Peer Review File

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Reviewer A

Comment 1: The review is ignoring the role of PGRN on immune system and there is no mention of receptors.
Reply 1: Thanks for your comments. This article was focus on the effects of PGRN on cancer cells and related molecular targets, so we ignoring the role of PGRN on immune system. May be in the future research we should discuss the role of PGRN on immune system in our article.

Comment 2: The authors have to make serious commitment to have their manuscript heavily edited for English grammar spelling and typos before it can be reviewed for content.
Reply 2: Thanks for your comments. We have asked a native speaker to modify my article.

Reviewer B

Comment 1: At first, the review needs language editing by a native speaker or an Editing service urgently.
The authors should be clearer in their statements, as e.g. “and so on” (at different places) is not satisfying/sufficient at all.
At several places the references are not sufficient or missing e.g.: Line 27 (not at all), line 96 (not at all), line 97 (not for colorectal cancer), line 132 (not for bladder cancer).
A few statements are not clear. What do the authors want to say with e.g.: Chemotherapy is a vital measure…(line 109)
Reply 1: Thanks for your comments. We have asked a native speaker for language editing and modified the maunuscript as your suggestion. We have modified all the “and so on” and deleted the references which are not sufficient. We have modified the statements “Chemotherapy is a vital measure…(line 109)”.
Changes in the text: Chemotherapy is important for patients with cancer and is widely used for the treatment of unresectable cancer.

Comment 2: What is an antisense cDNA (line 204)? Dong et al. applied a shRNA.
Reply 2: Thanks for your comments. Antisense cDNA technology is a method to inhibit or downregulate the production of a target protein by using antisense DNA or RNA molecules.

Comment 3: The part of PGRN as therapy target is rather short (line 198-209). Of course, there is no anti-progranulin therapy as clinical trial existing yet but here the

reviewer would expect that the authors explain more in detail the shRNA and antibody treatments and their effects.
Reply 3: Thanks for your comments. Indeed, the part of PGRN as therapy target is rather short and we should introduce the role of PGRN as therapy target for cancel treatment. But the therapy target of PGRN is just a small part in this manuscript, so we didn't explain much in detail.

Comment 4: Chapter 5 Future prospects of PGRN is almost only describing that autophagy is important in cancer research and that PGRN may act in the process of autophagy. This is not what the reader expects here. Here the authors may think how PGRN could be a potential target for anticancer therapy.
Reply 4: Thanks for your comments. PGRN is an important target for cancer therapy, and we introduced the effects and signal pathway to explain how PGRN could be a potential target for anticancer therapy. In the Chapter 5, we just want to guess the future effects of PGRN on cancer treatment and autophagy is the promising target.

Comment 5: There is one article describing that granulin (GRN) was upregulated in response to ionizing radiation in PC-3 prostate cancer cells. On the other hand, miRNA-107 enhances radiosensitivity by suppressing granulin in these cells (Lo et al. Sci Rep. 2020 Sep 3;10(1):14584). The authors should mention this article.
Reply 5: Thanks for your comments. we think it's a important information that we ignored and we have added is in our article.
Changes in the text: In addition, PGRN has effects on radiation. Granulin (GRN) was upregulated in response to ionizing radiation in PC-3 prostate cancer cells. On the other hand, miRNA-107 enhances radiosensitivity by suppressing granulin in these cells [52]

Comment 6: Reference 95 (Eissa et al. 2015) has not PGRN as subject.
Reply 6: Thanks for your comments. We have deleted the reference.

Comment 7: However, a loss or strong reduction of PGRN can result in neurodegenerative diseases as, e.g., frontotemporal lobar degeneration. There are already clinical trials ongoing that bring PGRN into patients with neurodegenerative diseases. Although, neurodegenerative diseases are not the subject of this review, the authors should also consider this part of PGRN since its inhibition might have side effects when applied systemically.
Reply 7: Thanks for your comments. Indeed, there are many researches about the role of PGRN in neurodegenerative diseases. But in this article, we focus on the role of PGRN on cancer, so we didn't mention its role in neurodegenerative diseases. Maybe, in the future we would discuss the role of PGRN in neurodegenerative disease, and the raletionship between its role in cancer and neurodegenerative disease.

Comment 8: There are several mistypes:
Line 160: progrnaulin -□ progranulin, line 160 motastasis-□ metastasis, line 182 cnacer-□ cancer, line 188 tussues-□ tissues, line 192 contact-□ correlated, line 193

progrssion-free-□ progression-free, line 214,215 prolgeration-□ proliferation, line 237 furture-□ future

Reply 8: Thanks for your comments. We have corrected all the mistypes.