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Title: Microenvironment and endocrine resistance in breast cancer: friend or foe?

Response to reviewers:

Reviewer 03087939:

The manuscript by xxx, et al. presents an important review on microenvironment and endocrine resistance in breast cancer. The manuscript is well written, and I have not made any other suggestion than that below. Major comments: On page 3, the authors described that "However, to date most experimental and clinical data on the plausible causes of resistance have been carried out in the context of Tamoxifen." This description might not be true. A lot of work has been performed on resistance to aromatase inhibitors, and an mTOR inhibitor, everolimus, has been developed and used in clinical practice.

We thank the reviewer for the comments on our Editorial. As suggested, we removed from the manuscript the following sentence:
"However, to date most experimental and clinical data on the plausible causes of resistance have been carried out in the context of Tamoxifen." Page 3.

Reviewer 00503459

In this article the authors describe the possible mechanisms by which tumor microenvironment may determine endocrine resistance in breast cancer. The article is well written and the topic analyzed of extreme relevance. However, although most on the potential mechanisms are described I suggest to deepen 2 aspects: 1) In the paragraph related to inflammation and endocrine resistance, it will be important to describe more in depth the role of CXCR4 and its ligand CXCL12. In fact, this chemokine system is extremely relevant in the breast cancer development and metastasis having a role in both tumor cells and stromal tissues. For example it was reported that the expression of CXCL12 within the tumor reduce the metastatic behavior, while the transactivation of EGFR by CXCR4 might bypass the ER activity in mediating proliferative stimuli. 2) In the paragraph stem cells and endocrine resistance, a better description on the mechanisms by which tamoxifen treatment may enrich tumors in CSCs.

We thank the reviewer for the positive comments on our paper. We have added information related to CXCR4 and endocrine resistance (page 4). On the other hand, as suggested in 2) we included a sentence with what we believe would be the cause of stem cell enrichment in the context of endocrine treatment (page 5).

In both cases the additional text is concise given that this article aims at setting the stage to further deliberate about the discussed topic, but not to be an in-depth informative review.