The Top 100 Most Highly Cited Original Articles on Immune and Gut Microbiota

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Abstract

Background

Crosstalk between the gut microbiota and the host immune system is related to multiple diseases, and in recent years, this crosstalk has gradually become a research hotspot. Because the research involves many diseases, the mechanisms are extremely complicated, so both the screening out of the high-quality articles from the massive amount of literature and the in-depth interpretation of their data are helpful in guiding the direction of research.

Methods

In this study, the top 100 most highly cited original articles were obtained from a total of 43,858 papers. According to the number of citations in the Web of Science database, the results are sorted in descending order. One may download the data obtained by Web of Science into tab-delimited (Win) format and import it into VOSviewer (Leiden University, Leiden, Netherlands) for subsequent bibliometric analysis. We summarized the country, institution, journal, author and other indicators for all publications. Through the online bibliometric platform, we analyzed the publication volume and growth trends for different countries/regions. VOSviewer was used to classify keywords into different clusters based on co-occurrence analysis and color them according to the time course.

Results

The number of citations for each article ranged from 914 to 5,460, and the most cited manuscript was written by PJ Turnbaugh and RE Ley. Washington University, the University of Colorado and Harvard University performed well in terms of the quality and quantity of publications. Manuscripts in NATURE, PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA and SCIENCE were the most influential. In addition, we identified six clusters of hotspots in the field of gut microbiota and immunity research.

Conclusions

Obesity and diabetes are the diseases most related to the gut microbiota, and their pathogenesis may be associated with a change in intestinal wall permeability and an imbalance of Bacteroides and Firmicutes. The balance of energy metabolism plays a key role in the crosstalk between host immunity and intestinal microbiota.

Background

In the progress of host immune system development, host–microbiota interactions are elemental. The human gastrointestinal system is more conducive to bacterial growth than other areas of the body are, so host–gut microbiota crosstalk is more frequent [1]. The steep rise in immune-mediated diseases such as autoimmune, allergic and chronic inflammatory disorders has followed rapid changes in environment and

lifestyle[2-4]. This may be a consequence of a decrease in the abundance and diversity of intestinal microbiota, which results in a change in the immune status of the intestine and an increase in the body's susceptibility to pathogenic microorganisms in the intestine[5-7]. Gut microbes can have an important influence on systemic innate immunity and specific immunity [8]. The latest evidence shows that microbiota on the barrier surface can affect the host immune system, which in turn affects the course and severity of a variety of immune-mediated diseases (IMDs) [9, 10]. The host immune system could also modulate gut microbiota communities, through cellular mechanisms such as gut-resident $CX3CR1^+$ intestinal mononuclear phagocytes (MNPs) and IgA, which could regulate the composition of the gut microbiota[11-13].

As an important component of the host, the gut microbiota have great potential to participate in the immune response of the body, as has been confirmed by a large number of studies. The microbiome is regarded as a rich resource that needs to be tapped and can provide new ideas and methods for the prevention and treatment of diseases. However, finding specific molecular mechanisms is still a common problem and challenge faced by scientists worldwide. The research on gut microbiota and host immunity is huge and complicated. Determining feasible research directions with high-quality content within the massive volume of literature will help to clarify the mechanism of interaction between intestinal microbiota and host immunity. Statistical bibliometrics research can be used to evaluate the contribution of articles in a specific field, which could provide new directions for the prevention and treatment of some diseases and also provide guidance for new directions for research that has become popular recently[14, 15].

The 100 most cited articles in the field of gut microbiota research related to immunity were identified in this study. This study was aimed at assessing the status and trends of the most-cited articles in the field of immunity and gut microbiota. Finding hotspots from numerous, complicated, multiple-direction studies to evaluate the current research performance and provide practical information for basic researchers will provide direction for the treatment of immune-related diseases through gut microbiota in the future.

Methods

Data source and retrieval strategy

On June 25, 2020, the top 100 most cited articles published on immune-related gut microbiota research were retrieved from the Web of Science (Thomson Reuters) database. The strategy was as follows: (intestinal microbiota OR intestinal flora OR gut microbiota OR gastrointestinal microbiome) AND (immunity), with no limits on language or document type. According to the number of citations in the Web of Science database, the results are sorted in descending order. Two researchers (KC and LT) independently screened abstracts to obtain qualified papers. The two researchers finally reached a consensus on the 100 most-cited articles with the verification of experts in related fields. One may download the data obtained by Web of Science into tab-delimited (Win) format and import it into VOSviewer (Leiden University, Leiden, Netherlands) for subsequent bibliometric analysis. All literature

searches and download records were completed on the same day to reduce errors caused by frequent updates of the database.

Bibliometric analysis

We summarized the country, institution, journal, author and other indicators for all publications. Through the online bibliometric platform, we analyzed the publication volume and growth trends for different countries/regions. VOSviewer can classify keywords into different clusters based on co-occurrence analysis and color them at the same time according to the time course. It can also be used for hotspot prediction.

