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Dear Editors,

We would like to thank the reviewer for their helpful comments and insights regarding our previous submission. We have made the changes discussed below to address the reviewer' concerns.

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: The authors aimed to do a concise review of the role of TNFa and TNF receptors related to the involvement of the enteric nervous system (ENS) in IBD. However, there have been a lot of review articles summarizing the role of TNFa or antiTNF thearapies in IBD. Therefore, the authors need to morely focus on the TNF receptors and ENS in IBD for the novelty of this review. #1 The authors might want to introduce more detailed mechanisms of the sTNF, mTNF and TNF receptors related to the ENS in IBD. #2 This article includes only one figure. More figures describing the mechanisms related to TNF receptors and ENS in IBD are needed.

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: The research idea is clear, the writing is clear, and the academic problem concerned is the thinking of IBD treatment based on a traditional inflammatory substance. If some high-quality mind maps can be added, the readability of the article may be improved

R: Thank you very much for reviewing the text. We have revised the text and added new information (it is written in red in the text) and new figures in the manuscript. A new revision of English was made in the manuscript. A new language certificate has been provided.

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Pag 7: "As expected, experimental animal models of colitis, enteric neuronal hyperplasia and hypoplasia may be associated with increased and reduced levels of TNFα production, respectively [75,76]. In addition, hypertrophy and hyperplasia of enteric neurons have been reported in IBD [77]. Although, the mechanism responsible for neuronal modulation of inflammation severity is still unclear, due to modulations of neuroimmune interactions, it is speculated that enteric neurons could produce and regulate cytokines involved in IBD [76]."

Pag. 9 " When TNF-α binds to TNFR1 and TNFR2, several intracellular pathways are activated, thus mediating cell death and/or survival response (Figure 1). When TNF-α binds to TNFR1, TNF receptor associated death domain protein (TRADD) is activated which, in turn, can induce the activation of three signaling pathways. In the first one, after TNFR1 activation, TRADD binds to FAS-associated death domain protein (FADD), which recruits caspase 8 proteins, culminating in the activation and cleavage of caspase 3, as well as leading to cell death by apoptosis [87]. The second TNFR1 pathway is related to the recruitment of TRAF2 and receptor-interacting protein (RIP) kinase via TRADD. TRAF2, in turn, recruits the IκB kinase (IKK) protein, which will be activated by RIP and will result in the phosphorylation of nuclear factor κB (NF-κB), which will mediate the transcription of proteins involved in the inflammation response and cell survival [87,88]. The third pathway resulting from TNFR1 activation is connected with activation of mitogen-activated protein kinase (MAPK) pathways via TRAF2, which activate MAPK kinase kinase 1/4 (MEKK1/4) and, upon phosphorylation, MEKK4/7 leads to activation of c-Jun N-terminal kinase (JNK), which is translocated to the nucleus and activate transcription factors such as activator protein 1 (AP-1), that can converge to activate the apoptotic and survival responses [89–91].

Although the pathways behind TNFR2 activation remains poorly understood, when the TNF-α binds to TNFR2, its activation is mediated by TRAF2, and TNFR2 has

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been widely known as a mediator of the activation of genes related to cell survival and proliferation [91–93]. After TNF-α binds to TNFR2, TRAF2 is activated which, through common signaling pathways to TNFR1 activation, can activate NF-κB through IKK, and AP-1 via MEKK, which can also be activated via apoptosis signal-regulating kinase 1 (ASK1) [94]. Furthermore, activation of TRAF2 via TNFR2 can lead to the recruitment of cellular inhibitor of apoptosis (cIAPS), which will partially inhibit caspase activation and, for this reason, reduce apoptosis response [95]. When both TNFR1 and TNFR2 are activated together, cIAPS recruitment is reduced and the caspase activity, mainly mediated by TNFR1, is activated [91]."

Pag. 10 "TNFR1 signaling pathways deserve attention, due to cytotoxic effects triggered by activation of TNFR1 via sTNF binding and it could be noted that some aspects regarding TNFR2 function are still unclear [91].

Some studies pointed to the presence of a functional cross-talk between TNFR1 and TNFR2, whichever TNFR2 would act as an complement-dependent cytotoxic effect of TNFR1, thus being responsible for the inhibition of anti-apoptotic pathways and for the increase in the cytotoxicity triggered by TNFR1 when both receptors are co-expressed and activated [91,98,99]. This finding could be seen as a distinct situation of the classic phenomenon in which the balance between apoptotic and anti-apoptotic signals triggered by TNF-α determines the accuracy in cell signaling [91]."

Pag. 11. "It is known that it can be indicated the presence of TNFR2 in the CNS, *i.e.*, in neurons of the cerebral cortex [83], and no data in the literature could identify the presence of TNFR2 in enteric neurons."

Pag 14. "Although the involvement of TNF-α in the ENS is poorly described in the literature, it is reported that the ENS has TNF-α receptors and responds to the

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inflammatory stimulus, can lead to changes in motility patterns and fluid and electrolyte balance, a condition often found in patients with IBD [128]. When comparing the intestine, under normal conditions, and the intestine in IBD, some aspects must be considered (Figure 3). Under physiological conditions, large populations of microorganisms (bacteria, virus and fungi) inhabit the gut, which constitute the gut microbiota [129]. This microbiota establishes a symbiosis with the host [130]. The intestinal barrier, composed mainly by mucus layer and epithelial, is an intact and functional structure [131]. There is a balance between the levels of pro-inflammatory cytokines TNF-α, IL12 and IL23, and anti-inflammatory cytokines such as transforming growth factor-beta (TGF-β) and IL-10 by innate immune cells, which leads to a balance between regulatory and effector T cells, inducing tolerance to microorganisms from the gut microbiota [130,132]. In physiological conditions, both submucosal plexus and myenteric plexus are functional and controls, respectively, fluid secretion and intestinal motility.

In IBD, there is an imbalance in the gut microbiota (dysbiosis), the intestinal barrier is compromised, with a reduction in the mucus layer, weakening of the intercellular junctions and consequently increased epithelial permeability and entry of microorganisms in the lamina propria [15,133]. Innate immune cells increase the secretion of pro-inflammatory cytokines such as TNF-α, L12 and IL23, which leads to a dysregulation of the immune system, which increases the activity of effector T cells which, in turn, recruit cells for the inflammatory response [134]. Morphological findings include submucosal edema, as well as a reduction in the number of neurons in the SMP, causing changes in secretion patterns and loss of neurons in the myenteric plexus, thus changing the motility patterns [51,52,135].”

Pag. 15 “Therefore, further studies on the role of mechanisms/signaling pathways of sTNF, mTNF, TNF-α and their receptors in enteric neurons in IBD are needed”.

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LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Once this step is completed, the manuscript will be quickly accepted and published online. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240.

R: A new revision of English was made in the manuscript. A new language certificate has been provided.

Sincerely yours,

Patricia Castelucci

Dr Patricia Castelucci, PhD
Associate Professor

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