Bibliometric Visualization Analysis of Microbiome-Gut-Brain Axis from 2004 to 2020

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Financial support: This study was supported by the Guizhou Provincial Health and Family Planning Commission (no. 2019XMSB00022878) and Guizhou Traditional Chinese Medicine Administration (no. 201815797)

Conflict of interest: None declared

Background: The microbiome-gut-brain axis (MGBA) is the biochemical signal of the digestive tract and central nervous system. MGBA disorders have been increasingly involved in the pathological process of neurological diseases. This study aimed to investigate the research hot spots of MGBA from 2004 to 2020.

Material/Methods: Using bibliometric analysis from the Web of Science Core Collection (WOSCC) database, 3993 documents on the MGBA were retrieved and visual analysis was conducted.

Results: The MGBA has received attention worldwide and will continue to be a research hot spot. Emerging research organizations and scholars of the MGBA and the research of John F. Cryan and colleagues from Ireland in the MGBA have been recognized by many scholars. However, the research of Chinese scholars and organizations appeared to have less impact due to lack of research innovation and collaboration with other countries/regions. Keyword analysis showed that neuroinflammation was a hot spot and that eminent scholars had begun to work in the field of MGBA.

Conclusions: This work provided an overall view of the literature on the MGBA worldwide, and the analysis provided a comprehensive overview of MGBA research. It further revealed the interaction between the gut microbiota (eg, Akkermansia, Parabacteroides) and the specific regulatory network of the gut microbiota and metabolites, neuroinflammation, and neural networks, which can facilitate the development of effective treatment strategies using microbiota for targeting neuroinflammation and conducting large-scale clinical trials of neurological diseases.

Keywords: Bibliometrics • Gastrointestinal Microbiome • Nervous System Diseases

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/936037
Background

A large number of bacteria, fungi, viruses, protozoa, and other microorganisms populate the normal human intestinal tract, and their collective genome that is found on and within the body comprises the microbiome [1]. There are more than 10^{14} bacterial cells in the gastrointestinal tract, the vast majority of which are located in the ileum and colon [2]. The digestive tract of a healthy person contains about 1000 kinds of microbes, and the total number of cells of these microbes is about 10 times the number of cells in the body [3,4]. The gut microbiome can be regarded as a functional organ, which is acquired after the individual is born. The number of genes encoded by the intestinal flora is about 150 times that of the host’s genes [3]. The sum of the genomic information of these intestinal microorganisms is also called “gut metagenome”, which is the “second genome” that controls the health of the body [4,5], and the host’s physiological metabolic activities are jointly affected through the interaction with the host genome [6]. The human gut microbiome is a complex ecosystem with important physiological functions and psychological activities in its host, such as digestion, metabolism, immunity, and emotion [7,8]. The use of 16S ribosomal RNA and whole genome sequencing techniques has enabled us to understand the diversity of intestinal flora [9]. Through metagenomics, metabolomics, and other omics analysis techniques, microbiome-wide association studies, host-reaction mechanism analysis, and germ-free animal disease replication models can be combined to determine the types of intestinal flora causing disease and the molecular mechanisms of specific interactions [10,11].

Over the past 2 decades, researchers have come to recognize the interconnection between gut microbiota and biomedical sciences and the important role microorganisms play in maintaining homeostasis and regulating body systems [1,7,8], including the central nervous system (CNS) [12,13]. The microbiome-gut-brain axis (MGBA) is the biochemical signal of the digestive tract and CNS. The intestinal flora and the brain have 2-way communication through the autonomic nervous system, intestinal nervous system, immune system, intestinal endocrine signals, neurotransmitters, branch-chain amino acids, bile acids, short-chain fatty acids (SCFA), spinal cord, hypothalamic-pituitary-adrenal axis, peptidoglycan, and other pathways and media [14,15]. Animal experiments are helpful to reveal the important roles of MGBA in brain development, neuroinflammation, anxiety, cognition, and pain [16,17]. Many reports have been devoted to explaining the bidirectional communication pathway between the gut microbiota and the CNS, and MGBA disorders are increasingly involved in the pathological process of nervous system diseases, such as multiple sclerosis (MS), Parkinson disease (PD), Alzheimer disease (AD), autism spectrum disorder (ASD), stroke, brain injury, epilepsy, and depression [16-19].

