The Journal of Physiology

Hepatic Stellate Cells in Physiology and Pathology

Dakota R Kamm and Kyle S McCommis
DOI: 10.1113/JP281061

Corresponding author(s): Kyle McCommis (kyle.mccommis@health.slu.edu)

The referees have opted to remain anonymous.

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Submission Date:	30-Nov-2021
Editorial Decision:	04-Jan-2022
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Accepted:	04-Feb-2022

Senior Editor: Ian Forsythe

Reviewing Editor: Maria Chondronikola

Transaction Report:

(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. Depending on transfer agreements, referee reports obtained elsewhere may or may not be included in this compilation. Referee reports are anonymous unless the Referee chooses to sign their reports.)

1st Editorial Decision **04-Jan-2022**

Dear Kyle,

Re: JP-TR-2021-281061 "Hepatic Stellate Cells in Physiology and Pathology" by Dakota R Kamm and Kyle S McCommis

Thank you for submitting your Topical Review to The Journal of Physiology. It has been assessed by a Reviewing Editor and by 2 expert referees and I pleased to tell you that it is considered to be acceptable for publication following satisfactory revision.

The reports are copied at the end of this email. Please address all of the points and incorporate all requested revisions, or explain in your Response to Referees why a change has not been made.

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I hope you will find the comments helpful and have no difficulty in revising your manuscript within 4 weeks.

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I look forward to receiving your revised submission.

Best wishes,

Ian

Ian D. Forsythe
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EDITOR COMMENTS

Reviewing Editor:

Thank you for your submission to the Journal of Physiology. The referees have favorably reviewed your manuscript with a few minor comments/suggestions. Once these comments have been successfully addressed, the manuscript will be acceptable for publication to Journal of Physiology.

Please also see 'Required Items' below.

Senior Editor:

Thank you for this interesting review. In addition to the amendments suggested by the referees, the authors should re-write the abstract so as to provide more factual information about the topics of their review and please come to a clear conclusion (you may say more work is needed, but that is always there case and is best left to that section of your main text). You also need a summary diagram or abstract figure and Ideally I wonder if you can add a figure to provide a general background to liver cell subtypes/function for your introduction (so as to make your work more relevant to a wider audience).

REFEREE COMMENTS

Referee #1:

Here, the authors review what is known about the functions of hepatic stellate cells (HSCs), integrating the historical view with recent data derived using modern methods (e.g. scRNA-Seq), then look toward the future of research in HSC biology. Overall, this is an excellent review: Thorough, balanced, and well-written. I have only very minor comments:

1) I would appreciate if the authors could provide a table to briefly summarize the major studies and/or effects of HSCs in development, regeneration, and as stem cells. This would provide an excellent quick-reference for readers.

2) In the section "The Quiescent Hepatic Stellate Cell," the authors provide a nice historical overview of HSC discovery and biology. For the sake of completeness, it may be worth mentioning that HSCs are also known as Ito cells after Toshio Ito, who re-discovered them after Kupffer decided late in his career that HSCs were actually just a sub-type of Kupffer cells. (Reuben. Hepatology. 2002.)

3) In the same section, the authors mention that serum RBP is used as a biomarker of retinoid deficiency. This is true, but it should be described as an adjunct to serum vitamin A measurement, the latter being the primary marker of vitamin A deficiency. The principal use of serum RBP is actually assessment of nutritional status because it is rich in essential amino acids and so synthesis decreases in malnutrition. It is also an acute phase reactant. Thus, it can serve as an adjunct for retinoid status, but it is neither sensitive nor specific for that.

4) In paragraph 2 of the section "Hepatic Stellate Cell Heterogeneity," the authors describe studies that identified "a total of 9 separate" HSC populations, but I only counted 7 in the following few sentences (then again, I'm reviewing this late at night so I could be miscounting). Can the authors correct this, or explain it more clearly to avoid confusion.

Referee #2:

Kamm and McCommis have provided a review of hepatic stellate cell biology and function. The review is informative, insightful, and well organized. There are a few topics that could also be discussed and there are also some suggestions for improvement.

One topic that could be better addressed is a discussion of the developmental origins of stellate cells, which doesn't seem to have been mentioned. How is the pool of HSCs replenished? Proliferation of the existing pool? What are the defining

markers of these cells?

There's some good discussion of lipid droplet lipolysis. Are the lipases or hydrolases that mediate this known?

In many types of fibroblasts, metabolic changes geared to turn glucose into collagens and other components of the ECM are known to occur. Is that the purpose of the metabolic changes with HSC activation?

There are several instances where the writing could be improved by word or phrase choice. Please carefully review the manuscript throughout. Here are some that could be considered.

1. P5 - vitamin A compounds - metabolites might be a better word

2. P6 - adipose should be followed by "tissue" or replaced with adipocytes

3. P7-8 "During quiescence" seems odd since it is a state not a period of time. Consider "In quiescent cells" - same sentence, I think that "are" should be "is" since it refers to "expression" which is singular

4. P13 and P14- two sentences in a row start with "In actuality" and "In fact". Seems weird to have two sentences in a row start with phrases like this.