Results

Citation status of 100 articles

As shown in TableS1, the highest number of total citations for a single article was 5,460, and the mean number of citations was 1,622.26. Eighty-seven percent of these articles showed more than 1000 citations. These articles were published between 2000 and 2015. The most recent was published in November 2015 in SCIENCE with 920 citations, and the most cited was published in December 2006 in NATURE with 5,460 citations. Fig 1 shows the total number of articles, and Fig 1B shows the total yearly citations from 2000 to 2015.

Contribution of countries and institutions to global publications

The top 100 most highly cited studies on gut microbiota and the immune system came from at least 114 different countries or regions (Fig 2A). The United States (n= 65) is the largest contributor, followed by France (n=16), Belgium (n=11), England (n=11), and Germany (n=11). We also evaluated the centrality of these countries and regions. Centrality can indicate the importance of nodes in a network; the higher the centrality, the more important the article, and thus Fig2B showed that the United States has the most impact on other countries (centrality =0.69), followed by France (0.23) and England (0.18) (Table 1). In terms of the number of studies by research institution (Fig2C), the top 10 included Washington University (n=18), the University of Colorado (n=16), Harvard University (n=12), the University of Copenhagen (n=8), and Inra (n=7) (Table 2). The top five institutions by centrality were Harvard University (0.41), Inra (0.35), the University of Colorado (0.34), Washington University (0.27), and the Catholic University of Louvain (0.24).

Journals and authors publishing research on gut microbiota related to immunity

The 10 most popular journals published 72% of all the studies (Table 3). Among them, the top 3 were NATURE (n=21), PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA (n=15) and SCIENCE (n=15), which combined accounted for 51% of all indexed literature. The highest IF belongs to the NEW ENGLAND JOURNAL OF MEDICINE (74.699), followed by the LANCET

(60.392) and NATURE (43.788). Among all 837 authors on this subject, Gordon JI, Knight R, Ley RE, Turnbaugh PJ, and Backhed F published the most papers (Table 4).

Analysis of research hotspots

Keywords were extracted from the top 100 most highly cited studies and analyzed by VOSviewer; all of them are listed in Table S2. A total of 162 keywords that appeared more than 5 times were included and classified into 6 clusters on the map, called clusters 1 to 6, in red, green, dark blue, yellow, purple, and light blue (Fig 3A). The larger the circle is, the higher the frequency of keywords. For example, mice appeared 102 times, gut microbiota 84 times, obesity 51 times, diet 51 times, inflammation 41 times, and metabolism 33 times. In Fig 3B, all keywords are colored according to the average time of word appearance, from blue to yellow, representing early to recent appearances, respectively. Metabolic diseases, especially obesity, are an obvious hotspot in the area of gut microbiota and immunity. Obesity was the 7th most frequent keyword, and many other keywords were related to obesity, such as diet (n=51), metabolism (n=33), diabetes (n=26), butyrate (n=9), and insulin resistance (n=9).

Discussion

A large number of studies have reported that the composition of the gut microbiota affects the body's mucosal immune system, immune response and immune communication and that the immune system and gut microbiota mutually benefit from their interactions[4]. There is frequent and complex crosstalk between the intestinal microbiota and the host immune system. This process is affected by many factors, such as the intestinal microbiota composition, the host itself, and environmental factors. The intestinal microbiota can act locally or remotely through metabolites and other means[16]. Our statistical and quantitative analysis revealed that the top 100 most highly cited research papers on gut microbiota and immunity have fluctuated in the last 20 years. In Fig 1 it can be seen that the largest number of articles occurred in 2012 and 2013. This was closely related to a burst of interest in the microbiota and the development of research methods such as 16S RNA sequencing and metagenomic sequencing. We also identified six keyword clusters to analyze research hotspots on gut microbiota and immunity. Among studies in the field of gut microbiota and immunity, obesity is the most intensively studied area. In the 100 most cited articles, “obesity” occurred 51 times, along with some keywords that are obviously related to obesity, such as “diet”, “diabetes”, “insulin resistance”, and “metabolic disorder”. Other keywords are also closely related to obesity, gut microbiota and immunity, such as “treg cell”, “firmicutes”, and “bacteroidetes”. Obesity and type 2 diabetes have observed changes in the ratio of Th17 to Treg in intestinal wall tissue[17, 18]. The ratio of Firmicutes and Bacteroidetes change is a new type of risk factor for obesity, which is obviously related to intestinal wall permeability and the level of intestinal inflammation[19].