Experiments have confirmed that intestinal barrier defects connect intestinal flora with immune activation, which can trigger a systemic inflammatory response, further damage the blood-brain barrier (BBB), promote neuroinflammation, and eventually lead to nerve damage and degeneration [15,20]. An abnormal MGBA is believed to cause the deposition of β-amyloid in AD and the neuropathological features unique to PD, including the misfolding and aggregation of α-synuclein. In some cases, specific microbial populations are closely related to the progression of diseases, such as the types of bacteria in the periodontal, oral, and nasal cavities of patients with AD and PD and the abundance of Helicobacter pylori in the gastric mucus layer of patients with PD [21]. Intestinal flora may influence the degree of neuroinflammation after stroke by regulating the transport of intestinal T cells to the brain. In animal models of cerebral ischemia-reperfusion injury, feeding animals Clostridium butyricum had neuroprotective effects [16]. Gut microbiota produce metabolites of dietary tryptophan that inhibited the behavior of microglia immune cells in the brain of MS mice, which in turn modulated astrocyte activity and reduced neuroinflammation [22]. In a small pilot clinical study, complex probiotics containing Lactobacillus, Bifidobacterium, and Streptococcus reversed changes in patients with MS and were shown to have anti-inflammatory properties, suggesting that the microbe targeting strategy is worth studying [23]. There was an increase in social behavioral deficits and repetitive behaviors in germ-free mice, suggesting that appropriate microbiota composition is necessary for normal social activities. The intestinal flora of patients with ASD was transplanted into sterile mice, and the results showed that the intestinal flora of infected ASD patients was sufficient to induce ASD behavior in mice [24]. The analysis of intestinal flora showed that the abundance of Firmicutes, Proteobacteria, Verrucomicrobia, and Fusobacteria were increased in patients with epilepsy, while Bacteroidetes and Actinobacteria were decreased. The ketogenic diet, probiotics, and fecal flora transplantation can improve intestinal flora disorders and epileptic seizures [25]. In addition, transplants of feces from anxiety-like mice promoted anxiety-like behavior in sterile mice and vice versa; it has also been confirmed in animal and clinical trials that probiotic supplementation can reduce anxiety and depression, and prevent anxiety caused by intestinal infection and immune deficiency [26]. Therefore, the gut microbiota has become a potential target for the diagnosis and therapy of multiple diseases [21,27].

In this work, we visually analyzed the research hot spots on the MGBA from 2004 to 2020 by bibliometric analysis from the Web of Science Core Collection (WOSCC) database. These data revealed the research hot spots of MGBA and new ideas for the molecular mechanism of the MGBA, and provided a new platform for the therapy and intervention of neurological diseases.
Material and Methods

Data Collection

We searched all literature data on the MGBA index in the WOSCC (Clarivate Analysis, Boston, MA, USA; http://apps.webofknowledge.com/WOS_GeneralSearch_input.do?product=WOS&SID=7DLaapxWMwSkqZf4LRr&search_mode=GeneralSearch). The publications from 2004 to 2020 (December 30, 2020) were searched, the language was set as English, and article and review were selected. The search terms “microbiota gut brain” OR “microbiota gut brain” OR “microbiome gut brain” OR “microbiomes gut brain” OR “microbial community gut brain” OR “microbial communities gut brain” were used. A total of 3993 documents on the MGBA were retrieved and then used to conduct bibliometric analysis.