5. P14 - perform paracrine signaling -P15 -regeneration is performed - consider replacing perform with more appropriate words. The connotation doesn't seem right

6. P15 - "it's" is possessive here and should be "its"

REQUIRED ITEMS:

-Please include an Abstract Figure. The Abstract Figure is a piece of artwork designed to give readers an immediate understanding of the Review Article and should summarise the main conclusions. If possible, the image should be easily 'readable' from left to right or top to bottom. It should show the physiological relevance of the Review so readers can assess the importance and content of the article. Abstract Figures should not merely recapitulate other figures in the Review. Please try to keep the diagram as simple as possible and without superfluous information that may distract from the main conclusion of the Review. Abstract Figures must be provided by authors no later than the revised manuscript stage and should be uploaded as a separate file during online submission labelled as File Type 'Abstract Figure'. Please ensure that you include the figure legend in the main article file. All Abstract Figures will be sent to a professional illustrator for redrawing and you may be asked to approve the redrawn figure before your paper is accepted.

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END OF COMMENTS

Confidential Review **30-Nov-2021**

EDITOR COMMENTS

Reviewing Editor:
Thank you for your submission to the Journal of Physiology. The referees have favorably reviewed your manuscript with a few minor comments/suggestions. Once these comments have been successfully addressed, the manuscript will be acceptable for publication to Journal of Physiology.

Thank you to the editors and reviewers for the kind words and interest in our topical review article. Please see below for our responses to individual critiques (in blue text). These were all very insightful suggestions and we feel these additions have certainly enhanced this review.

Please also see 'Required Items' below.

With this revised submission, we have included this response to reviewers document, the complete text document Word file, a Word file copy with changes highlighted in red text, an abstract figure, each figure as a separate high-quality file, and short author profile/pictures.
*The author instructions mentioned the possibility of figures being redrawn or enhanced by a professional illustrator, which I am certainly fine with! I am not much of an artist, but have tried my best!

Senior Editor:
Thank you for this interesting review. In addition to the amendments suggested by the referees, the authors should re-write the abstract so as to provide more factual information about the topics of their review and please come to a clear conclusion (you may say more work is needed, but that is always there case and is best left to that section of your main text). You also need a summary diagram or abstract figure and Ideally I wonder if you can add a figure to provide a general background to liver cell subtypes/function for your introduction (so as to make your work more relevant to a wider audience).

Thank you for these excellent suggestions. We have made significant changes to the abstract which we believe better summarizes the details of the review. We have also created an abstract figure, as well as a new suggested Figure 1 which describes the hepatic architecture with functions described in the figure legend.

REFEREE COMMENTS

Referee #1:
Here, the authors review what is known about the functions of hepatic stellate cells (HSCs), integrating the historical view with recent data derived using modern methods (e.g. scRNA-Seq), then look toward the future of research in HSC biology. Overall, this is an excellent review: Thorough, balanced, and well-written. I have only very minor comments:

Thank you for the kind words! Our response to specific critiques is marked in blue below.

1) I would appreciate if the authors could provide a table to briefly summarize the major studies and/or effects of HSCs in development, regeneration, and as stem cells. This would provide an excellent quick-reference for readers.

Thank you for this suggestion. While this is a great idea and would indeed be a nice reference for studies in these research areas, we believe it would be much too comprehensive of a table to add to this review. While HSC studies in development, regeneration, or as stem cells are far less prevalent compared to HSC fibrogenesis, the number of studies in these areas is still quite extensive. Due to Journal length and reference number limitations, we would not be able to provide an accurate description and citation to all of the studies in these areas. That said, we believe we have covered a

reasonable amount of this literature in the review. Additionally, we have cited several other review articles specific to studies of these topics, including a recent review from 2021. We hope that this response is satisfactory to the reviewer. Thank you.

2) In the section "The Quiescent Hepatic Stellate Cell," the authors provide a nice historical overview of HSC discovery and biology. For the sake of completeness, it may be worth mentioning that HSCs are also known as Ito cells after Toshio Ito, who re-discovered them after Kupffer decided late in his career that HSCs were actually just a sub-type of Kupffer cells. (Reuben. Hepatology. 2002.)

This is a good point, and a sentence along with this citation has now been added.

3) In the same section, the authors mention that serum RBP is used as a biomarker of retinoid deficiency. This is true, but it should be described as an adjunct to serum vitamin A measurement, the latter being the primary marker of vitamin A deficiency. The principal use of serum RBP is actually assessment of nutritional status because it is rich in essential amino acids and so synthesis decreases in malnutrition. It is also an acute phase reactant. Thus, it can serve as an adjunct for retinoid status, but it is neither sensitive nor specific for that.

Thank you for this clarification. We have modified this sentence to state that RBP in combination with serum vitamin A measurement.

4) In paragraph 2 of the section "Hepatic Stellate Cell Heterogeneity," the authors describe studies that identified "a total of 9 separate" HSC populations, but I only counted 7 in the following few sentences (then again, I'm reviewing this late at night so I could be miscounting). Can the authors correct this, or explain it more clearly to avoid confusion.

