Reviewer's report

Title: S100A4-neutralizing antibody suppresses spontaneous tumor progression, pre-metastatic niche formation and alters the T-cell polarization balance

Version: 3
Date: 18 November 2014

Reviewer: Laszlo Nyitray

Reviewer's report:

The authors provided interesting and important new result concerning the role of tumor microenvironment in progression and metastasis. Namely they provide compelling evidence that 1) S100A4 can regulate T-cell differentiation towards a pro-tumorigenic (Th2) phenotype by inducing different cytokine expression profile and 2) they show the efficacy of the previously described monoclonal anti-S100A4 antibody (6B12) in blocking tumor progression and pre-metastatic niche formation by (partially) reversing Th2/Th1 balance in a mouse breast cancer model. The methods they applied are appropriate, the presented results (including figures and tables) are sound and support their conclusion.

- Minor Revisions:
  1. line 273-274: „S100A4-dependent phosphorylation of both kinases” not correct because only Jak3 and not Stat3 is a protein-kinase

- Discretionary Comments, Revisions
  1. Since the authors use mouse models and T cells derived only from mouse for their in vitro experiments, they should comment on the recent concern of using murine models in studying certain (especially inflammatory) human immune responses (see e.g. Seok et al: PNAS 26;110(9):3507-12). Did you repeat or intend to repeat in the future any in vitro experiments with human T-cells to diminish these concerns?
  2. The mechanism of antibody action, from a biology perspective, is clearly explained in the manuscript, however there is an important unknown step in the mechanism of S100A4 action on T-helper cells: the receptor it binds to. You should mention it either in the introduction or discussion and at least speculate about the possible receptor(s).
  3. For the extracellularly added S1004 the authors use oligomeric recombinant protein and one mutant form (G47W). It is not clear from the ms if the latter is a non-oligomerizing form of the Ca-binding protein or simply cannot bind to the unknown receptor. Has it been checked whether the recombinant dimeric S100A4 is ineffective in shifting the Th1/Th2 balance? How about native S100A4 derived from culture medium the T-cells (or any other mammalian cell) – is it oligomeric and would it affect T cells in in vitro assays? Has it ever been checked?
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