Peer-review report

Response to the Reviewers' comments

Reviewer 1:

Thank you very much for your important contributions to improving our manuscript.

RESPONSE:

Thank you very much for your important contributions to improving our manuscript.

1.The subtheme "PLATELETS AND STEM CELLS INTERACTION", was modified as suggested and include a table with concise results.

PLATELETS AND STEM CELLS INTERACTION

In mice, ……

Interestingly, bone marrow-derived mesenchymal stem cells (BM-MSCs) produce cytokines and exosomes, promoting tumor growth and metastasis of cancer cells. Recently Wang Q et al. (2018) reported that BM-MSCs presented transdifferentiation TGFß dependent into cancer-associated fibroblasts (CAFs) and perivascular-like cells after co-incubation with platelets which is associated with an overexpression of vimentin, fibroblast activation protein and α-smooth muscle actin cells. Transdiffered-BM-MSCs cell medium had an interesting effect on gastric cancer cells: they became able to metastasize to lung and increased its proliferation and migration toward cancer cells[130-132].

Recently, efforts to create new therapies have been focused on targets related to pathways involved in stemness of breast cancer cells, many of which have already been reviewed in this work. These factors can be transported into platelets or they can be regulated by the platelet content released into the microenvironment. some developed therapies are mentioned in table 1.

On the other hand, several clinical studies suggest that treatment with anticoagulants (AC) or antiplatelets (AP) helps treat cancer by directly influencing platelet behavior and indirectly affecting tumor cells' behavior. A large cohort study of patients showed

that daily use of aspirin, the most commonly used antiplatelet agent was associated with a reduced incidence of malignancy[133] this effect is evident in colorectal, prostate and breast cancer[134,135] and for others types of cancer there is still controversy.

Other antiplatelet in addition to the aspirin has been studied, such as Dipyridamole and RA-233 in pancreatic cancer; Prasugrel in gastrointestinal cancer, Clopidogrel in the pancreatic cancer mouse model and hepatoma carcinoma, melanoma and breast cancer en overall with promissory results. It is clear that more studies are needed and to start thinking about the application of platelet-targeted therapies in cancer in a personalized way.

Table 1. Therapeutic targets related to BCSC pathways and platelet content

Breast Cancer	Target/ Pathway	Treatment Phase	Drug name	Reference
BC	CXCR4	-	Plerixafor	[136]
BC	TGFß	-	Trabedersen	[137]
BC	DDL4/Notch	I	Demcizumab	[138]
BC, TNBC	Notch3	I	AntiNotch3-ADC	[139]
BC	Wnt	I	Ipafricept	[140]
BC	PI3K	I	Alpelisib	[141]
TNBC	PI3K	I	Buparlisib	[142]
MBC	CXCR1	Ib	Reparixin	[143]
BC	EpCAM	II	Adecatumumab	[144]
TNBC	Notch	II	Nirogacestat	[145]
MTNBC	JAK	II	Ruxolitinib	[146]
MBC	VEGF	III	Bevacizumab	[147]

BC- Breast Cancer. TNBC- Triple-Negative Breast Cancer. MBC-Metastatic Breast Cancer. MTNBC- Metastatic Triple-Negative Breast Cancer

Reviewer 2:

Thank you very much for your important contributions to improving our manuscript.

RESPONSE:

1. The total of the cited references has considerably down.

2. The sub theme ROLE OF PLATELETS IN CANCER PROGRESSION AND METASTASIS, has been modified.

RESPONSE:

ROLE OF PLATELETS IN CANCER PROGRESSION AND METASTASIS

Platelets were discovered by the Italian physician Giulio Bizzozero in 1882. In 1906, JH Wright described them as anuclear cell fragments derived from megakaryocytes[65]……

In TNBC, the most aggressive and poorer outcomes form of breast cancer, there are molecules related to self-renewal signaling pathways that are highly activated in TNBC relative to non-TNBC, among them SRC, PTK7, CX26, USP2, PLK1[107].

On the other hand, Jansson et al.[108] reported that the platelet-derived growth factor (PDGF) has a higher expression in the TNBC subtype and concerning this, the prognosis of patients is even worse. Also Camorani et al.[109] considered to PDGFRß as "a reliable biomarker of TNBCs subgroup with invasive and stem-like phenotype[109]." In this sense, several PDGF receptor kinase inhibitors have been developed, among others, the Imatinib, Sunitinib, Sorafenib, Pazopanib, and Nilotinib. Also, it has been developed monoclonal antibodies directed against PDGF or PDGFR, such as MC-3G3 specific to PDGFRα and IMC-2C5, directed against PDGFRβ to delay the tumoral growth[110].

PRIVATE: TO EDITORIAL TEAM

Editorial Office's comments

Issues raised: I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

RESPONSE:

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