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Intestinal barrier in inflammatory bowel disease: A bibliometric and knowledge-map analysis

Intestinal barrier in inflammatory bowel disease

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Abstract

BACKGROUND

Barrier surfaces composed of specialized epithelial cells separate the host body from the external environment, and are essential for maintaining proper intestinal physiologic and immune homeostasis.

AIM

The aim of our study was to explore the development trends and research hotspots of intestinal barrier research in inflammatory bowel disease (IBD).

METHODS

The publications related to the intestinal barrier in IBD were obtained from the Web of Science Core Collection database. Bibliometric analysis and visualization were conducted using VOSviewer, CiteSpace and R software.

RESULTS

A total of 4,482 articles published between 2002 and 2022 were identified. The United States is dominant in intestinal barrier research, whereas the University of Chicago is the most active institution. Turner, Jerrold from Harvard Medical School was the most productive authors with the most citations. The journals Inflammatory Bowel Disease and Gastroenterology have made significant contributions in this field. The keywords appearing at high frequency related to the intestinal barrier in IBD were detected, including NF-kappa B, TNF- α , apoptosis, oxidative stress and probiotics. Among them, antioxidants, *Akkermansia muciniphila*, nanoparticles, short-chain fatty acids and extracellular vesicles have received growing interest in recent research.

CONCLUSION

The intestinal barrier field is developing rapidly with extensive cooperation. Targeting the gut microbiota and dietary metabolism to regulate the intestinal barrier has shown

promising prospective applications and has generated broad interest. The importance of the intestinal barrier in IBD is gradually being fully recognized, providing a new therapeutic perspective for improving inflammation and prognosis.

Key Words: Intestinal barrier; Inflammatory bowel disease; Bibliometrics; Visualization; Hotspots

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Core Tip: Specialized epithelial cells constitute barrier surfaces that separate host body from the external environment. The complete composition and function of intestinal mucosal barrier is essential for maintaining proper intestinal physiologic and immune homeostasis. There is growing evidence that the mucosal healing and reestablishment of barrier integrity are significantly associated with clinical remission and improved patient outcomes. However, with the rapid expansion of research field, it has become challenging for researchers to accumulate knowledge and actively collect evidence. Bibliometrics provides new angles to reveal the inherent features of the literature and predict the development prospects and trends of research fields through quantitative methods. The bibliographic analysis has been widely accepted to gain insight into cutting-edge trends and grasp research hotspots. In this study, we evaluated the research status, focus area and development trend of intestinal barrier in inflammatory bowel disease. The results showed that Intestinal barrier field is developing rapidly with extensive cooperation. Important research directions related to the intestinal barrier in inflammatory bowel disease (IBD) include NF-kappa B, TNF- α , apoptosis, oxidative stress, and probiotics. Among them, antioxidants, *Akkermansia muciniphila*, nanoparticles, short-chain fatty acids and extracellular vesicles have received growing interest in current research. Targeting the gut microbiota and dietary metabolism to regulate intestinal barrier shown promising prospective applications. This may provide

guidance and new insights for further research into improving IBD by modulating the intestinal barrier.

INTRODUCTION

Specialized epithelial cells constitute barrier surfaces that separate host body from the external environment. The complete composition and function of intestinal mucosal barrier is essential for maintaining proper intestinal physiologic and immune homeostasis^[1]. There is growing evidence that a deficit of in the intestinal barrier contributes to inflammation activation, especially in inflammatory bowel disease (IBD).

³ The intestinal barrier is mainly composed of intestinal epithelial cells, tight junctions and mucous layers. Genetic predisposition and environmental influences generally lead to disruption of the intestinal barrier in IBD, including tight junction changes, mucous layer defects, reduced antimicrobial peptide (AMP) expression, and autophagy dysregulation^[2, 3]. This imbalance in the intestinal barrier allows external antigens to invade the body through damaged intestinal barrier, causing inappropriate immune activation. A series of studies have shown that mucosal healing and reestablishment of barrier integrity are significantly associated with clinical remission and improved patient outcomes^[4-6]. Knowledge of the research status and focus hotpots of the current field is helpful to further explore the pathogenesis of IBD and search for potential therapeutic targets.

