Peer Review File

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Reviewer Comments

Reviewer A

Comment 1: I was interested to learn anything about CmP network, but I am as ignorant as before.

Reply 1: We really appreciate the reviewer for his/her expertise and deep understanding of the importance of our work. We genuinely appreciate the reviewer's suggestion, more detailed information about CmPn/CmP signal network are discussed in the revised manuscript.

Comment 2: Page 2, Lines 32: What is CCM?

Reply 2: We really appreciate the reviewer for his/her expertise and deep understanding of the importance of our work. We genuinely appreciate the reviewer's suggestion, we have added definition of CCM in the abstract of the revised manuscript, as "Cerebral cavernous malformations (CCMs), abnormal dilations of small blood vessels in the brain, is contributed by mutated genes like CCM1, CCM2, and CCM3 through the perturbed formation of the CCM signaling complex (CSC)."

Comment 3: Page 4, Lines 71-76: please rephrase and do not copy&paste Abstract

Reply 3: We really appreciate the reviewer for his/her expertise and deep understanding of the importance of our work. We genuinely appreciate the reviewer's suggestion, the revised and highlighted, as "Breast cancer is frequently detected and ranks second in terms of causing death among women due to cancer (1, 2). It constitutes around 30% of all newly diagnosed cancer cases (3-8). The survival rates of breast cancer are greatly influenced by the stage at which it is diagnosed, with early detection leading to higher chances of survival (3, 5, 7). Multiple factors such as family history, alcohol consumption, and hormone exposure play a role in the development of breast cancer (9-11)."

Comment 4: Page 4, Lines 77: please rephrase and do not copy&paste Abstract

Reply 4: We really appreciate the reviewer for his/her expertise and deep understanding of the importance of our work. We genuinely appreciate the reviewer's suggestion, the revised and highlighted, as "Triple-negative breast cancer (TNBC) is a highly aggressive and heterogeneous form of breast cancer, distinguished by the absence of three prominent receptors: estrogen receptor (ER), classic nuclear progesterone receptor (nPR), and Receptor tyrosine-protein kinase erbB-2 (HER2)".

Comment 5: Page 4, Lines 92-94: it is not the genes but their protein products

Reply 5: We really appreciate the reviewer for his/her expertise and deep understanding of the importance of our work. We sincerely appreciate the reviewer's suggestion and fully agree with them. The phrase has been revised and emphasized as requested, as "Deficiency of CCM1, CCM2, and CCM3 proteins, resulting from loss-offunction genetic mutations, contributes to this condition by disrupting the CCM signaling complex (CSC)".

Comment 6: Page 5, Lines 109-113: sentence does not make sense
Reply 6: We really appreciate the reviewer for his/her expertise and deep understanding of the importance of our work. The phrase has been revised as requested, as "This paper aims to provide a concise overview of the signaling networks linked to the CmP/CmPn pathways and their involvement in the development of triple-negative breast cancer. Additionally, it presents an evolving understanding of the role of mPRs in tumorigenesis"

Comment 7: Page 6, Lines 123-126: which tumors? Which tissue type?
Reply 7: We really appreciate the reviewer for his/her expertise and deep understanding of the importance of our work. The sentence has been revised as requested, as "in tumor formation of major types of cancers (37). CCM1, one of the CCM genes, exhibits expression in various tissue types, indicating its diverse contribution to cellular physiology and its broader involvement in tumorigenesis across multiple tissues.".

Comment 8: Page 6, Lines 128: what is reproductive cancer?
Reply 8: We thank the reviewer for their time helping us to improve this manuscript. Reproductive cancer refers to any cancer that originates in the reproductive organs or structures of the body. It can affect both males and females and includes cancers such as ovarian cancer, uterine cancer, cervical cancer, breast cancer, prostate cancer, and testicular cancer.

Comment 9: Page 7, Lines 154-159: please re-write
Reply 9: We thank the reviewer for their time helping us to improve this manuscript. The sentence has been revised as requested, as "The comprehension of mPRs' role in tumorigenesis has undergone an evolving process, in contrast to the well-established classic nPRs. Initially, it was proposed that mPRs are a novel progesterone receptor type that does not elicit genomic actions. However, several studies have identified progesterone receptors in different cellular locations, including the nucleus".

Comment 10: Page 7, Lines 164-167: please re-write
Reply 10: We thank the reviewer for their time helping us to improve this manuscript. The sentence has been revised as requested, as "In summary, this section provides an overview of the present understanding of the signaling networks related to the CmP/CmPn pathways. It investigates the role of these signaling pathways in the development of triple-negative breast cancer (TNBC) and discusses potential applications for future treatment strategies."

Comment 11: Page 8, Lines 173-175: please re-write
Reply 11: We thank the reviewer for their time helping us to improve this manuscript. The sentence has been revised as requested, as "This section aims to provide a brief summary of the factors associated with the CmPn network, the shift from CmPn to CmP (CSC-mPR-PRG) network in nPR(-) TNBC cells, and the significance of the CmP network in TNBC development. Furthermore, we will examine the possible application of these factors in forthcoming treatment strategies."

