Title: Consequences of the cooperation between macrophages and the breast cancer cells MDA-MB-231 for angiogenesis. Proposed molecular mechanism and effect of tetrathiomolybdate.

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Author’s response to reviews:

Dear Sir or Madam,

We would like to submit our manuscript, “Consequences of the cooperation between macrophages and the breast cancer cells MDA-MB-231 for angiogenesis. Proposed molecular mechanism and effect of tetrathiomolybdate,” for publication in BMC Cancer.

The prognosis for inflammatory breast cancer is known to be poor, in large measure due to increased angiogenesis. That there is a causal relationship between inflammation and cancer aggressivity is widely accepted, but many of the molecular and cellular mechanisms responsible remain unclear. Our study was designed to explore the role of the cooperation between macrophages and the aggressive breast cancer cells MDA-MB-231 in angiogenesis promotion. Two major strong points of this work deserve emphasis:

1) We delved further into the cellular and molecular mechanisms responsible for this increased angiogenesis in an experimental model where macrophages and MDA-MB-231 breast cancer cells are cultivated together, thus mimicking in vitro the inflammatory microenvironment of tumours in vivo, which is known to be constituted essentially of cells belonging to the monocyte/macrophage lineage. We found that cancer cells and monocytes interact, and confirmed that this interaction causes the monocytes to acquire an M2 phenotype, favoring angiogenesis and having diminished antitumoral activity. We further showed that the molecular mechanism leading to increased angiogenesis involves secretion
of both CC chemokines and CXC-type cytokines with an ELR motif.

2) We showed that the angiogenesis attributable to the cooperation between monocytes and cancer cells can be inhibited by tetrathiomolybdate. This potent copper chelating agent was already known to inhibit the angiogenesis induced by cancer cells. Our work with the chicken chorioallantoic membrane model extends and completes this observation, by showing that tetrathiomolybdate also inhibits the additional angiogenesis that results from the activation of monocytes by the cancer cells, but without modifying the profile of cytokines secreted in the co-cultures.

In summary, elucidation of the mechanism(s) responsible for angiogenesis in inflammatory cancers is of prime importance for developing effective treatments. However, research teams working on this subject have arrived at very different points of view as to the molecular pathways involved. The work we report here further refines our understanding of the phenomenon by providing important details that need to be taken into account when explaining this inflammation-associated angiogenesis and its inhibition.

Thank you for considering our article. We hope you will find it suitable for publication in BMC Cancer, and look forward to hearing from you soon.

Yours Faithfully,

Pr. Claudine SORIA