Data Analysis

The general information about the distribution of publication year, organization, journal, and authors were analyzed by the WOS-based literature analysis. The publication number, article type, and citation h-index were assessed by the “citation report” function of the WOS. The bibliometric analysis and network visualization were performed using VOSviewer (version 1.6.15; Centre for Science and Technology Studies, Leiden University, the Netherlands) and CiteSpace (version 5.7. R3; College of Information Science and Technology, Leisel University, USA), and the ranking order was performed using the standard competition ranking method. The parameters of the VOSviewer method (Linlog/modularity) and CiteSpace were conducted as described by Chen et al [27]. The parameters of CiteSpace were set as follows: Method (LLR), time slicing (2004-2020), years per slice (1), term source (all selection), term type (burst terms), node type (1 chosen at a time), selection criteria (top 50 objects), and pruning (pathfinder) [27].

Results

Publication Outputs

From 2004 to 2020, there were 159,316 publications related to the microbiota (76.75% articles and 13.02% reviews), while there were 2,262 (56.65%) articles, 1,402 (35.11%) reviews, and 329 (8.24%) other documents, such as editorials, meetings, book chapters, or letters, among the 3,993 documents on the MGBA. By contrast, the high proportion of reviews on the MGBA indicated that it has received more attention and deserved to be discussed. Publications related to the MGBA are shown in Figure 1. The data showed that the first publication of MGBA appeared in 2004. It was not until 2008 that a few more articles appeared, and then documents continued to be published, with the number rising steadily beginning in 2010 (Figure 1).

Countries/Regions and Organization

A total of 98 countries/regions were involved in research on the MGBA. The number of documents and citations for countries/regions are presented in Figure 2A and 2B, respectively. Some of the research was based on the cooperation between different countries/regions, such as the United States and Ireland (Figure 2B). Three of the 10 most productive countries/regions were the United States (1,355), China (660), and Canada (296) (Table 1). The United States and China were responsible for most of the study of the MGBA, accounting for about 50.06% of all publications. Although China had a large number of documents, the number of citations (9,451) was lower than that of Canada (14,602), the United Kingdom (10,213), Ireland (19,415), and the United States 39,757 (Figure 2B). This suggests that China needs to increase its influence by cooperating more closely with other countries/regions and producing more innovative research.
Figure 2. The documents on the microbiome-gut-brain axis (MGBA) in different countries/regions. (A) Map of the cooperation between 34 countries by the VOSviewer. (B) The cooperation between the United States and Ireland. Different colors indicate clusters of collaboration between countries, the size of the circle indicates citations to the publication, and the thickness of the line indicates the extent of collaboration. The network visualization was performed by VOSviewer (version 1.6.15; Centre for Science and Technology Studies, Leiden University, the Netherlands).
About 3835 organizations participated in the 3993 publications on the MGBA. Three of the 10 most productive organizations were the University College Cork, McMaster University, and University of California Los Angeles (Table 2). The biggest surprise was the University College Cork in Ireland, with 180 documents and 9154 citations. McMaster University had 98 documents, 8933 citations, and 52 total link strengths. Zhejiang University had 43 documents, 1104 citations, and 11 total link strengths. Another organization from Ireland, the National University Ireland University College Cork, also did well, with 68 documents and 9660 citations. However, the United States had a clear advantage in the number of institutions (the 5 US organizations had 276 documents and 10 827 citations). The co-authorship of the organization showed that some organizations existed in isolation, such as the Federal University of Rio De Janeiro and Basque Foundation for Science (Figure 3A).

It is clear that documents from Ireland had a wider range of influence, and University College Cork dominated the field of MGBA research with more cooperation with other organizations. The Chinese Zhejiang University had less cooperation with other organizations (Figure 3A). VOSviewer analysis showed that there were 193 organizations with a minimum of 10 documents, including Central South University in China (Figure 3B). Central South University was the most active organization with the most articles on the MGBA and it worked with institutions including the University California San Diego, University of Chicago, Yale University, University of Helsinki, and Nanjing Medical University (Figure 3B). This indicates that Central South University is an emerging research organization in the MGBA.