Comment 12: Page 10, Lines 223-243: please re-write
Reply 12: We thank the reviewer for their time helping us to improve this manuscript. The sentence has been revised as requested, as "Breast cancers exhibit significant clinical heterogeneity, and this variability is particularly prominent in TNBCs (52-55). TNBCs exhibit distinct variations in tumor aggressiveness, relapse rates, response to endocrine therapy, and sensitivity to cytotoxic chemotherapy (56-58). Hence, it is crucial to identify specific prognostic and predictive biomarkers unique to TNBC subtypes to guide clinical decision-making (59-62). Biomarkers, encompassing objectively measurable characteristics, play a vital role in predicting, diagnosing, prognosing, and assessing disease progression, regression, and treatment outcomes. Lehmann's proposed sub-classification of TNBCs has demonstrated variability, ranging from seven to four subtypes, each with advantages and disadvantages based on the context Technological advancements and expression profiling have significantly contributed to a more comprehensive characterization of TNBC subgroups, leading to the identification of precise biomarkers, therapeutic targets, and a better understanding of the underlying molecular mechanisms associated with TNBC (64-68). Tumor immune interactions in TNBCs are intricate and heterogeneous, influenced by diverse gene expressions within the tumor immune microenvironment. Various immune subtypes have been identified, impacting tumor-immune interactions and patient survival (69). Numerous biomarkers and signatures tailored to TNBC subtypes, addressing the challenges of immunotherapy, have been reported with prognostic value (16, 70-74). Early detection of breast cancer is crucial for saving lives, and diagnostic and prognostic biomarkers play a pivotal role in achieving this goal (72, 75-78). Biomarkers provide valuable information regarding cancer staging, location, and signaling cascades involved in cancer development (38, 7983). The discovery of novel biomarkers continues to advance our understanding of TNBC and holds promise for improved diagnosis and treatment."

Reviewer B

Comment 1: While this is a timely and important topic, the treatment of this topic in this review is superficial. Many comments are vague or not well supported by the existing data. Many comments are not fully cited.

Reply 1: We really appreciate the reviewer for his/her expertise and deep understanding of the importance of our work. We acknowledge and respect the reviewer's observation

that significant improvements are required in the writing. This manuscript was initiated by a group of graduate-level students who carefully reviewed our recent publications. It is possible that some superficial comments and vague discussions may have arisen from their limited understanding of the depth of our project. However, during this revision process, we have extensively revised the entire manuscript and included two additional figures to provide a more comprehensive review of the current progress. We believe that our efforts have successfully addressed the concerns raised by the reviewer.

Comment 2: Much of the cited work is over-interpreted - for example, the drug mifepristone is an antagonist for nPR, and also for GR and MR - unless research has proven a role for mPR, all the effects of this agent in TNBC may be due to block or GR or MR or both.

Reply 2: We really appreciate the reviewer for his/her expertise and deep understanding of the importance of our work. We genuinely agree with the reviewer's comments concerning mifepristone, albeit to a certain extent. Regarding the reviewer's comment on mifepristone acting as an antagonist for nPR, GR, and MR, we agree with the reviewer that mifepristone functions as a ligand for both GR and MR while also acting as an antagonist for nPR. However, it has been found, with substantial evidence, that mifepristone acts as an agonist when binding to mPR, contrary to what was mentioned before. Therefore, respectfully, we disagree with the suggestion that there is no research supporting a role for mPR. In fact, this was published last year in Cell Commun Signal (PMID 35971177), where we discovered that progesterone, in conjunction with mifepristone, disrupts the CSC. Moreover, only the knockdown of nPR, not GR or AR, can enhance this effect. Additionally, other works to explore the cellular effects of mifepristone binding to both GR and MR have been done, through omics studies. Our recent work, currently under review, attempts to elucidate the role of CCM1, one of the CCM proteins, by utilizing GR/MR omics data as filtration in an omics study conducted on mouse embryonic fibroblast (MEF) cells that lack GR expression. We understand that many experts in the field may not be aware of these recent results due to their novelty.

Comment 3: The article is also redundant in several areas - it is relatively poorly written, lacks mechanistic information or depth, and there are numerous mistakes. There is simply not much new or in-depth information here.

Reply 3: We really appreciate the reviewer for his/her expertise and deep understanding of the importance of our work. We acknowledge and respect the reviewer's observation that significant improvements are required in the writing. As previously mentioned, this manuscript was initiated by a group of graduate-level students who carefully reviewed our recent publications. It is possible that some superficial comments and vague discussions may have arisen from their limited understanding of the depth of our project. Recognizing this inadequacy, we undertook a thorough revision process, completely overhauling the manuscript. Extensive revisions were made, and we incorporated two

extra figures to offer a more comprehensive overview of the current progress. We are confident that our endeavors have effectively addressed the concerns raised by the reviewer.