Bibliometrics has become an important methodology for researchers to actively accumulate knowledge and collect evidence. The bibliographic and visual analysis provides new angles to identify development trends and predict research prospects of this field by mathematics and statistics^[7-9]. Therefore, this study ¹ aimed to explore the knowledge landscape of the intestinal barrier in IBD, hoping to provide guidance and new insights for further research in the field of IBD.

MATERIALS AND METHODS

Search strategies

Bibliometric and visualization analyses were conducted through the Web of Science Core Collection (WoSCC) database, which is one of the most widely used source for academic and bibliometric analysis. The WoS database covers a broad spectrum of academic disciplines and offers precise citation data, facilitating in-depth evaluation of topic development and trend evolution^[10-12]. The search strategy was as follows: TS (Topic)=(“inflammatory bowel disease” OR “ulcerative colitis” OR “crohn’s disease”) AND TS=(intestin* OR gut OR bowel) AND TS=(barrier OR integrity OR permeability). The publication period was between 2001 and 2021 with the publication type limited to original articles written in English (Figure 1).

Data collection

Bibliometric indicators were extracted from selected publications to quantitatively evaluate the characteristics of the literature and its trends, including titles, publication years, authors, affiliations, countries/regions, journals, abstracts, keywords, citations and references. The H-index of scholars, impact factor (IF) and Journal Citation Reports (JCR) division of journals were also obtained from the Web of Science. Inappropriate formulations of elements were modified and multiple phrases with the same meaning were merged into a single element. Scientific data were searched and collected independently by two researchers to ensure the reliability of the results.

Bibliometric analysis

Bibliometric analysis is a quantitative research method that is widely employed to evaluate academic development in a specific field. VOSviewer, CiteSpace and R package were used for constructing the scientometric network and knowledge visualization. VOSviewer was adopted to conduct co-authorship analysis of authors and countries/regions, co-occurrence analysis of keywords and co-citation analysis of journals. Co-authorship and co-occurrence relationships were defined as the simultaneous occurrence of two items, while co-citation relationships referred to two items being cited simultaneously by a third item^[13, 14]. The network graph generated by VOSviewer displays the size of nodes based on the number of publications, and the

connection represents the relationship between nodes. Closely related nodes were divided into clusters of the same color.

CiteSpace was used to calculate the node centrality and keyword burst trends. Centrality measures the quantity of all the shortest paths passing through a node in a network, with nodes having centrality greater than 0.1 identified as key nodes of significant importance. Burst detection was employed to identify keywords that experienced a sudden surge in their frequency of appearance during a specific time frame. The green line indicates the occurrence and development of keywords, while the red line represents the duration of the burst.

In addition, R software was used to develop the distribution of scientific productivity among authors and different countries/regions. Lotka's Law demonstrates the relationship between the frequency of scientific paper authorship and the number of publications, revealing an unbalanced distribution of author productivity.

RESULTS

Growth trend of publications

A total of 4482 publications related to the intestinal barrier in IBD were published between 2002-2022. There were only a small number of studies in the early stage, with less than 100 articles each year (Figure 2). During the middle period from 2006 to 2014, the number of publications showed a slow increase. Subsequently, annual publications have grown rapidly, with 53.8% of all publications occurring in the past two decades. Increasing attention to the intestinal barrier in IBD from researchers has driven further development of this field.

Countries/regions and institutions

Intestinal barrier research in IBD has been carried out at 4650 institutions from 89 countries/regions (Figure 3A). The United States is dominant in this field with the highest number of publications ($n = 1426$) and citations ($n = 89615$). The next most productive countries/regions were China and Germany (Table 1). In addition, Germany achieved the highest citations per publication at 73.2. These countries were divided into

seven clusters to show the extensive cooperation between nodes (Figure 3B). Multiple nodes played a strong bridging role in the collaboration, most notably for the United States, the United Kingdom and China.

