



### PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 59785

**Title:** Research advances of vasoactive intestinal peptide in the pathogenesis of ulcerative colitis by regulating interleukin-10 expression in Bregs

**Reviewer's code:** 02440884

**Position:** Editorial Board

**Academic degree:** MD

**Professional title:** Professor

**Reviewer's Country/Territory:** Germany

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-09-29

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2020-10-20 09:57

**Reviewer performed review:** 2020-10-22 17:26

**Review time:** 2 Days and 7 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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**Telephone:** +1-925-399-1568  
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#### **SPECIFIC COMMENTS TO AUTHORS**

The review addresses the role of vasoactive intestinal peptide in the pathogenesis of ulcerative colitis. An overview about VIP is given and its regulatory aspects are addressed. Comments 1. It comes not clear to the reader, why VIP is probably regulative in ulcerative colitis but not in the different types of Crohn's disease. This point should be addressed. 2. The scheme/ graphical abstract is very simple and should be improved.



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**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 59785

**Title:** Research advances of vasoactive intestinal peptide in the pathogenesis of ulcerative colitis by regulating interleukin-10 expression in Bregs

**Reviewer's code:** 00045989

**Position:** Peer Reviewer

**Academic degree:** AGAF, FACG, FACP, FASGE, MD

**Professional title:** Director, Professor

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-09-29

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2020-10-19 14:42

**Reviewer performed review:** 2020-10-22 22:50

**Review time:** 3 Days and 8 Hours

<b>Scientific quality</b>	<input checked="" type="checkbox"/> Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
<b>Conclusion</b>	[ ] Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
<b>Re-review</b>	[ ] Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

Your well-written REVIEW of Recent Advances of VIP in CUC is an expansion of current knowledge of the pathophysiology of CUC (TH1/TH2 balance) by Bregs [regulatory B cells] which negatively regulate intestinal immunity. You go on to suggest that VIP regulates IL-10 expression in colitis patients and may provide a novel strategy to treat CUC. Current PubMed review lists 5 articles or abstracts on VIP in the treatment of CUC between 1993 - 2014 and 12 abstracts and publications looking at the role of VIP in IBD. I was able to find a single publication by Wang et al reporting a decrease in regulatory B cells in CUC (J Crohns Colitis 2016;10:1212-23) and another that VIP stabilizes intestinal homeostasis through maintaining IL-10 expression in regulatory cells (Sun et al. Theranostics 2019;9:2800-2811) [reference 54]. Despite the fact that a number of your references had to do with RA, asthma, or autoimmunity in general, your manuscript builds a credible role for Bregs, VIP, and IL-10 in bowel homeostasis, and the potential role of VIP stabilized micelles (VIP-SSM) for CUC therapy in the future.



### PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 59785

**Title:** Research advances of vasoactive intestinal peptide in the pathogenesis of ulcerative colitis by regulating interleukin-10 expression in Bregs

**Reviewer's code:** 00503405

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Senior Lecturer, Senior Scientist

**Reviewer's Country/Territory:** Hungary

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-09-29

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2020-10-23 12:07

**Reviewer performed review:** 2020-10-23 14:16

**Review time:** 2 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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## **SPECIFIC COMMENTS TO AUTHORS**

In the review manuscript the authors aimed to summarize the current literature on the pathogenic role of VIP and Bregs in UC. The topic is of clinical importance, however, the presentation of the review need major revision. My comments to the authors: -The term „nodal-like” must be corrected to NOD-like - „Adaptive immunity is a highly specific and adaptive type of immunity.” This sentence must be rephrased to be more scientific - In the Intorduction the authors must pointed out why they review the role of VIP and Bregs in the context of UC pathogenesis. -"IL-10 is expressed in different cells involved in innate and adaptive immunity" - What are these cells? - In case of VIP the author describe that „VIP treatment reduced the levels of various chemokines and pro-inflammatory cytokines”- What are they? It is important to understand their pathogenic role. - The authors wrote: „Both T and B lymphocytes express the VIP-related receptors[41], suggesting that B lymphocytes may regulate their immune response through VIP[42]. „ This must be modified like this: „Both T and B lymphocytes express the VIP-related receptors[41], suggesting that B lymphocytes may regulate their immune response partly through VIP[42].” - What does „non neurons” means? - „In innate immunity, VIP inhibits the production of inflammatory cytokines and chemokines by immune cells, reduces the expression of co-stimulatory molecules on antigen-presenting cells” - what are these cytokines, chemokines an co-stimulatory molecules? - The use of TNBS-colitis in the review is confusing: sometimes it is referred as an animal model of Crohn’s disease, sometimes it is mentioned regarding to UC. This must be clarified. -A „Future perspective” is missing form the review: the sythesis of the VIP-Breg axis to the pathogenesis and possible therapeutic options of UC should have incorporated to strengthen the manuscript. - The title of the manuscript must be changed since the current title „Recent advances in research of vasoactive intestinal



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peptide and ulcerative colitis" in contrast of the last sentence of Conclusion „With further clarity on the mechanism of the regulation of IL-10 expression by VIP in Bregs of colitis patients, we believe that Bregs would provide a novel strategy for the clinical treatment of UC." does not reflect the importance of the role of Bregs. - English language needs minor polishing. After major revision I suggest to accept the manuscript for publication in WJG.



### PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 59785

**Title:** Research advances of vasoactive intestinal peptide in the pathogenesis of ulcerative colitis by regulating interleukin-10 expression in Bregs

**Reviewer's code:** 00039368

**Position:** Editorial Board

**Academic degree:** DA, PhD

**Professional title:** Academic Research

**Reviewer's Country/Territory:** Estonia

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-09-29

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2020-10-19 08:10

**Reviewer performed review:** 2020-10-26 14:44

**Review time:** 7 Days and 6 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

This is a well written review paper concerning the role of vasoactive intestinal peptide (VIP) in regulatory activity on intestinal immune response and its possible role in pathophysiology of ulcerative colitis. The authors have reviewed and analyzed a sufficient amount of literature (55 articles). In this review authors described well the role of regulatory B cells (Bregs) and IL-10 in intestinal immunity in ulcerative colitis patients, and pay attention on contribution of B cells to Treg homeostasis and their interactions in prevention of excessive immune response by colitis. In this review is well described the role of IL-10 in maintaining intestinal homeostasis and precisely described the role of VIP in regulation of expression of IL-10 in Bregs. Also the authors underlines that it should be taken into consideration the fact that there are yet many open pathophysiological mechanisms in behavior and co-stimulatory mechanisms concerning regulation of IL-10 expression by VIP in Bregs in pathogenesis of ulcerative colitis. Concerning the quality of this review paper it would be necessary also to mention in some words the methods which might estimate the detection of VIP, Bregs and Il-10 in ulcerative colitis patients.



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 59785

**Title:** Research advances of vasoactive intestinal peptide in the pathogenesis of ulcerative colitis by regulating interleukin-10 expression in Bregs

**Reviewer's code:** 02440884

**Position:** Editorial Board

**Academic degree:** MD

**Professional title:** Professor

**Reviewer's Country/Territory:** Germany

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-09-29

**Reviewer chosen by:** Jia-Ru Fan

**Reviewer accepted review:** 2020-11-16 07:36

**Reviewer performed review:** 2020-11-16 07:43

**Review time:** 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS



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160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-399-1568  
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The manuscript has been essentially improved. I have no further questions or suggestions.