27281-Answering reviewers

Dear Editor,

We would like to express our gratitude to the reviewers and the editorial board for constructive feedback on our manuscript. We have addressed all of the concerns within the 'revised manuscript' or in this 'response to reviewers' comments' file appropriately. We believe that the manuscript has been revised thoroughly and is now suitable for your consideration for publication in the *Journal*.

Reviewer 1: This article is informative and well written. I have two comments to make The sentence, "This is even more interesting of a question since MAPK signaling, particularly p38, has already been in clinical trials of asthma [21]." Needs rephrasing - Do authors mean inhibitors in clinical trials? p38 cannot be in clinical trials. RBM – definition?

Response: Thank you for your comment. We have rephrased the sentence as "This is even more interesting of a question since therapeutics targeting MAPK signaling, e.g. a p38 inhibitor, has already been in clinical trials of asthma and COPD".

The RBM (reticular basement membrane) is a commonly used term in respiratory tract for the fibrous extracellular matrix of tissue separating epithelium from the underlying connective tissue.

Reviewer 2: The commentary manuscript of Redhu and Soussi Gounni focused on the effect of IgE on airway smooth muscle (ASM) cells and how anti-IgE therapy may prevent the pathogenic changes of airway smooth muscle in asthma. The subject is interesting and suggests that ASM cells are playing a direct role on the pathogenic mechanisms of asthma. The manuscript has been well written. The different gaps that require further investigation are presented in the manuscript. The figure and references are appropriate. Minor points - A list of abbreviations could be included. - In page 4, line 12: "chronic obstructive pulmonary disease (COPD)" should be added.

Response: Thank you for your kind appreciation of our work. Please see a list of abbreviations in the manuscript. The phrase "chronic obstructive pulmonary disease (COPD)" has been added on page 4, line 12.

Reviewer 3: This manuscript describes a possible role for ASM cells in pathogenic mechanisms of asthma. The subject is interesting and well written. References are appropriate and the figure is helpful. The involvement of IgE is presented discussed. In general, reading is clear. However, in some parts to many facts are presented without proper discussion. Thus the reader loses the authors' point. A better organization of ideas would support the authors' arguments. Some comments to improve the manuscript:

Response: Thank you for all of your comments. We have addressed these concerns as follows.

Comment: The title concentrates on IgE, while the abstract centers the attention on the high affinity Fc epsilon receptor. Authors should decide where to put the readers' attention and maintain a similar point of view.

Response: Thank you for your excellent point. We have updated the abstract in line with the title which now reads as "The purpose of this commentary is to highlight the emerging role of IgE on Airway smooth muscle (ASM) cells function through activation of the high affinity Fc receptor of IgE (FcεRI). We discuss the potential implications of IgE-mediated ASM sensitization in airway inflammation and remodeling, the hallmark features of allergic asthma".

Comment: The manuscript contains too many abbreviations. This makes reading difficult. Some of them (COPD, and RMM for example) are not defined. The manuscript would be easier to read with much fewer abbreviations.

Response: We agree that having too many abbreviations is sometimes distracting. While these are some of very common abbreviations used in the field of allergic inflammation and asthma, a list of abbreviations has been provided in the revised manuscript for readers' convenience.

Comment: Authors indicate that "This is even more interesting of a question since MAPK signaling, particularly p38, has already been in clinical trials of asthma [21]." The molecule p38 cannot be in clinical trials. This needs revising.

Response: This has been revised, please see response to reviewer 1.

Comment: Authors suggest that ASM cells are the source of cytokines and chemokines. Although, this may be the case, other cells (including mast cells) can also contribute to the presence of cytokines, chemokines, and other mediators in ASM tissue. This should be properly discussed.

Response: Thank you for your concern. Since a role for mast cells in production of cytokines/chemokines cannot be ruled out, we have already discussed this issue briefly on page 8, paragraph beginning as "Of note, mast cells….". However, considering the length/word limit of this commentary, we prefer here to focus on highlighting the emerging role of IgE/FcεRI axis on ASM tissue.

Reviewer 4: Redhu and Gounni present a review on the role of IgE directly on airway smooth muscle. This is an interesting concept that supplements the more broadly known area of how IgE induces activation of mast cells and basophils. The anti-dogmatic focus of this review justifies the need for such a manuscript in the literature, as long as the conclusions are drawn in the context of the extensive mast cell literature. Some specific comments are below, in the order of appearance in the manuscript.

Response: Thank you for your valuable comments and excellent suggestions. Please see the response to your specific comments below.

Comment 1: The second paragraph of the commentary (starts with "The allergic cascade is…") includes the statement, "The ongoing TSLP expression via the IgE/FceRI pathway may in fact explain the atopic or pro-allergic state…" It is unclear exactly to what the authors refer. TSLP can be made by multiple subtypes, including mast cells. Further, mast cells use similar signaling pathways as described for airway smooth muscle. Adding clarity to this sentence and the preceding sentences would add in the interpretation of the authors' conclusions.

Response: Thank you for your comment. We have modified this paragraph as "Interestingly, mast cells also produce and respond to TSLP[17, 18], and it has been proposed that TSLP may bridge the ASM-mast cell cross-talk[18]. We propose that the TSLP produced by ASM and/or mast cells via IgE/FcεRI pathway may act in an autocrine/paracrine manner on ASM which might in fact explain the 'atopic' or 'pro-allergic' state...".

Comment 2: The other major section of the manuscript that asserts airway smooth muscle function is near the end (paragraph begins with "Of note, mast cells are known to infiltrate…" The third points being used to argue that mast cells are not involved do not support the conclusion. Inhibition of Syk would block mast cells and ASM. Even though no detectable contamination of mast cells was detected, the cytokines, chemokines, and other mediators released by mast cells can migrate substantial distance and penetrate the tissue. The fact that anti-IgE blocks functions, indicates that IgE is involved, but does not address the site of activity.

Response: We understand your concern and would like to reiterate that we do not fully exclude a possibility of mast cell-secreted factors to migrate ASM tissue. However, the available evidence from experiments involving more than 95% pure ASM populations and bronchial biopsies (Gounni et al 2005, Redhu et al 2009, 2013; Roth et al 2013, 2015), from anti-IgE induced reduction of smooth muscle actin staining in murine histology slides in OVA model (Kang et al 2010), or from clinical studies showing Omalizumab-mediated reduction in airway wall thickening (Riccio et al 2012, Hoshino et al 2012) suggest a potential direct influence of IgE on ASM function. While further studies are clearly needed to dissect ASM vs mast cell dichotomy in regard to IgE effects, cumulative data suggests ASM as a potential direct target.

Comment 3: In many places in the manuscript, the reader is lost in a sea of facts that are not assembled into a cohesive argument. Better organization would support the authors' arguments.

Response: We have revised this short commentary to organize it better. Thank you for your valuable comment.