

**Title: Palmitoylation in Crohn's disease: Current status and future directions**

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**Manuscript type:** Frontier

The manuscript has been improved according to the reviewers and editors:  
1Format has been updated

2Revision has been made according to the suggestions of reviewers

(1) **Reviewer:** 05386200

**Comments:** Based on the current available studies the authors summarize the most important findings and give a sufficient overview about this topic. Therefore the manuscript can be recommended for publication in WJG.

**Author's response:** Thank you very much for your valuable comment.

(2) **Reviewer:** 02997260

**Major comments**

**Comment: 1** To make it more informative and easier to read, I suggest merging the short descriptions of signaling pathways and their palmitoylation with an aim to present more clearly what are the consequences (positive, negative, questionable) of the palmitoylation process on the CD development and course.

**Author's response:** Thank you very much for your valuable comment. As required, we added a paragraph briefly introduces the role of palmitoylation in CD-associated pathways.

**See Page: 10, Lines:7-22 from the bottom.** The following paragraph has been added. [For example, a high frequency of mutations of NOD1/2 are found in IBD patients, while ZDHHC5-mediated palmitoylation of NOD1/2 is responsible for normal gut functions. However, most of the reported CD-associated pathways that undergo palmitoylation didn't specifically bridge CD and the palmitoylated factors, such as Myd88. Myd88 is a factor of TLR signaling and was reported to be palmitoylated by ZDHHC6, but its palmitoylation hasn't been associated with gut. In CD, Myd88 participates in the recognition of pathogen-associated molecular

patterns (PAMPs) localized extracellularly or in the intracellular vacuoles, which mediates sensing of microbial antigens(35). That is to say, the correlation between CD-associated factors and their palmitoylation needs further exploration. In addition, whether the effects of palmitoylation in CD are positive or negative might depends on the various types of factors. The present opinion tends to exhibit the functional roles of palmitoylation in remaining normal gut structures and functions, but we shouldn't consider it completely act as a good character. For instance, the NF- $\kappa$ B activation mediated by palmitoylation probably causes negative consequences in CD patients.]

**Comment: 2** In connection with this aforementioned suggestion, please, provide a more detailed analysis of how palmitoylation influences TLR signaling and what the consequences are for the CD course when NF- $\kappa$ B activation is impaired. A more strong justification of the role of palmitoylation in CD is highly desirable as the concluding remarks of the review.

**Author's response:** Thank you very much for your valuable comment. As required, we added the contents about how palmitoylation of TLR signaling and related NF- $\kappa$ B activation may influence the CD course.

**See Page: 12, Lines: 6-10 from the top.** The following paragraph has been added. [Though there is no report showing that Myd88 palmitoylation procedure has functions on CD, it may have influences related with the sensing of microbial antigens which is mediated by Myd88. However, as NF- $\kappa$ B activation showed high relevance with CD clinical manifestations, the impaired palmitoylation process resulted in NF- $\kappa$ B inhibition possibly have good meanings for CD patients.]

**Comment: 3** Please, provide full names for all abbreviations of molecules and genes when they are mentioned for the first time.

**Author's response:** Thank you very much for your valuable comment. As required, we corrected all abbreviations.

**Comment: 4** Please, provide a reference for this statement: "NOD1/2 mutations are also associated with IBD. Interestingly, several of these mutations decrease the palmitoylation of NOD1/2 and inhibit NF- $\kappa$ B activation."

**Author's response:** Thank you very much for your valuable comment. As required, we added the reference.

### (3) Science editor

#### Major comments

**Comment: 1** The title is too long, and it should be no more than 18 words.

**Author's response:** Thank you very much for your valuable comment. The

title is within 18 words.

**Comment: 2** The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

**Author's response:** Thank you very much for your valuable comment. We will upload the approved grant application form.

**Comment: 3** The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

**Author's response:** Thank you very much for your valuable comment. We will upload the editable figure documents.

**Comment: 4** PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout

**Author's response:** Thank you very much for your valuable comment. We added the missing PMID and DOI numbers in the reference list.

**Comment: 5** Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights.

**Author's response:** Thank you very much for your valuable comment. We didn't use any figure that is copyrighted or published elsewhere.