Number ID Review: 02540650.

The idea is not innovative and is frequently studied Details of the manuscript lacking role of aldehydes in organ transplantation language requires dramatic improvement

ANSWER:

- We are very grateful to Reviewer for your relevant comments and revision time.
- Now, the manuscript has been enriched with the role of aldehydes in organ transplantation (Please see pages 14, 15 and 16).
- The innovation has been increased by including newly reported data and perspectives on the activation of ALDH2 in fatty liver graft cold preservation, recently presented at the American Transplantation Congress held in Seattle, June 2-6, 2018 (Please see page 15). Please, see abstract accepted in ATC 2018. See Reference in Bibliography section.
- The new version of manuscript has been corrected by native English-speaking scientific editors employed by the Language Service of the University of Barcelona.
- Bibliography updated.

Number ID Review: 03074879 1.

This paper summarized the paper about ALDH2 on oxidative stress, autophagy and apoptosis in IRI, and elaborated the role of it, and listed the relevant paper. Not only on the mechanism are described, but also for the heart, brain, elaborates the role of the small intestine, kidney, and at the last channeling theory to practice, there may be a major role in organ transplantation. 2.The article has a clear idea, the language is rigorous and methodical, and the effect of ALDH2 on IRI is elaborated. In addition, the effect of oxidative stress and autophagy and apoptosis in IRI was illustrated with a graph. 3.In this paper, oxidative stress, autophagy and apoptosis are used to elucidate the role of IRI. It can be suggested that the authors add necrosis and pyroptosis to explain the role of IRI. Apart from the heart, brain, small intestine, kidney, liver, you can look up the function of eyes.

ANSWERS:

-We greatly acknowledge to the reviewer his important comments, considerations and devoted time for the revision of the manuscript. In the newest version of the manuscript we have reviewed necrosis and necroptosis under new light and we found new necroptosis markers affected by ALDH2, enriching the manuscript more than if it was just with apoptosis alone (Please see pages 7 and 8).

- Concerning piroptosis we found that is a programmed cell death that depends on the activation of caspase-1, a proinflammatory caspase that is not required for apoptosis to occur (*Miao et al., 2010*). Recently, the promotion of piroptosis by alcohol-induced activation of the inflammasomal pathway in hepatocytes has been observed both in liver samples from patients

with AH and in ALD animal models (*Heo, 2018*). However, as far as we know, the role of ALDH2 in pyroptosis has not been described. Nonetheless, future studies should be aware of that possibility.

Miao EA, Leaf IA, Treuting PM, Mao DP, Dors M, Sarkar A, Warren SE, Wewers MD, Aderem A. Caspase-1-induced pyroptosis is an innate immune effector mechanism against intracellular bacteria. *Nat Immunol.* 2010; **11**:1136–1142. [PubMed: 21057511

Heo MJ, Kim TH, You JS, et al. Alcohol dysregulates miR-148a in hepatocytes through FoxO1, facilitating pyroptosis via TXNIP overexpression. Gut Published Online First: 23 February 2018. doi: 10.1136/gutjnl-2017-315123

- Thanks to the reviewer suggestion we found more organs affected by ALDH2, in this case, the eyes, widening the perspective of this manuscript (Please see page 10).

-New references were included in Bibliography section.

Number ID Review: 03475142.

This review is designed to investigate the role of ALDH2 in ischemia reperfusion injury. It is the reviewer's opinion that the manuscript is quite interesting and easy to follow. It appears that there is a concern in the review. 1) It is clear in the review that ALDH2 modulates pathways involved in the pathophysiology of IRI associated to oxidative stress, autophagy and apoptosis. However it is not clear which type of cells play a role under ALDH2 administration. The authors should discuss about the point.

ANSWERS:

-We greatly acknowledge to the reviewer the suggestions concerning to the type of cells playing a role under ALDH2 administration. Surprisingly there are few examples of different cell type interaction regarding ALDH2 given the relevance of the topic (Please see page 17). Manuscript improved raising awareness about that matter.

-New references were included in Bibliography section.