Peer Review File

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Reviewer 1

Drs Snyder and Hunter in their review article presented literature evidence that disruption of tight junction function, excessive inflammatory responses in the immature gut led to increased gut permeability, and dysregulated translocation of substances and pathogens result in increased susceptibility to NEC.

However, the authors seem to simply repeat statement that the tight junction dysfunction and excessive inflammatory responses are the main risk factors for NEC. Yet failed to provide current progress made in elucidating tight junction integrity at
cellular and molecular level, and new perspective in understanding the molecular basis of homeostasis of the mucosal defense that is key.

Thank you for these comments. In order to better represent the complex molecular interactions that result in NEC we have made several major changes to the manuscript. We have now included current molecular advances in mucosal lining, epithelial cells, and TJs in relation to NEC. References numbers: 6, 7, 8, 13, 25, 26, 27, 28, 29, 32, 33, 34.

Reviewer 2

Manuscript is a review focused on the epithelial role in NEC pathogenesis. While the manuscript includes important topics related to the epithelium and NEC, some concerns remain.
1) The manuscript would be improved with thorough proofreading to correct grammar. Readability would also improve with editing for sentence structures.

Thank you for this comment. We have thoroughly reviewed the manuscript ensuring proper grammatical changes have been made.

2) There are important epithelial themes included. However, explanation of each remains somewhat vague. For example, it discussing mucus layer, it states "Changes in this production or quality of this mucus layer " but never fully explains exactly what these changes are. Similarly, in discussing junctions, an explanation of what changes occur in the tight junctions would help, rather than a vague sentence and listing the proteins involved. A better, more thorough description of each of the topics would greatly improve the scope and impact of the review.

Thank you for this comment. In order to provide more specific explanations were have expanded our discussion regarding the mucus layer (Main body: The intestinal barrier), intercellular junctions (Main body: The intestinal barrier), and enterocytes (Main body: The intestinal epithelium).

Overall, the review manuscript includes important topics of the epithelium in relation to NEC

pathogenesis. However, more comprehensive explanation/description of these elements is needed.

Thank you for this comment. We have ensured that all topics of discussion are expanded with a more comprehensive description throughout the review.

Specific comments

As for this article from Catherine Hunter, I strongly agree with reviewer 1 that the authors are pointing too strongly toward loss of epithelial junction integrity being THE cause of NEC. I think it is very important that our readers understand that what we are calling "NEC" is a diagnosis and not a specific disease. Under this diagnosis there are several different more distinct clusters with different pathophysiology. I have published on this as have others and the paradigm for what we call NEC will likely shift in the near future. I would strongly recommend that the authors use the term "intestinal injury" rather than "NEC".

Thank you for your insights, we have tempered our comments and provided more clarity to the importance the multi-factorial nature of NEC and the intestinal injury seen in the diagnosis.