Reviewer's report

Title: Intratumoral macrophages contribute to epithelial-mesenchymal transition in solid tumors

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Reviewer: Paola Allavena

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In this paper Bonde et al. investigated in vitro and in vivo the effect of macrophage-derived TGFbeta on intratumor EMT activation.

The authors highlight the correlation between EMT gene and protein expression and the presence of macrophage clusters in tumors. To demonstrate that macrophages produce molecules able to induce EMT, they treated two tumor cell lines with the conditioned medium of a macrophage cell line (activated with Th2 cytokines). They observe that epithelial markers decrease and mesenchymal markers increase when cells are treated with conditioned medium, with a TGFbeta-dependent mechanism. Furthermore they demonstrate that in patient samples of NSCLC there is a positive correlation between intratumoral macrophages densities and EMT markers. They conclude that tumor-associated macrophages modulate EMT by producing TGFbeta.

The study is performed with good accuracy and the results shown are convincing. The paper is also well written.

The function of TAM in tumors and the process of EMT are top-interesting topics in tumor biology.

What reduces a bit the enthusiasm for this paper is the fact that the two major findings:

1- TAM produce TGFbeta, 2-TGFbeta induce EMT, are largely established.

However, a large body of literature in the field of TAM is largely speculative. This study has the merit to demonstrate that this phenomenon indeed occurs in vivo and vitro. The analysis of a huge cohort of tumor specimens from NSCLC patients is also very valuable, and these results support the in vitro/vivo findings in mice.

Minor points:

• The intra-epithelial TGFbeta staining is not shown in the pictures, why?
• Although the use of the RAW macrophage cell line is widely accepted, these cells are not TAM. TAM could be prepared from the mouse tumors, to complement and confirm the findings. This, is just a suggestion to the authors, and not a requirement for this paper
• It is known that during EMT actin changes its distribution from cortical rings to stress fibers.
How is actin in control and treated cells? Is it informative in this system?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests’