.

Reviewer 1

Review Report (Round 1)

The manuscript by Sendker et al. is a well-written review article about the role of the microenvironment in pediatric AML. The manuscript has Novel insights in the pathophysiology of the bone marrow microenvironment in AML.

The bone marrow microenvironment is of importance for leukemia initiation, progression and therapy resistance. Novel therapeutic options influencing the niche are in development.

Besides, the text is clear and easy to read, the conclusions consistent with the evidence and arguments presented. And they addressed the main question posed.

Response: Thank you!

Reviewer 2

Review Report (Round 1)

The authors present an interesting, comprehensive and well-written review on the bone marrow environment in AML. The discussion on the microenvironment-mediated malignancy versus malignancy-mediated microenvironment is the strongest section of the review. Given the journal, I would recommend that the authors more explicitly state whether or not data is based on experimental models that were derived from pediatric patients or adult patients.

Response: Thank you for the comment. Where reasonable, we have pointed out available information about the origin of the reviewed research data to the corresponding parts within the manuscript.

In addition, it would be very valuable to the review if the authors could provide their view (or their best guesstimate) on the differences and similarities on benign and malignant bone marrow microenvironments between adults and children.

Response: We absolutely agree, that pointing out the differences between the bone marrow microenvironment in children and adults is crucial. In this regard, the section 3.3. "Developmental changes in the bone marrow microenvironment" is intended to accentuate age-dependent differences in the hematopoietic microenvironment. However, to date, to our best knowledge, pediatric based research data, specifically focusing the hematopoietic niche in children are rare. To answer this important research question more precisely, further research in this area is urgently needed.

Finally, I would recommend mentioning that a relatively new and increasingly accepted standpoint is that the bone marrow niche is actually one large niche with various compartments, as opposed to different types of niches, as mentioned by the authors (see <https://pubmed.ncbi.nlm.nih.gov/28363872/> for a discussion).

Response: Thank you for the thoughtful remark and drawing our attention to the mentioned publication. To address this appealing issue, we have included the suggested opinion (Hira et al.) in the revised manuscript, complementary to the brief discussion about different (sub-)niches within the hematopoietic bone marrow microenvironment at the end of chapter 2. "Hematopoietic cells and their microenvironment" (line 252-255).

Reviewer 3

Review Report (Round 1)

In this review, Sendker et al highlights the intricate intercellular communications that takes place in the leukemic niche. Overall, the manuscript content is interesting and nicely written. Few minor suggestions to correct:

1) there are several typographical errors throughout the manuscript that needs to be fixed.

Response: Thank you. We have checked the manuscript for typographical errors and corrected the identified spelling mistakes.

2) The hypoxia section seems to belong to section 2.3.

Response: We have edited as suggested.

Reviewer 4

Review Report (Round 1)

The aim of the review article is to summarize the current literature outlining the role of the bone marrow microenvironment in AML and providing evidence for its advantageous role in the survival and potential initiation of AML, including information on the most promising therapeutic targets currently under investigation.

This is a very good comprehensive review of the role of the bone marrow microenvironment in normal haematopoiesis and the changes which can occur in AML. The authors explain the microenvironment mediated malignancy and malignancy mediated microenvironment concept clearly and I agree with their conclusion of a complementary, bidirectional process. I also like that they have included a section on the developmental changes in the bone marrow microenvironment and highlights that there may be differences.

At the end of the introduction the authors state that they aim to emphasize promising future therapeutic directions in paediatric AML. All of the research data is largely from adult based in vitro or in vivo studies and the subsequent clinical trials are in adults. This is largely due to the fact that there are limited paediatric studies available and no clinical trials in children currently. I think is it important to highlight this within the manuscript and it may be worthwhile to include some specific paediatric only in vitro data examples (from the Redell group for example).

Response: Thank you for your valuable suggestions. We agree that preclinical and clinical studies in pediatric AML are rare and therefore we added a brief statement on the problem emphasizing the limitation of available research data in pediatric AML (line 565-568 and 576). In addition, we provided some data examples from pediatric in-vitro studies, considering the interesting data from the suggested publication (line 391-394: Long et al. 2019 and 441-444: Jonge et al.). Moreover, we provide additional pediatric in-vivo research data (line 420-424, Klusmann et al. 2010).

Specific comments:

Lines 55-60: The LSC population is described as CD34+CD38-. I think it is important to add information to explain that functional LSC can be found in the other CD34/CD38 quadrants in AML and that this is dependent on the immunodeficient strain of the mouse (papers for reference include Goardon et al and Tassig et al).

Response: Considering your thoughtful advice, we have added this information (line 58-61) referring the suggested references Goarden et al. as well as Taussig et al., as requested.

Line 470-471: Is this supposed to read neonatal mice as this sentence does not make sense to me?

Response: The reviewer is correct. We have edited as suggested.