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LETTER TO THE EDITOR

More on the interplay between gut microbiota, autophagy, and inflammatory bowel disease is needed

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Abstract

The concept of inflammatory bowel disease (IBD), which encompasses Crohn's disease and ulcerative colitis, represents a complex and growing global health concern resulting from a multifactorial etiology. Both dysfunctional autophagy and dysbiosis contribute to IBD, with their combined effects exacerbating the related inflammatory condition. As a result, the existing interconnection between gut microbiota, autophagy, and the host's immune system is a decisive factor in the occurrence of IBD. The factors that influence the gut microbiota and their impact are another important point in this regard. Based on this initial perspective, this manuscript briefly highlighted the intricate interplay between the gut microbiota, autophagy, and IBD pathogenesis. In addition, it also addressed the potential targeting of the microbiota and modulating autophagic pathways for IBD therapy and proposed suggestions for future research within a more specific and expanded context. Further studies are warranted to explore restoring microbial balance and regulating autophagy mechanisms, which may offer new therapeutic avenues for IBD management and to delve into personalized treatment to alleviate the related burden.

Key Words: Inflammatory bowel disease; Gut microbiota; Autophagy; Crohn's disease; Ulcerative colitis

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Core Tip: Further research is needed into the intricate interplay between the gut microbiota, autophagy, and inflammatory bowel disease with the aim of implementing possible new treatment protocols and/or specific public health policies to both alleviate the burden of inflammatory bowel disease and improve outcomes for affected patients.

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TO THE EDITOR

Inflammatory bowel disease (IBD) is a term that refers to a highly prevalent group of chronic diseases characterized by inflammation in the gastrointestinal tract, posing a significant health challenge worldwide[1]. Despite extensive research, its multifactorial origins and complex pathogenesis remain incompletely understood. Several variables, including the host's immune system, the makeup of the intestinal microbiota, genetic predisposition, and environmental variables, affect the onset and course of IBD[2].

However, it is known that the interconnection between the gut microbiota, autophagy, and the host's immune system is a key nexus in IBD development. In this connection, nutritional and other possible influences on gut microbiota and their impact on IBD, in addition to their potential to target the microbiota and modulate autophagic pathways for IBD therapy, are important topics to be discussed and researched in more detail.

The onset of IBD often coincides with dysregulated autophagy, leading to the accumulation of pathogens and the breakdown of immune tolerance, resulting in chronic intestinal inflammation[3]. At the same time, the composition and function of the gut microbiota are also disrupted in individuals with IBD, thereby contributing to the ongoing inflammatory response[4]. A better understanding of these interactions may provide new insights for developing more effective treatments in the evolving landscape of microbiome and immunology research, as well as assist in a more accurate subclassification of IBD phenotypes. In line with this, recent scientific focus on this subject has converged on the interplay between gut microbiota, autophagy, and IBD, recognizing their pivotal roles in the development and progression of the disease[5].

The present manuscript briefly discussed the intricate relationships between these three entities, gut microbiota, autophagy, and IBD, within a concise framework. By exploring their interactions, mechanisms, and therapeutic implications, we also aimed to provide additional insights into potential avenues for future research, especially aimed at better outcomes for IBD patients.

Gut microbiota and IBD

First, dysbiosis, characterized by an imbalance in microbial composition, is closely linked to IBD pathogenesis. Changes in gut microbial diversity and function influence the host's responses, including immune and metabolic responses, aimed at restoring the balance in host-microbe interactions. This host response encompasses elements such as antimicrobial peptides, reactive oxygen species, immunological mediators, mucus, and other modifications that influence the structure and functioning of the gut microbial community, effectively altering the local ecosystems within the gut immune responses, mucosal integrity, and inflammation, which may exacerbate IBD symptoms[6]. The human gastrointestinal microbiota, comprised of trillions of microorganisms, plays a pivotal role in host health, including nutrient metabolism, immune modulation, and defense against pathogens[7]. A recent study has identified reduced microbial diversity and changes in the abundance of bacterial taxa in IBD patients compared to healthy individuals, thus highlighting the intricate relationship between gut microbiota dysbiosis and IBD pathophysiology[8].

As a result, mindful dietary choices, among other healthy habits, are essential in IBD management. By selecting foods that promote healthy gut microbiota, support the integrity of the mucosal barrier, and directly influence the immune response, individuals can play an active role in reducing the impact of IBD on their daily lives[9].

Autophagy in gut homeostasis

Autophagy is an essential cellular function shared by all eukaryotic species, which is essential to the preservation of regular physiological processes. In addition, it is relevant in a variety of circumstances, including famine, decreased availability of growth factors, and elevated energy requirements. Under these circumstances, autophagy is activated to provide energy and sustain vital metabolic functions. Dysfunctional autophagy, in turn, has been implicated in IBD onset and progression, leading to exacerbation of inflammation and impairing immune regulation[5,10].

The intricate mechanisms of autophagy involve several major pathways, including macro-autophagy, micro-autophagy, and chaperone-mediated autophagy. Macro-autophagy, the most extensively studied pathway, involves the formation of autophagosomes that engulf cellular components for degradation[11]. Dysregulated autophagy in IBD is associated with impaired clearance of intracellular pathogens and dysfunctional immune responses, thereby perpetuating chronic inflammation and mucosal damage[5,10].

Intersection of gut microbiota, autophagy, and IBD

The dynamic interplay between the gut microbiota and autophagy significantly influences IBD pathophysiology, potentially compromising pathogen clearance, while disrupting microbial balance and causing chronic inflammation in the gut[5,10]. Deciphering these reciprocal effects is crucial to understanding the molecular mechanisms underlying IBD progression. In light of this, examining how imbalances in gut microbiota composition or autophagy may enhance the inflammatory response should offer important insights for prospective treatment approaches. Moreover, by focusing on

the complex relationships between autophagy and the gut microbiota, new approaches to the management and treatment of IBD may become possible.

