

**Comments and questions from reviewers and Answers to these questions
re ESPS Manuscript 52101**

Zhen Zeng, Arjudeb Mukherjee, Adwin Pidiyath Varghese, Xiao-li Yang, Sha
Chen, Hu Zhang

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1. Comments and questions from reviewers

Reviewer #1: Excellent review: clear and focused please change the term CD patients (or similar) to "patients with CD" in all locations.

Reviewer #2: 1) Inclusion of a figure depicting the main signaling pathways elicited by the GPCRs discussed in the present review would be very helpful for the reader. 2) The roles of autonomic nervous system GPCRs (i.e. adrenergic & muscarinic cholinergic) in IBD (e.g. see: Brinkman et al. Cells. 2019;8(7). pii: E670; Siryk-Bathgate et al. Drug Des Devel Ther. 2013;7:1209-22) have been completely ignored and should be (briefly) mentioned/discussed.

2. Answers to reviewers' questions

Reviewer #1: Excellent review: clear and focused please change the term CD patients (or similar) to "patients with CD" in all locations.

Answer: We would like to thank you for thinking that our review is clear and focused. We are very grateful for your positive and informative advice about changing the nonstandard expressions. We have thereby changed the nonstandard terms as follows: the term "CD patients" has been changed into "patients with CD", the term "UC patients" has been changed into "patients with UC", and the term "IBD patients" has been changed into "patients with IBD". Modifying these nonstandard terms makes our manuscript more precise.

Reviewer #2: 1) Inclusion of a figure depicting the main signaling pathways elicited by the GPCRs discussed in the present review would be very helpful for the reader.

Answer: We appreciate and would like to thank the reviewer's kind reminder with regard to inclusion of a figure depicting the main GPCR signaling

pathways discussed in our text. We have followed the advice to improve our content and make it more legible to the reader. The picture has been indicated within the manuscript as follows.

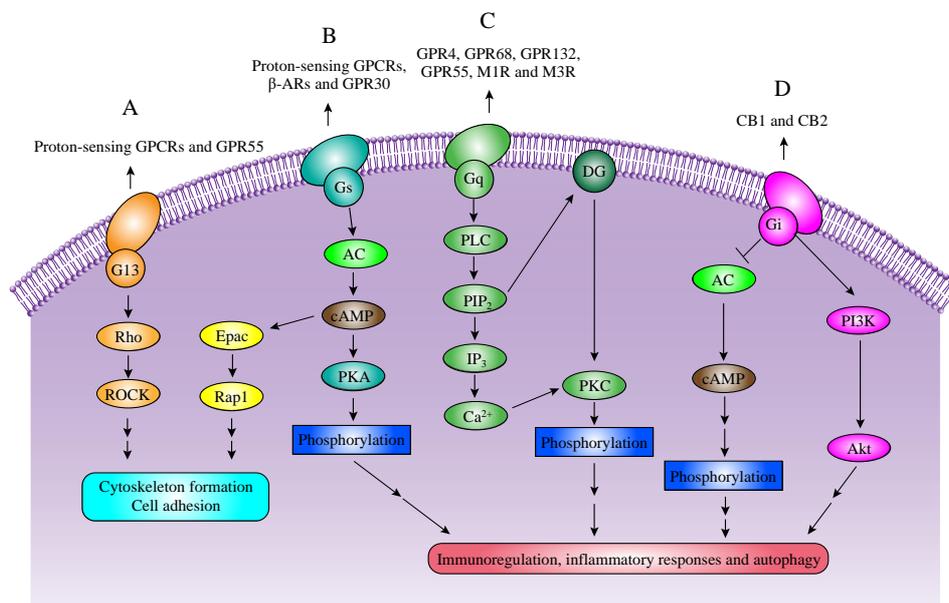


Figure 1 Main signaling pathways of GPCRs. A: Proton-sensing GPCRs and GPR55 are coupled to G13 proteins and are involved in G13/Rho signaling pathways, mediating the modulation of cytoskeleton formation and cell adhesion. B: Proton-sensing GPCRs, GPR30 and β -ARs are implicated in Gs/AC/cAMP signaling pathways and multiple phosphorylation events, and then mediate immunoregulation, inflammatory response and autophagy. Besides, GPR4 is also implicated in cAMP/Epac signaling pathways, and then affects cell adhesion. C: GPR4, GPR68, GPR132, GPR55, M1R and M3R bind to Gq proteins and involve in Gq/PLC/ Ca^{2+} signaling pathways, then phosphorylate target proteins, mediating the regulation of immune response, inflammatory reaction and autophagy. D: CB1 and CB2 are coupled to Gi proteins and are involved in immunoregulation, inflammatory response and autophagy through Gi/AC/cAMP and Gi/PI3K/Akt signaling pathways. Proton-sensing GPCRs: GPR4, GPR68, GPR65 and GPR132. β -ARs: β 1-, β 2- and β 3-adrenergic receptor. Phosphorylation: NF- κ B, ERK/p38MAPK etc.

2) The roles of autonomic nervous system GPCRs (i.e. adrenergic & muscarinic cholinergic) in IBD (e.g. see: Brinkman et al. *Cells*. 2019;8(7). pii: E670; Siryk-Bathgate et al. *Drug Des Devel Ther*. 2013;7:1209-22) have been completely ignored and should be (briefly) mentioned/discussed.

Answer: We'd like to thank you for your kind reminder about the need to discuss the roles of autonomic nervous system GPCRs in our text. We have carefully read the two papers you mentioned and other related papers. As per your kind advice, we have briefly discussed the roles of adrenergic and muscarinic cholinergic receptors in the pathogenesis of IBD and their

potential clinical value. For more details, please refer to the newly submitted text.