The University of Chicago conducted the largest number of studies ($n = 8236$), followed by Emory University ($n = 6437$) and the University of Calgary ($n = 4064$). Among them, the University of California San Diego exhibited the highest average citations of 102.3. Cooperation between institutions is more evident than that between countries, which enables further exploration and collaboration on the subject (Figure 3C).

2 Authors and cited authors

A total of 26,245 authors have participated in the field of intestinal barrier research in IBD. Seventy-six percent of the authors contributed one article, whereas only 6.0% contributed more than 3 articles (Figure 4A). Turner, Jerrold ($n = 33$), Rogler, Gerhard ($n = 26$) and Neurath, Markus F. ($n = 25$) were the most productive authors (Table 2). Although Turner, Jerrold from Harvard Medical School also has the most citations ($n = 3399$), the nodes of these scholars were more dispersed across different clusters rather than being aggregated (Figure 4B). Close communication and similar research directions exist in the nodes of the same cluster. In addition, the clusters displaying different colors are not entirely independent and exhibit a relatively low level of connections.

Journals and cited academic journals

There were 1,045 journals involved in the publication of intestinal barrier research in IBD. Inflammatory Bowel Diseases contributed the most articles ($n = 258$), while Gastroenterology received the most citations (Table 3). The next most productive journals were PLoS One ($n = 145$) and the American Journal of Physiology-Gastrointestinal and Liver Physiology ($n = 119$). Articles published in established journals exhibit a higher average citation count, which is consistent with the impact factor of the journal.

Among them, the majority of journals had an early initiation into this field (Figure 5A). Despite being relatively new to the field, *Frontiers in Immunology*, *Food & Function* and *Scientific Reports* demonstrated rapid development. As shown in Figure 5B, these journals were divided into five clusters based on the similarity of their themes. The higher the number of co-citations between two journals, the stronger is the link between the two nodes.

Keywords co-occurrence, clusters and bursts

Keywords were extracted for multidimensional analysis to determine the research hotspot and exploration direction in the specific field. The keywords appearing at high frequency related with intestinal barrier in IBD were identified, including molecules, pathological processes and treatments (Table 4). NF- κ B ($n = 418$), TNF- α ($n = 329$) and IFN- γ ($n = 173$) were the most commonly implicated molecules. Apoptosis ($n = 292$), oxidative stress ($n = 232$) and metabolism ($n = 88$) were widely involved in research on the intestinal barrier. Regarding treatments, probiotics ($n = 237$), nanoparticles ($n = 77$) and antioxidant ($n = 73$) have attracted extensive attention.

The network map was classified into four clusters by co-occurrence analysis, which portrayed the fundamental knowledge structure of related research fields (Figure 6). Based on the closeness between nodes, the largest blue cluster contains keywords associated with clinical characteristics, such as risk, children and therapy. The red cluster was mainly composed of tight junctions, permeability and transport, which drew attention to barrier function in IBD. The yellow cluster mainly focused on the gut microbiota, including probiotics, metabolism and dysbiosis. The green cluster was involved in the regulation of inflammation, with keywords such as apoptosis, NF- κ B and oxidative stress.

The visual keyword burst trend was constructed to show the major research interests in the intestinal barrier field (Figure 7). Early keyword bursts were mainly concentrated on intestinal barrier function and related inflammatory molecules, where intestinal permeability showed strong bursts. During the middle period, only a limited number of keywords exhibited an outbreak trend, such as autophagy, matrix

metalloproteinase, and vitamin D. In contrast, targeted intestinal barrier therapy has been receiving growing interest from researchers, with a particular focus on antioxidants, *Akkermansia muciniphila*, nanoparticles, short-chain fatty acids, and extracellular vesicles as recent areas of research attention.