### Journal Analysis

The 3993 documents on the MGBA were published in 1190 journals from 2004 to 2020, and the top 15 journals are listed in Table 3, including Scientific Reports, Nutrients, and Brain.

### Table 1. The top 10 most productive countries/regions on the microbiome-gut-brain axis.

| Rank | Country/Region | Documents | Citations | Total link strength | Links |
|------|----------------|-----------|-----------|---------------------|-------|
| 1    | USA            | 1341      | 39757     | 818                 | 67    |
| 2    | China          | 661       | 9451      | 305                 | 31    |
| 3    | Canada         | 297       | 14602     | 307                 | 46    |
| 4    | Italy          | 295       | 6760      | 251                 | 47    |
| 5    | United Kingdom | 276       | 10213     | 411                 | 46    |
| 6    | Ireland        | 270       | 19415     | 211                 | 31    |
| 7    | Germany        | 200       | 5719      | 276                 | 40    |
| 8    | Australia      | 194       | 4449      | 224                 | 32    |
| 9    | France         | 184       | 8384      | 216                 | 38    |
| 10   | Netherlands    | 158       | 4490      | 247                 | 37    |

### Table 2. The top 10 most productive organizations.

| Rank | Organizations | Country | Documents | Citations | Total link strength |
|------|---------------|---------|-----------|-----------|---------------------|
| 1    | Univ Coll Cork| Ireland | 180       | 9154      | 107                 |
| 2    | Mcmaster Univ | Canada  | 98        | 8933      | 52                  |
| 3    | Univ Calif Los Angeles | USA | 76       | 7111      | 42                  |
| 4    | Natl Univ Ireland Univ Coll Cork | Ireland | 68       | 9660      | 18                  |
| 5    | Univ Illinois | USA | 56        | 1633      | 22                  |
| 6    | Karolinska Inst | Sweden | 51        | 5163      | 28                  |
| 7    | Univ Calif San Diego | USA | 50        | 2312      | 25                  |
| 8    | Harvard Med Sch | USA | 50        | 1246      | 49                  |
| 9    | Univ Calif Davis | USA | 44        | 825       | 21                  |
| 10   | Zhejiang Univ | China | 43        | 1104      | 11                  |
Behavior and Immunity. The journal with the most publications was *Scientific Reports* with 96 documents (impact factor [IF] 3.998, and journal citation reports [JCR] Q1). For the JCR partition analysis, 8 journals were Q1, 1 journal was Q1/Q2, 4 journals were Q2, and 2 journals were Q2/Q3. *Scientific Reports, Nutrients,* and *Brain Behavior and Immunity* may be the most popular journals and have different IF distributions. In general, documents on the MGBA have been accepted by excellent journals, which helps to promote the awareness of the MGBA to a wide range of readers and researchers.

**Figure 3.** Co-author analysis of organizations. (A) The co-authorship of organizations showed the collaboration of University College Cork and Zhejiang Univ. (B) The average published year showed the recent active organization, Central South University. The color shows the average published year. The network visualization was performed by VOSviewer (1.6.15 versions; Centre for Science and Technology Studies, Leiden University, the Netherlands).
A total of 17,357 authors participated in the publication of MGBA-related documents. A total of 338 authors with at least 5 MGBA-related documents were visualized. As shown in Figure 4A, the overlay visualization shows the co-authorship relations of authors. John F. Cryan and his colleagues, Timothy G. Dinan, Gerard Clarke, Catherine Stanton, and Fergus Shanahan, are linked with the red cluster, indicating they had close cooperation in MGBA authorship (Figure 4A). However, authors including Dong H. Kim, Kenji Hashimoto, and Jasmohan S. Bajaj lack contact with other peripheral scholars (Figure 4A). Furthermore, John F. Cryan had more extensive cooperation with other peripheral scholars (Figure 4B), and Emeran A. Mayer also had collaborated with other authors, including John F. Cryan, Rob Knight, and Yolanda Snaz (Figure 4B). The top 10 core authors in MGBA research from 2005 to 2020 are listed (Table 4), including John F. Cryan, Timothy G. Dinan, and Gerard Clarke. John F. Cryan and his colleagues Timothy G. Dinan, Gerard Clarke, Catherine Stanton, and Fergus Shanahan from the University College Cork accounted for 5 seats. John F. Cryan was the first with 187 documents and 16,808 total citations and was followed by Timothy G. Dinan with 169 documents and 16,131 citations (Table 4). Fergus Shanahan was the last who was from University College Cork, with 22 documents and 1681 citations. John F. Cryan and Dong H. Kim had an h-index of 88 and 84, respectively. Thus, this indicates that the research on the MGBA of John F. Cryan and his colleagues is widely recognized.

