Peer Review File

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Reviewer Comments

Comment 1:

INTRODUCTION

Please provide the main pieces of direct evidence that link autophagy, angiogenesis and immune to dormancy. Clarify preclinical and clinical studies.

Reply 1:

Autophagy: The expression of autophagy markers can be found in dormant breast cancer stem cells, and the dormant state of breast cancer stem cells can be reversed by autophagy inhibitors.

Angiogenesis: If tumor cells cannot induce complete tumor angiogenesis, they will enter into dormancy, that is, the balance between pro-angiogenic factors and anti-angiogenic factors or the enhancement of anti-angiogenic factors will inhibit tumor growth and lead to tumor dormancy.

Immune: It has been found in some clinical cases that tumors are prone to relapse after immunosuppressive treatment. Immunosuppressants are considered to evade immune system monitoring by down-regulating specific tumor-associated antigens or destroying host immune system and activating tumor dormancy.

Comment 2:

Fig 1

Include the list of other factors.

Consider to display the fig as potential "hallmarks" of tumor dormancy.

Reply 2: we have modified Fig1 as advised.

Changes in the text: we have modified Fig 1 as advised.

Comment 3:

AUTOPHAGY

Line 65. Please specify what nutrients and the role of Pfkfb3 enzyme on the regulation of autophagy in tumor cells.

Reply 3: Autophagy inhibition elicits emergence from metastatic dormancy by inducing and stabilizing Pfkfb3 expression. Pfkfb3 interacts physically with autophagy machinery, specifically the UBA domain of p62/sequestosome-1. Disrupting autophagy and this event enables Pfkfb3 to drive dormant BCSCs and metastatic lesions to recur.

Comment 4:

Lines 74-86. Besides ROS and Atg7, there might be other vulnerability autophagy checkpoints to consider, particularly in the context of chemoresistance in colorectal cancer (PMID: 30842415), liver cancer (PMID: 30786811), brain tumors (PMID: 30719230), and melanoma (PMID: 30563872). Please include evidences.

Reply 4: we have modified our text as advised.
Changes in the text: we have modified our text as advised.

Comment 5:
Line 109. Please correct gene nomenclature to Beclin 1 for mouse.
Reply 5: we have modified our text as advised.
Changes in the text: we have modified our text as advised.

Comment 6:
Lines 114-117. Please consider to expand and clarify the information (autophagy dual role) about this paragraph or remove.
Reply 6: we have modified our text as advised.
Changes in the text: we have modified our text as advised.

Comment 7:
Lines 118-129. Regarding individualized therapy, genetic data regarding gene variation needs to be provided rather than environmental. For example, PI3K/AKT/mTOR pathway is altered in germline and somatic tissues downstream PTEN (PMID: 30614812) and this could be exploited as actionable mutations or to stratify patients treated with approved inhibitors (eg sirolimus, PI3K inhibitors, etc)
Reply 7: we have modified our text as advised.
Changes in the text: we have modified our text as advised.

Comment 8:
Lines 130-137. It is an interesting topic the effect of nutrient sensing and availability in regards of dormancy. Are there any evidences of sensing changes in dormant cells vs normal cells.
Reply 8: No relevant literature has been found.

Comment 9:
ANGIOGENESIS

It is worth mentioning that the isolation of angiogenic factors lead to the hypothesis of inhibiting angiogenesis to block vessel formation and result in tumor dormancy (PMID: 4332371, PMID: 27197239). Involvement of angiogenesis in dormancy is key for the regulation of tumor growth in mice (PMID: 7585012, PMID: 17056717, PMID: 16537511). Is this also true in humans?
Reply 9: Yes
Changes in the text: we have modified our text as advised.

Comment 10:
Anti-tumor targeted therapy with anti-angiogenic drugs and their targets that block nutrient availability is a pillar of cancer treatment. This constitutes an opportunity to provide some evidence and/or propose new hypothesis about the mechanisms of

resistance and efficacy in the context of target tissue, vessel and immune system, which is the following topic. For example, anti-VEGF monoclonal antibody reduced vascular density and tumor growth in mice bearing xenografts of glioblastoma multiforme, leiomyosarcoma and rhabdomyosarcoma (PMID: 7683111). Another example is the efficiency of metronomic chemotherapy in lung cancer, leading to anti-tumor and anti-angiogenic effects without causing toxicity (PMID: 30305062).
Reply 10: we have modified our text as advised.
Changes in the text: we have modified our text as advised.

Comment 11:
IMMUNE SYSTEM

This is probably the most interesting topic and well elaborated. Please clarify preclinical and clinical evidences for the reader.

Also, consider to add a comment and small review on SASP factors as essential components mediating dormancy, and the interplay with cellular senescence (PMID: 23143977, PMID: 25263564, PMID: 25156255, PMID: 27448982, PMID: 32028565).
Reply 11: We thank the reviewer for this constructive suggestion. we have modified our text as advised.
Changes in the text: we have modified our text as advised.

Comment 12:
Fig 2 Please state the relevance of this balance for current immunotherapy.
Reply 12: we have modified our text as advised.
Changes in the text: we have modified our text as advised.