DISCUSSION

The intestinal barrier refers to the physiological barrier composed of intestinal epithelial cells and mucous layers, which plays a crucial role in the onset and progression of inflammatory bowel disease (IBD)^[15-17]. The disruption of the intestinal barrier in IBD patients is closely related to the severity of intestinal inflammation and immune response. The significant increase in the number of annual publications indicates a rapidly growing interest and recognition of the intestinal barrier field.

The United States occupied the dominant places in the intestinal barrier field with the highest number of publications and citations. Although China is developing rapidly in this field, it exhibits lower average citation rates. Other countries such as Germany and the United Kingdom have conducted more in-depth research and have the highest average citation rates. It is necessary to increase the depth and influence of research to address the imbalance between the number of publications and citations. Extensive collaboration is observed in countries such as the United States and the United Kingdom, however, institutional collaboration tends to show a trend of geographic alignment in terms of its distribution.

The author's productivity is consistent with Lotka's Law. Turner Jerrold from Harvard Medical School has made significant contributions to intestinal barrier research. His group found that MLCK-dependent tight junction dysfunction can cause immune system activation and experimental colitis induction^[18, 19]. Johan D. Soderholm mainly examined how different cytokines, such as corticotropin-releasing hormone, acetylcholine and vasoactive intestinal peptide^[20-22], affect the intestinal barrier. In contrast, Ali Keshavarzian investigated the role of different protein kinase C isoforms in regulating intestinal barrier injury and repair^[23-26]. These findings demonstrate the

feasibility of improving inflammatory bowel disease through barrier repair, which could become a strong candidate for nonimmune suppressive methods to achieve or maintain disease remission.

Intestinal barrier research was initially published in gastroenterology journals, particularly in Inflammatory Bowel Disease. The exploration of the intestinal barrier has revealed extensive relationships between this field and several other research areas, such as physiology, biochemistry and immunology. As a result, there has been an increase in the number of interdisciplinary journals to better cater to the needs of this rapidly expanding field. Comprehensive journals have a wide readership and are more conducive to interdisciplinary collaboration.

The integrity of the intestinal barrier has been found to be closely associated with host defense and regulates the progression of IBD. Keywords in the field of the intestinal barrier mainly revolve around four aspects, encompassing clinical characteristics, barrier function, the gut microbiota, and inflammation regulation. Studies have reported that disruptions in the intestinal barrier lead to persistent intestinal symptoms and poor prognosis in IBD patients^[27-29]. The increase in intestinal permeability is a marker of intestinal barrier dysfunction. The tight junction between intestinal epithelial cells are dynamic structures capable of swift adjustments, which determine the mucosal permeability^[30, 31]. The active transcellular transport of ions and water relies on the presence of intact tight junction barriers. Damage to epithelial cells triggers the release of inflammatory cytokines such as TNF and IFN- γ ^[32]. Stimulation of TNF downregulates the expression of tight junction proteins and changes their localization in colonic epithelial cells^[33-35]. Insufficiency of IL-10, excessive production of nitric oxide (NO), and impaired autophagy can also induce an overactive immune system and enhance barrier loss^[36-38], which in turn causes further leakage of luminal substances and amplifies local inflammation. The homeostasis of intestinal barrier can be affected either directly by inducing intracellular signaling pathways, or indirectly by the gut microbiota as an interacting partner to a greater extent^[39, 40]. Reduced intestinal community richness in patients with IBD leads to loss of intestinal homeostasis and

inappropriate immune activation, which is characterized by a decrease in *Firmicutes* and proliferation of facultative anaerobic *Enterobacteriaceae* and adherent invasive *Escherichia coli*^[41-43].