### Citation Analysis

The top 10 co-citation analysis of documents on MGBA are listed in Table 5 and include 3 reviews and 7 articles. A recent article “Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson’s disease” (Cell, 2016) by Timothy R. Sampson had 869 citations and revealed the relationship between gut bacteria and neuroinflammation and motor symptoms [28] (Table 5). The articles of MGBA with high citations have been widely accepted and have inspired recent research, and these recent studies will have a positive influence on this field.

### Keyword Analysis

A total of 5928 keywords were included in the 3993 documents on the MGBA and 220 authors were visualized. According to the number of occurrences, the keywords included gut-microbiota, microbiota, microbe-gut-brain axis, probiotics, inflammation, depression, gut microbiome, stress, anxiety, Alzheimer’s disease, dysbiosis, obesity, Parkinson’s diseases, microbiota-gut-brain-axis, and neuroinflammation. Mapping analysis shows the relevant author keywords related to microbiota-gut-brain-axis, inflammation, or probiotics (Figure 5A). According to the statistical analysis of the author keywords, many events were associated with the blood-brain barrier, hippocampus, and microglia, including the processes of inflammation, neuroinflammation, and oxidative stress, which were involved in depression, stroke, ASD, MS, PD, and AD (Figure 5A). The average publication year for the keyword neuroinflammation was 2019 (Figure 5B).
Figure 4. Co-authorship analysis of authors. (A) Map of the cooperation between 338 authors by the VOSviewer. (B) Analysis of the authors who cooperated with John F. Cryan or Emeran A. Mayer. Different colors indicate clusters of collaboration between authors, the size of the circle indicates citations to the publication, and the thickness of the line indicates the size of collaboration. The network visualization was performed by VOSviewer (1.6.15 versions; Centre for Science and Technology Studies, Leiden University, the Netherlands).
### Table 4. Core-authors on the microbiome-gut-brain axis.

| Rank | Authors          | Organizations                  | Documents | Citations  | h-index |
|------|------------------|--------------------------------|-----------|------------|---------|
| 1    | John F. Cryan    | University College Cork        | 187       | 16808      | 88      |
| 2    | Timothy G. Dinan | University College Cork        | 169       | 16131      | 81      |
| 3    | Gerard Clarke    | University College Cork        | 74        | 6485       | 45      |
| 4    | Catherine Stanton| University College Cork        | 53        | 3137       | 66      |
| 5    | Emeran A. Mayer  | University of California at Los Angeles | 39     | 3067       | 77      |
| 6    | John Bienenstock | McMaster University            | 30        | 2827       | 46      |
| 7    | Premysl Bercik   | McMaster University            | 26        | 2482       | 40      |
| 8    | Paul Forsythe    | McMaster University            | 23        | 2694       | 30      |
| 9    | Dong H. Kim      | Kyung Hee University           | 23        | 184        | 84      |
| 10   | Fergus Shanahan  | University College Cork        | 22        | 1681       | 80      |

