Reviewer's report

Title: Microenvironment alters epigenetic and gene expression profiles in Swarm rat chondrosarcoma tumors

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Reviewer: Suhu Liu

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Major Compulsory Revisions
1. The questions posted by the authors are well defined in this paper. The idea of tumor microenvironment influencing tumor biology has been appreciated and is an informative field to investigate. Here the authors observed a significant tumor size difference when SRC tumors cells were either transplanted subcutaneously or into the tibia of rats. Tumors injected subcutaneously grew much larger compared to tumors transplanted into tibia. As for the lung tumors observed when tumor cells are transplanted into the tibia, it is the result of colonization after tumor cells injection rather than tumor metastasis. So according to the paper, tumor size is the only difference the authors observed. But it is conceivable that the difference in tumor size may readily be explained by the local organ structure, for example the limited space and solid structure in tibia compared to skin tissue. This might hardly be the results of tumor cells aggressiveness. And it might hardly be a special character of SRC. It is very much likely other types of tumor cells also form different sized tumor when injected either subcutaneously or into the tibia. Or are there any data or reported literature the authors can provide to show that this tumor size difference is unique for chondrosarcoma?

2. I guess the authors want to convey the idea that SRC tumors from tibia and from skin are different, possibly due to the microenvironmental clue. So how different are they? Which one is more aggressive? In the paper, it was mentioned in the introduction that “transplantation of the SRC tumor into the tibia results in the formation of a higher grade tumor compared to those derived from extraosseous transplantation”. So here when the author emphasis their finding that tumors transplanted subcutaneously were much larger than tumors from tibia, what kind of argument do the authors want to convey here? Thus, more discussion was necessary for this issue.

3. Why did the authors set out to compare the tumors from tibia with tumors subcutaneously? I may understand why the tumor cells are transplanted into tibia because it is supposed to be a chondrosarcoma model. But why compared with subcutaneous tumors? Is this the frequent location of metastasis of chondrosarcoma?

4. The methods were appropriate and well described.

5. The data are not great but are honest presentation of what they had observed.
6. Basically, the manuscript adheres to the relevant standards for reporting and data deposition.

7. But most of the discussions are speculative and could be shortened. Since no significant data was achieved from this research, the conclusion is weak and ambiguous. Three genes, thymosin-#4, c-fos and CTGF, were selected from the differential expression data to further characterize their functions in SRC tumor in their in vivo animal models. Unfortunately, the results of thymosin-#4 are very much ambiguous and the results from c-fos and CTGF are in the contrary to the currently reported literature.

8. The limitations of this work is mentioned and indicated in the paper, but not clearly stated.

9. The authors clearly acknowledge the work upon which they are building.

10. The writing is acceptable

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.