Recently, there has been widespread research interest in improving the intestinal barrier by targeting gut microbiota and dietary metabolism. Exogenous administration of probiotics can influence the composition and characteristics of the intestinal microbiota to exert intervention effects, typically in combination with prebiotics. The colonization of the beneficial bacterium *Akkermansia muciniphila* increased the number of goblet cells and upregulated the expression of genes encoding mucin^[44, 45]. Although fecal microbiota transplantation (FMT) has been shown to induce clinical remission of ulcerative colitis, the long-term effects of FMT as maintenance therapy have not been validated in IBD^[46]. Microbial and dietary metabolites also demonstrate a regulatory influence on the intestinal barrier. Short-chain fatty acids produced by dietary fiber fermentation are the main energy source of colon cells, promoting the integrity of epithelial tight junctions and mucus secretion, which may be related to the activation of AMPK and STAT3^[47, 48]. The observed abnormality in bile acid metabolism may contribute to an enhanced epithelial inflammatory response. The reduction in secondary bile acids weakens the inhibition of IL-8 secretion^[49] and the activation of TGR5 receptors in intestinal stem cells^[50]. In addition, extracellular vesicles produced by host cells and microorganisms are also involved in cellular communication. Immune cells such as mast cells can secrete extracellular vesicles containing miR-223 to regulate intestinal permeability with downregulation of tight junction proteins^[51]. Notably, extracellular vesicles themselves also represent a natural nanomaterial for drug delivery, that can improve the therapeutic effect and reduce systemic exposure in healthy tissues to promote remission of IBD^[52].

The bibliometric analysis offers novel and objective insights into evolving intestinal barrier research hotspots and trends across multiple dimensions. Inevitably, there were several limitations to this study. The data were extracted from the WoSCC database, potentially omitting some information from other sources. Furthermore, while

bibliometric methods based on natural language processing are susceptible to biases from subject categorization and citation behavior, a sufficient sample size helps ensure the accuracy of research findings to some extent.

CONCLUSION

In conclusion, the intestinal barrier field is developing rapidly with extensive cooperation. Targeting the gut microbiota and dietary metabolism to regulate the intestinal barrier shown promising prospective applications and has generated broad interest. The importance of the intestinal barrier in IBD is gradually being fully recognized, providing a new therapeutic perspective for improving inflammation.

ARTICLE HIGHLIGHTS

Research background

Barrier surfaces composed of specialized epithelial cells separate the host body from the external environment, and are essential for maintaining proper intestinal physiologic and immune homeostasis. There is growing evidence that the mucosal healing and reestablishment of barrier integrity are significantly associated with clinical remission and improved patient outcomes.

Research motivation

With the rapid expansion of research topics, it has become challenging for researchers to accumulate knowledge and actively collect evidence in specific field. The bibliographic and visual analysis provides new angles to identify development trends and predict research prospects of this field by mathematics and statistics.

Research objectives

With the rapid expansion of research topics, it has become challenging for researchers to accumulate knowledge and actively collect evidence in specific field. The

bibliographic and visual analysis provides new angles to identify development trends and predict research prospects of this field by mathematics and statistics.

Research methods

The publications related to intestinal barrier in IBD¹ were obtained from the Web of Science Core Collection database. Bibliometric analysis and visualization were conducted using VOSviewer, CiteSpace and R software.

Research results

A comprehensive analysis of 4,482 articles published between 2002 and 2022 has revealed significant insights in the realm of intestinal barrier research. Intestinal barrier research mainly focuses on four aspects, including clinical characteristics, barrier function, gut microbiota, and inflammation regulation. The keywords appearing at high frequency related with intestinal barrier in IBD were detected, including NF-kappa B, TNF- α , apoptosis, oxidative stress and probiotics. Among them, antioxidants, Akkermansia muciniphila, nanoparticles, short-chain fatty acids and extracellular vesicles have received extensive interest in current research.

Research conclusions

The intestinal barrier field is developing rapidly with extensive cooperation. Targeting the gut microbiota and dietary metabolism to regulate intestinal barrier shown promising applied prospective and has generated broad interest.

Research perspectives

The importance of the intestinal barrier in IBD is gradually being fully recognized, providing a new therapeutic perspective for improving inflammation.

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