Thank you for pointing this out. It is difficult to describe these since almost all of the 9 populations contain some amount of cells from each condition. But we have made a few changes that we hope makes this more clear.

Referee #2:

Kamm and McCommis have provided a review of hepatic stellate cell biology and function. The review is informative, insightful, and well organized. There are a few topics that could also be discussed and there are also some suggestions for improvement.

Thank you for the kind words! Our response to specific critiques is marked in blue below.

One topic that could be better addressed is a discussion of the developmental origins of stellate cells, which doesn't seem to have been mentioned. How is the pool of HSCs replenished? Proliferation of the existing pool? What are the defining markers of these cells?

Thank you for this excellent suggestion. We have now included a paragraph in the liver development section to address these points.

There's some good discussion of lipid droplet lipolysis. Are the lipases or hydrolases that mediate this known?

This is an excellent question and we have now added a sentence and citations regarding several lipases that have been shown to play a role in retinyl ester liberation from these lipid droplets.

In many types of fibroblasts, metabolic changes geared to turn glucose into collagens and other components of the ECM are known to occur. Is that the purpose of the metabolic changes with HSC activation?

This is an interesting question, and to our knowledge this specifically has not been described for HSCs. There is predominantly an upregulation of glycolytic flux and lactate production, akin to the Warburg effect of cancer cells. We have now expanded on this section to add this information.

There are several instances where the writing could be improved by word or phrase choice. Please carefully review the manuscript throughout. Here are some that could be considered.
1. P5 - vitamin A compounds - metabolites might be a better word

Thanks, we have changed all instances to “metabolites” instead of “compounds”.

2. P6 - adipose should be followed by "tissue" or replaced with adipocytes

Thank you, we have changed it to “adipose tissue” on pages 5 and 6.

3. P7-8 "During quiescence" seems odd since it is a state not a period of time. Consider "In quiescent cells" - same sentence, I think that "are" should be "is" since it refers to "expression" which is singular

These are good points and we have made these changes as suggested.

4. P13 and P14- two sentences in a row start with "In actuality" and "In fact". Seems weird to have two sentences in a row start with phrases like this.

Thank you, we agree. We have removed the “In fact,” from the beginning of the 2nd sentence.

5. P14 - perform paracrine signaling -P15 -regeneration is performed - consider replacing perform with more appropriate words. The connotation doesn't seem right

Thank you, we have replaced perform in these contexts with “act as paracrine signals” or “regeneration is primarily accomplished by …”

6. P15 - "it's" is possessive here and should be "its"

Thank you, we have corrected this on page 14.

REQUIRED ITEMS:
-Please include an Abstract Figure. The Abstract Figure is a piece of artwork designed to give readers an immediate understanding of the Review Article and should summarise the main conclusions. If possible, the image should be easily 'readable' from left to right or top to bottom. It should show the physiological relevance of the Review so readers can assess the importance and content of the article. Abstract Figures should not merely recapitulate other figures in the Review. Please try to keep the diagram as simple as possible and without superfluous information that may distract from the main conclusion of the Review. Abstract Figures must be provided by authors no later than the revised manuscript stage and should be uploaded as a separate file during online submission labelled as File Type 'Abstract Figure'. Please ensure that you include the figure legend in the main article file. All Abstract Figures will be sent to a professional illustrator for redrawing and you may be asked to approve the redrawn figure before your paper is accepted.

We now include an abstract figure, and the abstract figure legend can be found in the manuscript word files. I am a terrible artist, so hopefully this is an adequate idea for the abstract figure, and I welcome redrawing by a professional!

-Please upload separate high quality figure files via the submission form.

We now include separate high-resolution files for each figure.

-Author profile(s) must be uploaded via the submission form. Authors should submit a short biography (no more than 100 words for one author or 150 words in total for two authors) and a portrait photograph of the two leading authors on the paper. These should be uploaded, clearly labelled, with the manuscript submission. Any standard image format for the photograph is acceptable, but the resolution should be at least 300 dpi and preferably more. A group photograph of all authors is also acceptable, providing the biography for the whole group does not exceed 150 words.

We now include two picture files and a written author bio that covers both authors.

Dear Kyle,

Re: JP-TR-2022-281061R1 "Hepatic Stellate Cells in Physiology and Pathology" by Dakota R Kamm and Kyle S McCommis

I am pleased to tell you that your Topical Review article has been accepted for publication in The Journal of Physiology, subject to any modifications to the text that may be required by the Journal Office to conform to House rules.

See a minor note below about adding labels to Figure 1. As an invited paper, your figures can be redrawn - we will have the opportunity to amend the figures at that stage. Or perhaps you would like to send a new figure 1 now? - and we can pass that on to the illustrator? Let us know.

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Best wishes,

Ian

Ian D. Forsythe
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EDITOR COMMENTS

Reviewing Editor:

Congratulations for your publication to the Journal of Physiology!

Senior Editor:

Thank you for an interesting review. I look forward to reading it in press.

Please consider adding cell type labels to figure 1 to increase clarity.

REFEREE COMMENTS

Referee #1:

I have no additional comments.

Referee #2:

My previous concerns were addressed.

1st Confidential Review **14-Jan-2022**