### Table 5. Top 10 co-citation analysis of documents on the microbiome-gut-brain axis.

| Rank | Title                                                                 | First author          | Source                  | Publication year | Total citations |
|------|------------------------------------------------------------------------|-----------------------|-------------------------|------------------|-----------------|
| 1    | Host-Gut Microbiota Metabolic Interactions                           | Jeremy K. Nicholson  | Science                 | 2012             | 1914            |
| 2    | Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour | John F. Cryan         | Nature Reviews Neuroscience | 2012             | 1622            |
| 3    | Normal gut microbiota modulates brain development and behavior       | Rochellys D. Heijtz   | PNAS                    | 2011             | 1383            |
| 4    | Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders | Elaine Y. Hsiao       | Cell                    | 2013             | 1364            |
| 5    | Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve | Javier A. Bravo       | PNAS                    | 2011             | 1333            |
| 6    | Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice | Nobuyuki Sudo        | The Journal of Physiology | 2004             | 1028            |
| 7    | Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson’s Disease | Timothy R. Sampson   | Cell                    | 2016             | 869             |
| 8    | Gut-brain axis; how the microbiome influences anxiety and depression | Jane A. Foster       | Trends in Neurosciences | 2013             | 836             |
| 9    | Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma | Mauro Castellarin   | Genome Research         | 2011             | 769             |
| 10   | Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits | Filipe De Vadder      | Cell                    | 2014             | 748             |
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DATABASE ANALYSIS
Figure 5. Co-occurrence analysis of author keywords. (A) Map of the relevant author keywords of microbiota-gut-brain-axis, inflammation, or probiotics. (B) The average published year shows the relationship of neuroinflammation between other author keywords. The color shows the average published year. The network visualization was performed by VOSviewer (1.6.15 versions; Centre for Science and Technology Studies, Leiden University, the Netherlands). (C) Top 20 keywords with the strongest citation bursts by Citespace (5.7. R3 versions; College of Information Science and Technology, Leisel University, USA). γ: 1.0; minimum duration: 2.

Discussion

This is the latest application of bibliometric analysis on MGBA research, involving 3993 publications retrieved from the WOS core database. The results of bibliometrics analysis presented a comprehensive overview of the development of MGBA articles over the past 15 years. The field of MGBA research has increased tremendously over the last decade. The number of MGBA publications rapidly increased from 12 in 2010 (n=12) to 1078 by December 30, 2020. Some rapidly developing or ganizations and scholars joined the research work in this field. Increases in recent studies have further revealed the important role of the MGBA in neurological diseases, and the scope of research has also become more extensive, including pre-clinical animal experiments and numerous clinical trials. The MGBA will continue to attract a great deal of interest and research and to be a hot topic in the coming decade, revealing detailed signaling pathways and molecular mechanisms associated with diseases.

| Keywords                        | Years | Strength | Begin | End | 2004-2020 |
|---------------------------------|-------|----------|-------|-----|-----------|
| Irritable bowel syndrome        | 2004  | 9.85     | 2014  | 2020|           |
| Behavor                         | 2004  | 6.00     | 2012  | 2020|           |
| Enteric nervous system          | 2004  | 5.06     | 2013  | 2020|           |
| Animal model                    | 2004  | 5.02     | 2009  | 2020|           |
| Intestinal microbiota           | 2004  | 5.01     | 2010  | 2020|           |
| Epigenetics                     | 2004  | 4.69     | 2014  | 2020|           |
| Autoimmunity                    | 2004  | 4.40     | 2008  | 2020|           |
| Infection                       | 2004  | 4.17     | 2016  | 2020|           |
| Stroke                          | 2004  | 4.17     | 2016  | 2020|           |
| Central nervous system          | 2004  | 3.72     | 2011  | 2020|           |
| Short chain fatty acid          | 2004  | 6.62     | 2014  | 2020|           |
| Immunity                        | 2004  | 3.49     | 2018  | 2020|           |
| Brain-gut axi                   | 2004  | 3.48     | 2009  | 2020|           |
| Behaviour                       | 2004  | 3.40     | 2015  | 2020|           |
| Gluten                          | 2004  | 3.38     | 2013  | 2020|           |
| Vagus nerve                     | 2004  | 3.34     | 2016  | 2020|           |
| Biomarker                       | 2004  | 3.24     | 2013  | 2020|           |
| Constipation                    | 2004  | 3.12     | 2016  | 2020|           |
| Endotoxin                       | 2004  | 3.09     | 2013  | 2020|           |
| Hypothalamic-pituary-adrenal axi| 2004  | 3.02     | 2014  | 2020|           |
| Lipopolysaccharide              | 2004  | 2.93     | 2017  | 2020|           |
| Bifidobacterium                 | 2004  | 2.91     | 2015  | 2020|           |

