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1 SPECIFIC COMMENTS TO AUTHORS

I have read with great interest and enthusiasm this review article. Authors present an extensive overview about role and mechanisms related to hypoxia in pancreatic cancer. They show all the relationships between hypoxic environment and other factors involved in pancreatic cancer. The major point of interest of this paper is represented by the interactions between hypoxia and tumor microenvironment components; in fact they play a crucial role in pancreatic cancer progression and resistance to current treatments. The manuscript is well written and clear. I only suggest to improve the manuscript adding some datas about potential treatments directed against hypoxia (i.e. evofosfamide), underlining how and why these agents have failed to demonstrate survival benefit in pancreatic cancer therapy up to date. As for the references, I just to advise to consider the citation of the paper published by Parente P. et al in 2019 in Gastroenterology Research and Practice (Crosstalk between the tumor microenvironment and immune-system in Pancreatic Ductal Adenocarcinoma: potential targets for therapeutic approaches). Based on these considerations, I recommend the paper for publication after improving it with these minor revisions.

Comment 1: I only suggest to improve the manuscript adding some datas about potential treatments directed against hypoxia (i.e. evofosfamide), underlining how and why these agents have failed to demonstrate survival benefit in pancreatic cancer therapy up to date. As for the references, I just to advise to consider the citation of the paper published by Parente P. et al in 2019 in Gastroenterology Research and Practice (Crosstalk between the tumor microenvironment and immune-system in Pancreatic Ductal Adenocarcinoma: potential targets for therapeutic approaches). Based on these considerations, I recommend the paper for publication after improving it with these minor revisions.

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Reply: Thank you very much for your comments on our manuscript and for your suggestions regarding potential treatments directed against hypoxia. We have included a new section at the end of the manuscript, which we have entitled “Potential treatments directed against hypoxia”. New bibliography has been cited (including that suggested by the reviewer) and the bibliography list has been updated.

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2 SPECIFIC COMMENTS TO AUTHORS

The proliferation of pancreatic tumor cells is often accompanied by the underdevelopment of blood microcirculation, and hypoxia leads to the activation of different intracellular pathways and alterations in cellular energy metabolism, all of which are in turn regulated by hypoxia. This paper focuses on the latest research progress on how pancreatic tumor cells adapt to hypoxia, with a novel idea, abundant content, clear arguments and sufficient arguments, but as a whole, there are some problems: 1. some contents in the paper are not marked with references. 2. There are more cytokines involved in hypoxia and MAPKs signaling in pancreatic cancer, and it is suggested to provide a vivid schematic diagram to show more intuitive. 3. The role of ERK5 in the development of pancreatic cancer in the main text is suggested to be further explained. 4. Figures 1, 2, 3 and 4 are not labeled properly, and legends should be provided.

Reply: Thank you very much for reviewing our manuscript, for your suggestions and for drawing our attention to the different points raised.

Comment 1: Some contents in the paper are not marked with references.

Reply: Thank you very much for this observation. We have paid attention on the contents in the paper that were not marked with references. New references have been cited and the bibliography list has been updated.

Comment 2: There are more cytokines involved in hypoxia and MAPKs signaling in pancreatic cancer, and it is suggested to provide a vivid schematic diagram to show more intuitive.

Reply: Following the reviewer´s comment we have included in the revised version of the

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manuscript information about more cytokines involved in hypoxia and MAPKs signaling in pancreatic cancer. New references have been cited and the bibliography list has been updated. We also have worked on the diagram to show more intuitive.

Comment 3: The role of ERK5 in the development of pancreatic cancer in the main text is suggested to be further explained.

Reply: Thank you very much for this observation. A search on the role of ERK5 in the development of pancreatic cancer has been carried out. However, the bibliography found was not abundant. Comment to this has been included in the revised manuscript. The research that we have found has been mentioned and the bibliography list has been updated.

Comment 4: Figures 1, 2, 3 and 4 are not labeled properly, and legends should be provided.

Reply: Thank you very much for calling our attention on this point. At the submission time, we were asked to upload text and figures separately. This could have been the reason why the figures appeared without number and legends. We have included the figures in the whole file of the manuscript, together with the legends to figures. We will maintain the organization of the manuscript as we state here, unless the editor requests the opposite for submission guidelines.