In this regard, emerging evidence suggests bidirectional interactions between the gut microbiota and autophagy pathways in modulating IBD pathogenesis. Dysbiosis-induced changes in microbial composition and metabolites influence autophagic activity, while dysregulated autophagy compromises mucosal barrier function and immune homeostasis, thereby exacerbating gut inflammation[5].

A study revealed that mutations in autophagy-related genes like the autophagy-related 16 like 1 single nucleotide and nucleotide-binding oligomerization domain-2 genes have been strongly linked to Crohn's disease. The autophagy-related 16 like 1 single nucleotide plays a crucial role in the autophagic process. Mutations in these genes impair autophagy, leading to an inadequate response to gut microbiota and promoting chronic inflammation[12,13]. Clinical trials have shown that fecal microbiota transplantation can help restore healthy microbial imbalance in IBD patients, leading to significant improvement in the composition of gut microbiota and a reduction in inflammatory markers[14]. Several preclinical studies have monitored changes in gut microbiota composition following treatment with autophagy-inducing agents[15]. A deeper understanding of the crosstalk between the gut microbiota and autophagy pathways should be promising and imminently needed within this research scope.

Therapeutic implications and future perspectives

Addressing defective autophagy holds promise in modulating the development of IBD, thus restoring intestinal homeostasis, rebalancing the gut microbiota, and improving the clearance of intracellular pathogens. Innovative therapies targeting autophagy pathways, such as dietary interventions[16] and gene therapies[17], may offer potential avenues for advancements in personalized IBD management and treatment.

Genetic polymorphisms in autophagy-related genes have been implicated in IBD susceptibility, highlighting the therapeutic potential of modulating autophagic pathways in disease management[18]. Furthermore, microbiota-based therapies, including fecal microbiota transplantation[19] and targeted probiotics[20], show promise in restoring gut microbial balance and alleviating IBD symptoms. Within this perspective, more effective and individualized therapeutic strategies are imminently needed for IBD patients, taking into account the relationships among gut bacteria, autophagy, and the immune system.

Suggestions for further research in the field of IBD

Table 1 summarizes our suggestions for future research for more promising management and treatment of IBD cases in the short, medium, and long term.

Final consideration

In reaction to the above discussion, further research into targeted interventions and personalized treatment approaches is warranted to alleviate the burden of IBD and improve patient outcomes. Therefore, the continuity and proposition of new clinical trials and investigations focusing on different interconnected aspects, such as autophagy modulation, microbiota-based treatments, and novel techniques are also essential to the goal of developing more potent medicines and effective treatments for IBD. The growing understanding of the relationships among gut microbiota, autophagy, and IBD is bringing us one step closer to a time when patients will no longer have to endure many of the severe consequences of this difficult and multifaceted condition.

Table 1 Potentially promising research proposals related to inflammatory bowel disease

Suggestions	Scope	Possible research methods and expected outcomes
(1) Additional experimental and human studies on IBD pathophysiology	Considering more specifically the interrelationship between gut microbiota, autophagy, and IBD	(1) Usage of genetically engineered mice (IL-10 knockout mice, TNFΔARE mice) to mimic human IBD; (2) Use CRISPR/Cas9 technology to create targeted mutations in autophagy-related genes to study their effects on gut inflammation; (3) Recruit a diverse cohort of IBD patients including those with Crohn's disease and ulcerative colitis, as well as healthy controls, to better understand the pathophysiology of IBD; and (4) Employ bioinformatic tools to model the complex interactions between genes, proteins, and microbiota in IBD
(2) Development of more effective medicines and therapies for IBD patients	Considering more specifically the interrelationship between gut microbiota, autophagy, and IBD	(1) Utilizing primary intestinal epithelial cells, immune cells, and patient-derived organoids to test drug efficacy and toxicity; (2) Developing monoclonal antibodies targeting specific cytokines (TNF-α, IL 12/23) involved in IBD inflammation; and (3) Developing formulations of beneficial bacteria or prebiotic fiber to restore gut microbiota imbalance
(3) Development of new and more effective personalized treatment approaches	Considering more specifically the interrelationship between gut microbiota, autophagy, and IBD	(1) Developing microbiome-based biomarkers for IBD diagnosis, prognosis, and treatment response; and (2) Utilizing biomarkers to stratify patients and tailor treatments based on individual profiles to enhance personalized therapeutic intervention
(4) Periodic epidemiological monitoring studies on the burden, years of life lost, or years	Expanded scope	Performing data collection, analysis, and interpretation, ensuring reliable results for analyzing the distribution patterns

living with disability in cases of IBD		
(5) Assessment of the quality of life of affected patients according to new medicines used or treatment protocols	Expanded scope	Using appropriate quality of life measurement tools (Short form health survey or EuroQol 5D questionnaire) designing a robust study, collecting, analyzing, and interpreting the results
(6) More comprehensive pharmacovigilance studies involving affected patients	Expanded scope	Designing a structured approach to monitor, assess, and understand the safety profiles of medications
(7) Studies on scientific misinformation related to IBD	Expanded scope	Utilizing a systematic approach to identify, analyze, and understand the spread and impact of misinformation related to IBD

CRISPR/Cas9: Clustered regularly interspaced short palindromic repeats/associated protein 9; EuroQol 5D: European quality of life-five dimensions; IBD: Inflammatory bowel disease; IL: Interleukin; TNF-α: Tumor necrosis factor-alpha; TNFΔARE: Tumor necrosis factor, adenylate-uridylate-rich element deletion.

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FOOTNOTES

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