ANSWER TO REVIEWERS

General comments

We would like to thank the reviewers and editor for their comments and constructive criticism, we are thankful for the interest in our draft and hope that in this revision have improved the quality of our manuscript to your satisfaction, bellow we will answer the reviewers and editor´s comments and point to the modifications in our text.

To the editor:

We have reviewed the text according to both your comments and the reviewers´ comments as well as the crosscheck report. The changes that have been made to the original manuscript have been highlighted in yellow in the revised manuscript and the figures and legends placed in the end of the file as requested.

Name of journal: World Journal of Transplantation

Manuscript NO: 42034

Title: Immunometabolism: a target for the comprehension of immune response toward transplantation

Reviewer's code: 03742333

Reviewer's country: United Kingdom

Science editor: Ying Dou

Date sent for review: 2018-09-13

Date reviewed: 2018-09-13

Review time: 22 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

I have read with great interest the manuscript entitled "Immunometabolism: a target for the comprehension of immune response toward transplantation". In this minireview the authors explore how the modulation of the metabolism of immune cells can affect their function and, consequently, interfere on transplant outcomes. The manuscript is well written and reads well, however it may benefit from the amendments described below.

We are happy the subject spikes the interest of the reviewer and finds the text is well-written. Major comments: 1. The aim of the review is not clearly stated along the document. The inclusion of a clear statement at the end of the introduction may clarify the objective of the review to readers. Hence, it would make the manuscript easier to be followed. *We agree with suggestion and have added statement paragraphs at the end of the introduction and other sections. In the end of the introduction we have added the following statement: "Understanding the impact of cell metabolism on the fate and function of immune cells is important to design therapeutic strategies which increase chances of a successful transplantation outcome. In the following sections, general metabolic pathways as well as some of the distinct metabolic features and requirements observed in effector and suppressive cell subsets will be discussed."* p2. The second session of the manuscript is entitled "The crosstalk between cell metabolism and immune response", however it predominantly focusses on description of cellular metabolic pathways. The crosstalk between this and immune response is not explored in detail. The title of the session or its content should be amended accordingly. *We have now divided this section into two sections, the first entitled: "MAIN METABOLIC PATHWAYS INVOLVED IN IMMUNE CELL FATE" which gives the general overview of metabolic pathways which are most described in immune cell fate, in this section the text itself has not suffered great alterations but we created a second section entitled "THE CROSSTALK BETWEEN CELL METABOLISM AND IMMUNE RESPONSES" which focuses in the changes of metabolic pathways in resting and activated states of DCs and T cells* 3. Figure 1, legend. Please expand the title of the figure. "Six general metabolic pathways" is used without any other context. For example, "Six metabolic pathways highly relevant for immune cells functions". *The figure legend now reads: Six main metabolic*

pathways relevant for immune cell function. 4. First paragraph, session "Metabolic reprogramming of immune cells and transplantation", please clarify which important stress pathways can be activated. Additionally, the paragraph has only one phrase. Splitting it in 2 phrases, at least, would facilitate the interpretation. *"Metabolic reprogramming in immune cells is discussed in section "THE CROSSTALK BETWEEN CELL METABOLISM AND IMMUNE RESPONSES" and intervention in this metabolic pathways and transplantation are now more thoroughly addressed in section "TARGETING METABOLIC PATHWAYS IN TRANSPLANTATION"* 5. Last paragraph, session "Metabolic reprogramming of immune cells and transplantation", In which context it was demonstrated that the combined treatment promoted allograft survival? Was it an animal model? Was it a transplant model? *The text has been modified to clarify these questions* e.g. *"Using murine models of skin and heart allograft transplantations, another study showed the effects of glycolysis and glutamine metabolism inhibition*" 6. In the conclusion, it is said that there are a "handful of studies which have specifically targeted metabolic pathways to promote transplant tolerance". Those are not easily identifiable throughout the manuscript. To enhance the comprehensiveness of the paper, I would suggest to authors create a table detailing the existing studies, the metabolic pathways targeted and the evidence of tolerance/ immune cells affected. *We recognize that the term handful has been ill placed and unfortunately studies specifically targeting metabolic pathways are lacking, a table would indeed be very instructive in case of summarizing a large number of case studies and preclinical interventions, which is not the case, we are still in the initial phases of understanding how metabolic reprograming affects immune cells thus intervention studies are still in the next step. We did add an extra figure depicting preferred metabolic pathways in different populations of T cells (Figure 2). In conclusions the phrase which contains handful of studies has been altered to "Immunometabolism is a very new field to be explored, studies which have specifically targeted metabolic pathways in the field of transplantation are only beginning to emerge..".* Minor comments: 1. First paragraph, session "The crosstalk between cell metabolism and immune response", the abbreviation ATP is introduced without any definition. Please define the abbreviation on the first use. For example, "adenosine triphosphate (ATP)". 2.

Last paragraph, session “Metabolic reprogramming of immune cells and transplantation”, one bracket is inserted probably by mistake (“immune) ameliorated”), please remove it. Additionally, between references 31, 32 and 33 the word “regulation” is left alone and out of context, please amend it. *Manuscript has been proofread and alterations have been made.*

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PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

Manuscript NO: 42034

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Science editor: Ying Dou

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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

an excellent and timely review article , a pleasure to review

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PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

Manuscript NO: 42034

Title: Immunometabolism: a target for the comprehension of immune response toward transplantation

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Science editor: Ying Dou

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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
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SPECIFIC COMMENTS TO AUTHORS

This mini review briefly introduced metabolism and its impact on immune system. I think this is a very interesting review and it will help reader to understand the impact of metabolism on prevention and treatment strategies in transplantation. However, some

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aspects of this manuscript should be improved. 1. Authors should provide one or two illustrations for the crosstalk between metabolism and immune responses, particularly focusing on T cell. It will be helpful for reader to understand this field We have added a second figure in the manuscript depicting metabolic pathways in naïve, effector T cells and Tregs. 2. Authors should discuss more about targeting few candidate metabolic molecules that play important roles in organ transplantation as the title stated. *We haved expanded on this section and enriched discussion, unfortunately as it is a very fresh subject there is more data on DC and T cell metabolism and not so many specifically in transplantation but we now cite some possible targets such as pharmacological intervention such as activation of AMPK signaling by* ***peroxisome proliferator-activated receptor gamma coactivator (PGC) and Resveratrol*** *to enhance PGC-1a activity has been demonstrated to generate tolDCs (Svajger U,, et al. doi:10.1111/j.1365-2567.2009.03205.x)", inhibition of glycolysis by* ***targeting mTORC1 or 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3),*** *to reduce GVHD mortality and morbidity (Nguyen et al DOI: 10.1172/JCI82587) and inhibition of glycolysis* ***by 2-deoxyglucose (2-DG), 6-diazo-5-oxo-L-norleucine (glutamine metabolism inhibitor) and metformin*** *to prevent or delay rejection in fully mismatched skin and heart murine allograft transplantation models Lee et al, DOI: 10.1016/j.celrep.2015.09.036* 3. Few recent publications in T cell metabolism should be cited. *We haved added a few extra recent publications e.g. (Almeida, L., et al (2016). Semin Immunol 28(5): 514-524.; Franchina, D. G., et al (2018). Cancer Lett 412: 216-223.; Galgani, M., V. et al (2016). J Immunol 197(7): 2567-2575.). Because it is a minireview we wish to keep the size of the manuscript concise so unfortunately we cannot expand too much.*

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