Reviewer’s report

Title: Cancer associated fibroblasts (CAFs) are activated in cutaneous basal cell carcinoma and in the peritumoural skin.

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Reviewer: Eloi Marsol Garí

Reviewer’s report:
In this manuscript, the authors describe in situ the activation of cancer associated fibroblasts (CAF) around basal cell carcinoma (BCC) tumor and in perilesional skin. By using NGS they show the mRNA expression pattern from tumoral and peritumoral tissues and, the results reveal high expression of genes involved in matrix metabolism and also expression of markers of CAFs. The authors have verified the NGS data by qRT-PCR and have also localized the expression of some markers on the CAFs around the tumor, in the fibroblasts of the peritumoral region, but not in normal skin. They have also showed that CAFs (around the tumor and in perilesional regions) express chemokines and cytokines involved in the tumor progression and immunosuppression. Overall, the manuscript is well written, consistent and the approaches are valid. Previous to the acceptation a few comments should be considered by the authors:

1- A main concern is the quality of the images in figure 2 and 4, probably just in the pdf copy available, but this problem must be solved. The pattern of localization is quite arduous to appreciate.

2- I know that it is very difficult to obtain considerable amounts of total RNA from normal and peritumoral skin samples. The high number of tumor cells and CAFs in BCC samples (mainly in nodular BCC) makes easier the efficiency of RNA recovery. Regarding NGS, the authors cited that the library was prepared from 100 ng of RNA, but probably the total amount of extracted RNA was quite different among BCC and peritumoral samples. What was the total RNA amount for the different samples? Do the differences alter the representation of genes in NGS? Please comment this point.
3- The authors show by qRT-PCR differences among BCC and peritumoral samples in the expression of chemokines and cytokines. Did the authors also detect these differences in the NGS approach?

4- Regarding the activation of fibroblasts associated to BCC, Sellheyer and Krahl, 2011 showed that the peritumoral stroma of BCC was positive for nestin. It should be interesting to know whether your results confirm this data. I think that this paper and also Lacina et al, 2007 complete background information about BCC and CAFs and should be discussed in the paper.

5- The authors use Student t-test (normal) or MW U-test (non-normal) for statistical analyses. Which are the group of samples in figures 1 and 3 not normally distributed? To compare three different "groups", BCC, peritumoral and buttock, ANOVA and suitable post-test would be most appropriate.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.
Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.
Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.
Yes

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.
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