The data show that neuroinflammation is a hot spot of research and eminent scholars have begun to work in field of the MGBA.
The United States has been the most productive country in MGBA research, followed by China, probably due to the launch of the second phase of the Integrative Human Microbiome Project by the National Institutes of Health in 2013 and the Microbiome Program of the Chinese Academy of Sciences in 2017, which has attracted a wide range of scholars with an interest in the field of the MGBA and has provided substantial financial support. Since then, the MGBA has become immensely popular and has had many citations [28-32]. However, John F. Cryan and Timothy G. Dinan from University College Cork (Cork, Ireland), are among the top 2 authors with publications in this field, are far ahead of other authors, and have led the work of research in Ireland and worldwide in the field of MGBA. John F. Cryan, Timothy G. Dinan, Sarkis K. Mazmanian, Paul H. Patterson, Jeremy K. Nicholson, Sven Pettersson, and other scholars in the fields of gastroenterology, microbiology, and neurology suggest discoveries for new research fields, which provide an emerging platform for treatment and intervention of multiple diseases, such as depression, autoimmune disease, MS, ASD, PD, and obesity.

Keyword analysis suggested that inflammation and neuroinflammation are the research hot spots in the field of MGBA. The MGBA involves the host immune system [33], and unbalanced immune-inflammatory issues cause neurological disorders [34]. In recent years, communication of the peripheral immune cells to the brain and the MGBA has received increasing attention for its ability to modulate brain function [35]. Gut microbiota alteration impairs cognitive functioning via an increase of systemic inflammation [36]. The microbiota metabolic and immune-inflammatory axes are involved in brain development and behavior and CNS diseases via the MGBA [32]. The process of neuroinflammation that underlies several neurological disorders, such as PD, AD, ASD, and MS, may involve, or be strengthened by, peripheral inflammatory processes, such as the NF-κB, JAK/STAT, MAPKs, PPARs, NLRP3, and other signaling pathways involved in chronic intestinal inflammation [37].

In the past 2 decades, neuroimmunology has gradually become a research hot spot [38]. Some preclinical studies have found that the gut microbiome is critical for the pro-inflammatory and anti-inflammatory activities of microglia [39]. Therefore, gut microbiota imbalance may interfere with the maturation and activity of these brain-resident immune cells and may be a key driver in nervous system disorders. A high level of α-synuclein in the gut is positively correlated with brain damage, neuroinflammation, and neurodegeneration of dopaminergic neurons in patients with PD [40,41]. Extensive evidence from human samples and animal models support the involvement of inflammation in the onset or progression of PD [42], and fecal samples from patients with PD present low levels of Prevotellaceae and SCFA [43], in particular butyrate, acetate, and propionate [43], while treatment with microbially produced SCFAs modulates microglia-mediated α-synuclein aggregation and neuroinflammation and improves PD pathophysiology [28]. Intestinal flora play an important role in the inflammatory infection hypothesis of AD [44,45], which is a very promising area of therapeutic intervention [46,47]. A meta-analysis indicated that probiotics improved cognitive performance in patients with AD or mild cognitive impairment, possibly by downregulating inflammatory and oxidative biomarkers [25]. For MS, dietary tryptophan metabolites produced by intestinal bacteria inhibited the behavior of brain microglia immune cells and TGF-α and VEGF-β production, which in turn regulated the activity of astrocytes and reduced neuroinflammation; similar mechanisms exist in the human brain with MS [48]. In a small, preliminary clinical study, compound probiotics with lactic acid bacteria, Bifidobacteria, and Streptococcus reversed changes in the intestinal flora of MS patients, demonstrating an anti-inflammatory effect [49]. The crosstalk of inflammation and the gut microbiota is also involved in ASD and depression [16,50,51]. Gut microbiota composition in patients with ASD is changed, and ASD is related to levels of TNF-α, Clostridia, Desulfovibrio, and Bacteroidetes/Firmicutes; in the Chinese ASD population, ASD may be correlated with Acidobacteria, Enterobacteriaceae, Megamonas, Pseudomonadaceae, and Veillonellaceae abundance [16]. Furthermore, the abundance of Bacteroidales, Fusobacteriales, and Verrucomicrobiales are decreased, while Clostridiales and Enterococcus are increased in patients within 72 h after TBI [52]; however, Prevotella and Bacteroides are absent or reduced and the abundance of Ruminococcaceae is relatively high in patients with TBI for several years [53], and the bidirectional MGBA creates a cascade of inflammation and disease [54].

