

## Answering Reviewers

### 1. Reviewer's code: 02650654

#### **SPECIFIC COMMENTS TO AUTHORS**

If possible, state the clinical applications of agents lowering Portal Hypertension.

#### **Answer:**

Some drugs related to signaling pathways have been mentioned, such as statins, sodium ferulate, celecoxib and octreotide. The pathways in which these drugs work are briefly explained. Since this paper mainly studies the basic signaling pathways involved in the development of PHT, and most of the drugs used in clinical practice have not involved the corresponding signal pathways, so no further details have been given.

### 2. Reviewer's code: 02528832

#### **SPECIFIC COMMENTS TO AUTHORS**

Well structured manuscript that deals with a complex issue, summarizing some recent research about some molecular alterations observed in portal hypertension. I have some minor suggestions: 1. Although many abbreviations are clarified in the text, I prefer - as the authors state- that they are ALSO written in full at the beginning of the manuscript. 2. Figure legends should also provide the full name of the abbreviated receptors/transcription factors depicted. 3. I think that English could be improved.

**Answer:** The abbreviations referred to in the text have been enumerated in detail at the beginning of the article, and the full name of the abbreviation is also explained below each figure. The language of the article has been improved.

### 3. Reviewer's code: 00006459

#### **SPECIFIC COMMENTS TO AUTHORS**

This ms has good, albeit limited, content, but it is not well organised, nor is it edited for clarity. It is difficult for most readers to digest: Organising by subtopic and providing headings and subheadings will be helpful. Then reconsider the title. Is vasoconstriction pro-fibrotic? Is hypertension profibrotic? Cellulose is mentioned as a product of HSC; what word was

intended? Cellulose is a plant product. The suggestion that Nrf2/HO-1 is a target is over-stated. Many things are unclear; eg that celecoxib is a COX2 inhibitor. The figures need to have greater clarity. FIG 1 is far too complex to communicate to readers. In both figs, the cell type that each pathway is in must be clear. There must not be a mixture of intracellular pathway, pathological process and cell types all in a single diagram. For example, lines from COX2 to inflammation and angiogenesis is not helping clarity. For example, the one pathway in fig 2 cannot occur in all cell types relevant to 3 processes; fibrosis, vasodilation and angiogenesis. Figure legends should define acronyms, such as COX, used in fig. Fig 2: ADMA links to AGXT2, which is an important enzyme, but is not considered. COX2 inhibition is anti-fibrotic; this is not considered. Regarding individual signaling pathways, please add discussions on how each of these pathways may be contributing to PHT pathophysiology. Calling JAK/STAT “newly discovered” is not correct. The author contribution statement is odd; it is a review so there was no experiment. The English needs improvement. Examples include 3rd sentence of Core Tip, page 5 “It [what?] may be ...” Page 5: “promotes splitting” doesn’t make sense.

**Answer: 1. The subtitle has been set in the article so that the reader can better understand the article. 2. Fibrosis and vasoconstriction promote the formation and development of portal hypertension. 3. Cellulose is a writing error, and what is meant in the text is the production of fibrillar collagen. 4. The suggestion that Nrf2/ HO-1 is the target has been removed. 5. In order to let the reader better understand the meaning of the picture, I have divided the picture into three parts. In addition, the signaling pathways will eventually evolve from upstream to downstream to participate in PHT through fibrosis, vasoconstriction, etc. So, the pathological changes involved also are placed in the picture to facilitate the readers have a better understanding. 6. Line from COX2 to inflammation and angiogenesis has been removed in Figure 3. In addition, the relationship between ADMA and AGXT2 has been described in the text. 7. The language of the article has been improved.**