36498-Answering reviewers

Reviewer #1: In the section Introduction, the sentence “Fecal microbiota transplantation (FMT) is also used to treat UC.” is not appropriated because only in the context of experimental studies, trials or case report, this has been considered as treatment. I think that before the section "intestinal microbiota" the authors should briefly discuss on the pathogenesis of UC. This discussion could be summarized considering reviews as that of Actis GC et al. Minerva Medica 2016;107:401-12.

Answer:

I have changed the sentence “Fecal microbiota transplantation (FMT) is also used to treat UC.” The new statement is that “Faecal microbiota transplantation (FMT) also shows promise in UC”. I have briefly discuss on the pathogenesis of UC considering reviews as that of Actis GC et al. Minerva Medica 2016;107:401-12.

(The pathogenesis of UC is complex and it is believed to be mediated by genetic susceptibility, microbial dysregulation, and environmental factors and environmental factors. In UC, mucosal permeability increases and the inflammatory reaction is caused by excessive reaction below the lymphoid tissue. There exists impaired ileum barrier function, the reduction of mucin and goblet cells which produce mucin, and the decrease of epithelial NLRP6 in UC patients)

Reviewer #2: The review from Shen Z and Co. deals with an important issue in ulcerative colitis. Data about the intestinal microbiota in UC and a possible treatment of the disease with probiotics and fecal microbiota transplantation are well reported and discussed in deep. The review is well written and updated, and its educational role is unquestionable. I checked for doubled references. On my opinion, no further changes are required.

Answer:

Thank you for your praise. I think I will do better according to your constructive and positive comments.

Reviewer #3: Please elaborate more on the role of microbiota in the pathogenesis of UC. Figure legend needs to be more descriptive.

Answer:

I have elaborated more on the role of microbiota in the pathogenesis of UC.

(There is close relationship between the pathogenesis of UC and intestinal microbiota. The steady state of the intestinal microbiota is important in preventing the excessive growth of certain microorganisms. Dysbiosis of the intestinal microbiota may be a contributing factor in some diseases and conditions, such as obesity, metabolic syndrome, autoimmune diseases, necrotizing enterocolitis, skin disease, UC, Crohn's disease, and irritable bowel syndrome [16]. When the balance of intestinal microbiota is broken, the intestinal defense function and immunoregulatory function are decreased, the immunity of the body is reduced, and the relative pathogenic factors are increased so as to cause the intestinal mucosal invasion or aggravate the diseases.

A large number of bacteria are adhered to intestinal epithelial cells of CD patients compared with healthy people. Microbiota might be one of the key factors of activating the intestinal immune system and inducing CD. In addition, the dysregulation of resident microbiota may be the major factor of inducing IBD. The occurrence of intestinal inflammation might cause the produce of a variety of different types of instant cell factors.)

Figure legend has been more descriptive.

(Different types of bacteria have different effects on T cell differentiation. SFB has an effect on TH17. Clostridum cluster IV, XIVa, XVIII and Hsp65-LL can influence the differentiation of Treg cells. B.fragilis might affect the ratio of Th1/Th2 via TLR2.)

Reviewer #4: Ulcerative colitis [UC] is associated with colonic mucosa barrier defects and bacterial dysbiosis, but these features may simply be the result of inflammation. The authors report that that probiotics improve intestinal mucosa barrier function and immune system function and promote secretion of anti-inflammatory factors, thereby inhibiting the growth of harmful bacteria in the intestine. Fecal microbiota transplantation (FMT) can reduce bowel permeability, and thus the severity of disease, by increasing the production of short-chain fatty

acids and the authors emphasize the role of intestinal microbiota in the pathogenesis and treatment of UC. There is an important missing point and there is no discussion, which I consider highly relevant. Despite the absence of ileitis, UC patients display ileal barrier depletion illustrated by reductions in mucin-containing goblet cells and mucin production and altered epithelial NLRP6 expression. In both CD patients with ileitis and UC patients with normal histology, bacteria coated with IgA and IgG penetrate the TI mucin layer. Please read, discuss the findings and cite this reference of Dr. Alipour! Here is the reference: Alipour M, Zaidi D, Valcheva R, Jovel J, Martínez I, Sergi C, Walter J, Mason AL, Wong GK, Dieleman LA, Carroll MW, Huynh HQ, Wine E. Mucosal Barrier Depletion and Loss of Bacterial Diversity are Primary Abnormalities in Paediatric Ulcerative Colitis. J Crohns Colitis. 2016 Apr;10(4):462-71. doi: 10.1093/ecco-jcc/jjv223. Epub 2015 Dec 9. PubMed PMID: 26660940; PubMed Central PMCID: PMC4946763. Moreover, the phenomenon of dysbiosis under therapy needs to be expanded.

Answer:

I have increased the discussion of ileum barrier function and and cite this reference of Dr. Alipour.

(There exists impaired ileum barrier function, the reduction of mucin and goblet cells which produce mucin, and the decrease of epithelial NLRP6 in UC patients.)

In addition, the phenomenon of dysbiosis under therapy has been expanded.
(In gastrointestinal homeostasis, the diversity of the microbiota prevents colonization and overgrowth of pathogens. FMT can reduce intestinal permeability by increasing the production of SCFAs, thereby reducing the severity of disease. Increased SCFAs, especially butyrate, which is the main source of energy in colonic epithelial cells, maintain the integrity of the epithelial barrier by reducing intestinal permeability. FMT can also restore the dysbiosis of microbiota. The proportions of beneficial bacteria are increased and the diversity is also increased. FMT can make the composition of microbiota be more likely to the donors for a long time.)

Respond to editor's suggestions

Answer:

I have added Manuscript NO, Manuscript type, Running title, postcode, ORCID number, Author contributions, the Corresponding author's name, title, and detailed address, Core tip, Audio core tip, PubMed citation numbers and DOI citation to the reference list and so on.

The tables are provided with the editable forms.

I have put all figures and tables after the references list.

I have provide the grant application form(s) or certificate of funding agency for every grant

The manuscript was edited by English Edit OT and the professional editor has further edited my paper.