The MGBA, as a bridge between inflammation and CNS diseases, is an attractive strategy, but still, some questions need to be answered: Which species or groups of bacteria play a dominant role in different diseases? What is the significance of the different microbiota represented by the same disease in different stages or different populations? What is the interaction between different microflora? Lastly, what is the specific regulatory mechanism of microbiota in inflammatory and oxidative biomarkers? For example, a ketogenic diet or treatment with both Akkermansia and Parabacteroides mediate and confer anti-seizure effects via regulating the amino acid γ-glutamylate and hippocampal GABA/glutamate; however, there is no significant antiepileptic action after enrichment of either Akkermansia or Parabacteroides alone [55]. This suggests that the functions of some bacteria depend on the crosstalk with other bacteria. With purified Akkermansia muciniphila, TLR-2 is verified as a target of Akkermansia [56], while Akkermansia is related to inflammation [57,58]. Membrane protein purified from Akkermansia muciniphila or pasteurized bacteria has confirmed to regulate T lymphocytes in mice [59]. Thus, by pasteurizing or directly purifying the membrane protein of bacteria, the regulation mechanism and signal transduction between inflammation and other related molecules were further explored to reveal the regulatory network of gut microbiota and...
its metabolites, neuroinflammation, and neural network, which can facilitate the development of effective treatment strategies for targeting neuroinflammation in large-scale clinical trials.

There were some limitations to this bibliometric analysis of the MGBA. Firstly, the publications were limited to the WOSCC database with the deadline of December 30, 2020. Although the WOSCC is the most frequently used database for bibliometric analyses, not all MGBA-relevant publications were contained in our search terms of the title, abstract, keywords, literature type, and language. Secondly, the document type labels assigned by WOS may be inaccurate. Thirdly, the bibliometrics method did not weigh the quality or scientific rigor of any individual publication. However, we still believed that the present findings provided an effective representative of the overall situation and general trend for MGBA research.

Conclusions

This work provided an overview of the further literature analysis of MGBA worldwide, and the analysis provided a comprehensive overview of MGBA research. This field is gradually gaining interest by many scholars, and we believe the MGBA will be a hot spot in the coming decade, revealing detailed molecular mechanisms and providing a new platform for the therapy and intervention of neurological diseases. The MGBA, as a bridge between inflammation and CNS diseases, is an attractive strategy. We further revealed the interaction between the gut microbiota (eg, Akkermansia, Parabacteroides) and the specific regulatory network of the gut microbiota and metabolites, neuroinflammation, and neural networks, which can facilitate the development of effective treatment strategies using microbiota for targeting neuroinflammation and conducting large-scale clinical trials of neurological diseases. Therefore, this work presents the characteristics and trends of MGBA research that provide viewpoints for scholars for future studies of neurological diseases.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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