



October 2, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5326-review.doc).

Title: ATX and LPA signaling in lung pathophysiology

Author: Christiana Magkrioti and Vassilis Aidinis

Name of Journal: *World Journal of Respiriology*

ESPS Manuscript NO: 5326

All editorial format requests were accommodated, as detailed in our response to editorial requests which can be found below, with an exception in the format of references.

We are grateful to the reviewers as their comments have improved the paper. Please find below our point-by-point response to reviewer' comments.

We hope that you will now find our manuscript acceptable for publication in the *World Journal of Respiriology*.

Sincerely,

A handwritten signature in blue ink, appearing to read 'V. Aidinis', with a horizontal line underneath.

Vassilis Aidinis, PhD
BSRC Alexander Fleming

Response to editorial requests

The manuscript was submitted as a docx file, as prompted.

Author contributions were added in the first page, together with “supported by” grant info.

The title (and the name) of the corresponding author was added in “corresponding author” section. Moreover, the asterisk indicating the corresponding author in the author list was removed according to the format of published manuscripts in WJR.

A core tip was added, as instructed.

We removed spaces between the last word and a citation in the text, as prompted.

Please note that we are not able to implement some of the format requirements for the references section (Bold first name author, DOI) due to limitations of our reference software (EndNote). Please send us an endnote reference style file for the journal, or if you would be so kind, please fix it internally.

Response to reviewers comments

Reviewer 1

The authors have compiled a comprehensive review of LPA and ATX in the context of pulmonary physiology. The review is put together fairly well considering the amounts of information presented. Apart from some odd sentences, typos, and relative minor redundancy, the article is acceptable.

1. *p10: needer -> needed*

The typo was corrected along with many others

2. *2 p9: the last sentence of the 2nd paragraph: unclear and should be rewritten.*

The sentence was rewritten as instructed

3. *3. p 12: line 3, check the references. Decreased TER and accumulation of E-cadherin have opposing effects.*

In fact the whole paragraph was deleted as results from this publication are rather controversial.

4. *4. A concluding remark or paragraph is in order.*

A “concluding remarks” paragraph was added at the very end of the manuscript

Reviewer 2

This paper described about the review of ‘ATX and LPA signaling in lung pathophysiology’. The paper is well-written. However, from the standpoint of cancer research, the paragraph of ‘Lung cancer’ is needed to be revised, because both LPA and ATX are recent topics in cancer research field and much is already known in detail. Apart from lung, expression profiles of LPA receptors in various human cancer tissues were investigated. And now, LPA2 receptor is known to be highly expressed in various human cancer tissues. That is, in ovarian, colon, and thyroid cancers, malignant transformation resulted in aberrant expression of LPA2 (and LPA3 in ovarian cancer), suggesting that shifts of LPA receptor expression during malignant transformation were involved in ovarian, colon, and thyroid carcinogenesis. There is an important paper describing that expression of ATX and LPA receptors increases mammary tumorigenesis, invasion, and metastases (Cancer Cell 2009:539-550). Moreover, there is also a paper about ATX and LPA receptor signaling in cancer (Cancer Metastasis Rev 2011:557-565). Thus, cancer researchers want to know about not only the relation between ATX-LPA and cancer, but also LPA receptors and cancer. The authors mentioned about LPA receptors expression of cancer cell lines, which is not always consistent with that of human cancer tissues. Therefore, LPA receptors expression of cancer cell lines is not important. Is there any paper describing about LPA receptors expression of human lung cancer tissues, as well as ATX expression?

We are thankful to the reviewer for his constructive criticism. The entire section was completely rewritten. In our review we are focusing exclusively on the lung and therefore lung cancer. Major general reviews on the role of ATX/LPA in cancer have been cited in the introduction, along with the two most important (and the only high impact) papers on the role of ATX/LPA/LPARs in other organs, including the suggested Cancer Cell one (which was already included in the introduction of the original version of the manuscript).

Concerning LPA receptors, we do agree with the reviewer, that LPA receptor expression in cancer cell lines is not that important – except when examining a specific signal transduction pathway. Accordingly we are only briefly discussing the issue throughout the paper, and most of the information is summarized in Table 1. We are also mentioning throughout the paper that there is limited consistency between the results from different labs. As stated in the text: “different LPA receptors are expressed in the lung tissue of healthy mice, although their relative abundance in different cell types will have to wait for the emergence of specific antibodies and/or conditional KO mice”. The same is true for LPAR expression in human cancer samples. Nevertheless, there has been no publication on LPAR expression in human lung cancer.

Concerning the suggested paper on “*shifts of LPA receptor expression during malignant transformation*” and as stated above, we have reviewed papers only on lung cancer and not other organs. Moreover, the concept of LPAR expression shifts during malignant transformation, although very interesting, is not, in our opinion, adequately supported experimentally yet.

Reviewer 3

This manuscript is a comprehensive review of autotaxin and LPA signaling in lung physiology and pathophysiology. The authors have done a nice job compiling a large amount of studies, as the field of LPA signaling has increased enormously over the past decade. The manuscript is clearly written and the authors do well in pointing out results in the literature that may be considered contradictory. As the authors suggest in their cover letter, there are occasional instances where the language may be improved, but otherwise the writing is well done. The only suggestion for improvement here is the addition of a Summary section that would put the literature so far into some perspective, along with the authors' suggestions of potential future directions for the field.

We have completely revised the sections on asthma and cancer, added future directions in almost all sections and subsections, included a “concluding remarks” paragraph at the end of the paper, as well as a “core tip” at the beginning. Please note that we have tried to be as objective as possible when evaluating the literature, and we have tried not to choose sides in controversial issues, or provide

experimental working hypotheses, waiting for further experimental proof.