Dear Editors and Reviewers:

Thank you for your letter and for the reviewer's comments concerning our manuscript entitled "A novel perspective in pancreatic cancer therapy: targeting ferroptosis pathway". Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer's comments are flowing:

[Introduction]

1) Page 2 line 22; The author used the term of "deterioration". This term is not quite commonly used in the practice. Please specify what you would like to indicate using this term and consider changing the term from another proper technical term.
Response: Thank you for your valuable suggestion. As your concerning, we change the word "deterioration" to "high probability of malignancy".

2) Page 3 line 1-2; The recent adjuvant chemotherapy for PDAC should be considered. Please refer the following articles: a) Uesaka et al. Lancet. 2016 Jul 16;388(10041):248-57. doi: 10.1016/S0140-6736(16)30583-9. (Adjuvant S-1 chemotherapy) b) Conroy et al. N Engl J Med. 2018 Dec 20;379(25):2395-2406. doi: 10.1056/NEJMoa1809775. (Adjuvant modified FOLFIRINOX)
Response: We have added new adjuvant chemotherapy drugs about PDAC in recent years (Page 3 line 3-8).

3) Page 3 line 15-16; The author stated "More than 90% of PDAC have mutations in KRAS that both promote proliferation and alter cellular metabolism". The reference No.12 does not contain the role of KRAS mutation. Please add correct reference article. Also, the oncogenic KRAS plays a key role for invasion and metastasis of pancreatic cancer. Please mention about these roles of KRAS and cite appropriate articles.
Response: Sorry for our mistake. We have attached the correct references and mentioned that KRAS mutation will affect invasion and autophagy (Page 3 line 22).

4) Page 3 line 21-22; Indeed, the ferroptosis plays a critical role for RCD, the following sentence may give readers an impression of authors' personal opinions. Please reconsider the sentence.: "Ferroptosis is closely related to cystine/cysteine and ROS, so we consider that ferroptosis is a critical RCD of PDAC that may be selectively targeted as an anticancer therapy."
Response: Thank you for your suggestion. Our sentences do have some personal opinions and we have replaced them.

[2.2 Characteristic]
1) Page 4 line 1; The authors stated the points of difference of ferroptosis from other

RCDs. However, the points of difference between ferroptosis and each RCD should be clarified. Please describe these points by each RCD (necrosis, apoptosis and autophagy). It may be more easily to understand if the authors make a figure or table describing the points of difference.
Response: To better understand the difference between these RCDs as you concerned, we have added table 1 to described RCDs in more detail.

[3 Current status of ferroptosis in PDAC]
1) Page 5 line 8-11; In the figure2, it is not clearly stated that the relation between ferroptosis and PDAC. The figure should describe the relation between PDAC and ferroptosis depending on the citation articles. Also, the contents of the figure should be written in the main text. Please reconsider the contents of the figure2 and main text.
Response: Thank you for your valuable suggestion. We redrew Figure 2 and paid more attention to the mechanism of ferroptosis in PDAC and divided the mechanism into four clearer components.

[3.1 Ferroptosis regulated by iron metabolism in PDAC]
1) Page 5 line 14-24; the dynamics of Fe3+ is relatively complicated. Please consider making a figure to explain the main text in this section.
Response: In this chapter, we have described iron metabolism in more detail, added some new ideas, and added the figure 2.

[3.2 Autophagy-dependent ferroptosis in PDAC]
1) Page 7 line 4-7; the sorafenib failed to show the significant contribution for overall survival in pancreatic cancer. If authors would like to mention about the sorafenib, please refer the following article related to sorafenib and pancreatic cancer and explain why the sorafenib failed to this clinical trial: Sinn et al. Eur J Cancer. 2020 Oct; 138:172-181. doi: 10.1016/j.ejca.2020.06.032.
Response: According to your comments, we have added relevant content (Page 10 line 4-11).

[3.5 Ferroptosis regulated by tumor microenvironment in PDAC]
1) Page 10 line 3-6; the authors stated “The tumor microenvironment, including tumor cells, tumor vascular system, extracellular matrix, and immune cells, is an important factor affecting tumor therapy. An article reported that a kind of ferroptosis inducer works by affecting the tumor microenvironment, such as blood flow status, oxygen content, pH value, etc”. This paragraph seems a summary of ferroptosis. If the authors would like to describe multiple roles of ferroptosis in this section, please make a table or figure to explain specific key roles of ferroptosis by each points of view (pH, immune system etc).
Response: Thanks a lot for your points of view. Actually, we mainly convey a new idea that ferroptosis can be induced by changing the microenvironment, and the core step is the generation of ROS. And the original article (Dai Y, Xu C, Sun X, Chen X.

Nanoparticle design strategies for enhanced anticancer therapy by exploiting the tumour microenvironment. Chemical Society reviews 2017; 46(12): 3830-3852 [PMID: 28516983 PMCID: PMC5521825 DOI: 10.1039/c6cs00592f]) is mainly about the specific mechanism, so we don 't have much to do with the specific mechanism, of course we will also change the way of expression so that people can better understand.

[5 Summary and perspective]

1) Page 12 line 27-28; In this section, the authors mentioned about the photo dynamic therapy (PDT). There are few evidences to prove the PDT contributes pancreatic cancer patients' survival (Wang et al. Photodiagnosis Photodyn Ther. 2020 Sep; 31:101876. doi: 10.1016/j.pdpdt.2020.101876.). Also, there is no citation to reveal the relations between PDT and pancreatic cancer, and PDT and ferroptosis. If the authors would like to mention about PDT, please describe specific mechanism why the PDT contributes to pancreatic cancer treatment, or, please consider cut these sentences.

Response: We have removed this inference considering that the evidence may not be sufficient.

Minor points **[Introduction]**

1) Page 2 line 23; There is a significant consideration whether the following sentence is grammatically correct: "Surgery is the only cure for PDAC, but most patients are diagnosed as advanced and lack of opportunity for radical surgery due to the absence of distinctive clinical symptoms."

Response: We change this sentence to "Surgery is the only way to cure PDAC, but due to the lack of distinctive clinical symptoms, most patients are diagnosed as advanced and lack the opportunity for radical surgery."

[3.4 Ferroptosis regulated by lipid metabolism in pancreatic cancer]

1) Page 9 line 7-8; The author stated "Therefore, we can study ferroptosis by studying the key enzymes (ACSL4, LPDACAT3, and ALOXs) in lipid oxidation." It seems that the sentence includes the authors speculation. Please consider to move this sentence for "4 Inducing ferroptosis to treat pancreatic cancer" section.

Response: According to the suggestion, we remove it to a suitable position (4.3 Lipid metabolism).