

November 27, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ProteomicsReview.revisions2.docx).

Title: Systems biology unravels interferon responses to respiratory virus infections

Author: Andrea L Kroeker, Kevin M. Coombs

Name of Journal: *World Journal of Biological Chemistry*

ESPS Manuscript NO: 6241

The manuscript has been improved according to the suggestions of reviewers:

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer #00289673

(2) Reviewer #00253956

Thank you again for publishing our manuscript in the *World Journal of Biological Chemistry*.

Sincerely,

Andrea Kroeker, B.Sc.(Honours)

Ph.D. Candidate, Department of Physiology

University of Manitoba

Winnipeg, MB

R3E 3P4 Canada

E-mail: umkroe17@cc.umanitoba.ca

The review article entitled “systems biology unravels interferon responses to respiratory virus infections” by Kroeker & Coombs 2013 details some of the host-virus interactions that influence interferon production. This is a field of therapeutic interest and a review of the literature will be useful to many readers and will warrant publication. However, I would suggest the following items be addressed for review prior to publication:

1.It would be beneficial to readers to understand more explicitly the classes and anti-viral roles of interferons. Hence an introduction that broadly introduces types of interferons and their anti-viral action will provide valuable background for the broad journal audience.

We agree that the background could have benefited from a discussion of interferon biology and have added a paragraph to address this (lines 39-61).

2.Abbreviations and acronyms are used throughout the review, many of which are not defined, so all of these needed to be listed.

Definitions of abbreviations were added to the text to clarify.

3.A final summary diagram of interferon anti-viral activity mechanisms and how they may be evaded by viruses would provide a clear summing up of the review and take home message for the reader.

A figure was added to summarize the mechanisms that were discussed.

In this short paper the authors review recent advances in our understanding of the genes and proteins involved in interferon signaling pathways, with an emphasis on systems biology impact in this understanding. There have been a number of other papers published on this topic in recent years, although the amount of genuinely new and conclusive evidence regarding the genetic and biochemical mechanisms underlying an integrative understanding of interferon signaling pathways is, in my view, somewhat limited. My major comment regarding this review is that the authors simply presented a repertoire of published works that were presented in a fragmented manner, making it very difficult to put the pieces together in order to arrive at meaningful conclusions and allow development of hypotheses.

In order to add a better overview of the published works, we decided to reorganize part of the review into short discussions, e.g. about the role of interferon in viral-induced pathogenesis, and differential signalling in different cell types (lines 168-351).

Despite these reservations this is a valuable contribution to scientific community. Specific comments

1-The introduction is very short and does not include an adequate introduction on interferon signaling pathways and how systems biology is impacting the advances in this field. For example, a figure of a schematic presentation of the general interferon pathways (including activation of PRRs and IRFs, and mitochondrial response...) would be very helpful.

The background could have benefited from a discussion of interferon biology and have added a paragraph to address this (lines 39-61).

In addition, this reviewer believes that the title of the manuscript is misleading as it does not reflect the content of the review and some acronyms were superfluous. The authors should clearly define what they mean by “systems biology”. Do they mean here that systems biology is simply the use of global microarrays and proteomics strategies?

We agree that we could have incorporated a broader definition of systems biology and have reorganized our discussion to better reflect this. We decided to focus on quantitative methods (lines 165-276) and viral-host interaction studies (lines 279-351).

Also the introduction (and other sections of the manuscript) contains statements that are confusing and need some explanatory text. For example, the statement “ While one of the great advantages to systems biology tools is that they provide a relatively unbiased discovery approach,...” is vague and has no meaning in the context of this review. No reference was provided to support this statement.

This statement was explained in more detail (lines 28-30).

2-The manuscript contains too many abbreviations, which makes it very difficult to follow without some explanatory text or figures.

Definitions of abbreviations were added to the text to clarify and an overview of interferon signalling was added (Figure 1).