Response to Reviewers' comments

We firstly thank the reviewer for his/her valuable comments. And also, I would like to thank the editor for giving us the opportunity to revise our paper. We have read the comments from the reviewer carefully and have made great efforts to modify and revise our paper as required. A point-by-point response to the reviewer' comments was as follows:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Correction requested.

Answer: Thank you for your advice. We have revised our manuscript as required. Besides, we have already invited native English speakers to polish our manuscript. The editorial certificate has been uploaded. Please check it.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Comments about the manuscript: "The Role of Tumor-Associated Macrophages in Common Digestive System Malignant Tumors" Cancers of the digestive system have a high incidence and mortality rate. Among the factors of the tumor environment, macrophages associated with tumors can have an effect on the prognosis of these cancers of the digestive system. Indeed, the phenotype of these macrophages can be antitumor (M1) or on the contrary pro-tumor (M2) and in the latter case, macrophages can play a crucial role in tumor invasion, growth, angiogenesis, presence of metastases, immunosuppression and resistance to cancer treatments. The aim of the review presented in this manuscript was to summarize the role of tumor-associated macrophages in oesophageal, gastric, colorectal, pancreatic and hepatic cancers. This particularly interesting article gives an overview of this question and it

seems to me useful both for doctors, researchers, students and for all those interested in this public health issue. I have no comments to make on the content, very rich and clearly explained.

I have only a few minor remarks to make to improve the understanding of the manuscript. There are many abbreviations. It would be useful to give a list with their meaning, at the beginning or at the end of the text.

Answer: Thank you for your advice. We extremely agree with your idea. We have added the list of abbreviations at the end of our manuscript. Please check it.

Page 45, figure 1: I really appreciate this figure and figure 2, useful for following the text, but I think a quick summary of the different parts of the figure in the legend would be useful. Page 46, figure 2: same comment as above.

Answer: Thank you for your suggestions. We extremely agree with your idea. We have added the figure legends in both figures 1 and 2, which is as follows:

Figure 1 TAMs can promote the development of tumors. TAMs can affect cancer progression through multiple mechanisms, which are varying in EC, GC, CRC, PC, LC. Color differences indicate various strategies the TAMs use on their targets, the arrows represent secretory or regulatory behaviors, and braces represent combined action of the factors. Moreover, the pink icons stand for common signaling pathways and the green icons, biological processes. In EC, GDF-15 and TGFR are involved in regulations. In GC, stimulation with anti-inflammatory triggers, growth factors, chemokine, exosomes and enzymes, leads to expression of transcription factors. In CRC, TAMs work with exosomes, MMP and cathelicidin, concerning signaling pathways, cell cycle transition, metabolic reprogram, inflammatory pathways and oxidative stress. In PC and LC, TAMs regulate their development similarly through interleukins and TLR4, leading to activation of transcription factors and EMT of tumors. Thus, TAMs can regulate digestive system malignant tumors by diverse direct and indirect mechanisms.

Figure 2 TAMs act as potential therapeutic targets for tumors. Multifarious strategies for modulation of TAMs are unveiled for therapeutic applications, which are varying in different digestive system malignant tumors. Color differences indicate

various approaches to regulate TAMs' behaviors, the arrows represent secretory or regulatory behaviors, and braces represent combined action of the factors. Moreover, the pink icons stand for common signaling pathways, the green icons stand for biological processes, and the purple icons stand for different reactions of TAMs, including TAMs' polarization, activation, recruitment, trafficking, infiltration, transcription, and so on. Tumor and immune cells secrete growth factors, cytokines, chemokines, metabolites and extracellular vesicles that promote TAM protumor polarization. Besides, RNA, virus and specific cells also exert influence on TAM plasticity and activation. Several key signaling pathways are involved in these regulation processes, including PI3K-Akt-mTOR, NF-κB, STING, and so on. Thus, TAMs can act as a promising potential therapeutic target for digestive system malignant tumors.

Page 47, table 1: like for figures 1 and 2, this useful table requires some explanation in the legend. Page 49, table 2: like for figures 1 and 2, and table 1, this useful table requires some explanation in the legend. Tables 1 and 2 contain a great deal of information available to the reader. However, these tables lack a reading key: the indications are so abundant that the reader like me feels a little drowned in the information. It would seem useful to me that the content of each table be explained in the legend. Similarly, the abundance of abbreviations seems to me to require a glossary of these.

Answer: Thank you for your advice. We extremely agree with your idea. We have added some explanations in both tables 1 and 2, which is as follows:

Table 1: TAMs contribute to the development of EC, GC, CRC, PC and LC. The effective factors are TAMs and their derivants or secretions. The function indicates that how these factors exert influence on tumor progression, concerning proliferation, invasion, metastasis, migration and so on. In addition, the mechanism indicates the corresponding signaling pathways or regulatory intermediates, through which TAMs and their derivants promote or suppress development of the cancers. The last column indicates the corresponding reference of the entry.

Table 2: In EC, GC, CRC, PC and LC, there are multifarious approaches to regulate TAMs, the effective factors of which, and corresponding types, are presented in the

second and third column. The targets indicate which behaviors of TAMs that are modulated. In addition, the functions, mechanism and reference section are similar as Table 1.

Very minor: Page 10: use italics to write H. pylori.

Answer: Thank you for pointing this. We have corrected it in our manuscript as required. Besides, we have already invited native English speakers to polish our manuscript. The editorial certificate has been uploaded. Please check it.

Page 16: “high serum levels of taurocholic”: write "High" (upper case for the first letter).

Answer: Thank you for pointing this. We have corrected it as required. Please check it.

Editorial Office's comments

Company Editor-in-Chief: To the Editor The manuscript has an excellent quality and very clear exposition.The most important aspects of role played by macrophages in the tumor environment and the possible effect of the target terapy are explained with remarhable expertise. However no comment was made of the interaction of macrophages and Tcells refered by many authors. We enclose a manuscript in which T cells are described.Depend the accetance by the authors the publicationsi nce in the present,reffered as a review it is incomplete. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8073377/ Cancers (Basel). 2021 Apr; 13(8): 1946. Published online 2021 Apr 18. doi: 10.3390/cancers13081946 PMCID: PMC8073377PMID: 33919517 The Role of Macrophages in Cancer Development and Therapy Ewa Cendrowicz,1 Zuzanna Sas,2 Edwin Bremer,1 and Tomasz P. Rygiel2,*

Answer: Thank you for your advice. We extremely agree with your idea. We have added the part “Interaction of TAMs and T cells” in our manuscript as required. Please check it.