The global prevalence of obesity has increased substantially over the past 40 years, from less than 1% in 1975 to 6–8% in 2016[20]. Intestinal microbiota is a new mechanism that may explain the development of obesity, and it has received extensive attention in recent years. With the progress of research, the

relationship between intestinal microbiota and obesity has evolved from correlation to causation. In the normal state, probiotics in the intestinal system could directly compete for nutrients and attachment sites and produce antibacterial substances to resist infection by pathogenic microorganisms, promoting the proliferation and differentiation of epithelial cells and maintaining a complete mucosal surface. Through the maturation T and B lymphocytes and the differentiation of dendritic cells promotes the development of intestinal-associated lymphoid tissues. When intestinal microbiota imbalance occurs, these functions are affected, causing the occurrence and development of obesity[21, 22]. Therefore, based on the analysis of hot keywords, we propose that hosts and environmental factors (such as a high-fat diet) affect the composition and abundance of gut microbiota, resulting in a shift in the levels of intestinal metabolites (such as LPS and short-chain fatty acids) and immune factors (such as IgA and IL-17), mediating disorders in immune cell components (such as Treg and Th17 cells) and intestinal wall function, causing intestinal permeability and subsequent changes in the levels of various metabolites (such as butyrate) in the host and transferring metabolic signals into cells to dysregulate the expression of various genes (such as Toll). Eventually, cell function changes in the body (such as insulin resistance) are caused, and changes in hormone levels eventually cause abnormal energy metabolism to further aggravate obesity, forming a positive feedback loop.

In the analysis of countries, we found that the top five countries in this area are the United States (n= 65), France (n=16), Belgium (n=11), England (n=11), and Germany (n=11). These countries are developed countries with greater scientific research strength. Interestingly, according to the global obesity epidemic model, these countries are all in stage 3[20]. The obesity rate of people with lower socioeconomic status is higher than that of people with higher socioeconomic status. Based on our research, international cooperation in this field is still not sufficient, and it is expected that these countries will cooperate with more countries in stages 1 and 2. We observed only rRNA sequencing in the list of keywords. More advanced metagenomics and multiomics studies are needed to improve microbiome biomarkers and accurately clarify the correlation between specific gut microbiota or metabolites and diseases, which may be a hotspot for future research.

The gut microbiota may regulate the development and function of the immune system under the interaction of changes in dietary structure and human genetic constitution. At the same time, the immune system regulates the dynamic balance of the microbiota in some way. The imbalance between the two is an important cause of obesity and other metabolic diseases. In-depth study of this imbalance may bring revolutionary changes in prevention and control strategies for metabolic diseases. Recent studies have pointed out that the balance of energy metabolism plays a key role in the crosstalk between host immunity and intestinal microbiota. For example, the microbiota and its metabolites (short-chain fatty acids) promote energy production in the host by weakening the immune response mediated by TNFα[23]. Intestinal microbiota can also regulate transcription factors in mitochondria to affect ROS production, thereby regulating proinflammatory signals[24]. At the same time, the abnormal mitochondrial function caused by host mitochondrial gene mutations also affect the composition and activity of the gut microbiota[25]. In summary, energy metabolism is connected to the entire process of crosstalk between the intestinal microbiota and the host immune system. Therefore, other diseases closely related to energy

metabolism are also very likely to become potential hotspots for future research on gut microbiota and immunity. That is, hotspots in the future will be other diseases closely related to energy metabolism, including nonalcoholic fatty liver and osteoporosis, with possible mechanisms also through the interaction of the intestinal microbiota with the host immune system. Mitochondrial dysfunction is an important mechanism for the pathogenesis of NAFLD[26]. Decreased β-oxidation levels and increased adipogenesis lead to the production of reactive oxygen species and liver cell damage, ultimately leading to liver damage and fibrosis[27]. This inflammatory intestinal microbiota, which is closely related to energy metabolism, is very likely to be involved. Osteoporosis is newly defined as a metabolic disease that is closely related to energy homeostasis[28]. The unique function of osteoblasts requires substantial energy production, especially during states of bone formation and remodeling. Studies have shown that osteoblasts secrete endocrine factors that connect the metabolic needs of bone formation with overall energy balance by regulating insulin production, eating behavior, and fat tissue metabolism[29]. There have been studies showing the role of intestinal microbiota, intestinal wall permeability, and Treg cells in osteoporosis[30], but the mechanism still needs further research.

This study has some limitations. We only searched the Web of Science database collection database, with other databases such as PubMed and Scopus unsearched. Some influential articles may be missed in our bibliometric analysis. Because we counted the total impact factor, which is closely related to the chronological order of article publication, all articles in the top rank were published before 2015, and thus some valuable new articles may have been missed.

Conclusion

In this study, all manuscripts in the field of gut microbiota and immunity were summarized by means of bibliometrics. An in-depth interpretation of the top 100 most cited manuscripts indicated that gut microbiota and immunity-mediated obesity is the current research hotspot, energy metabolism is an important mechanism, and diseases closely related to energy metabolism may become research hotspots in the future.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent of publication

Written informed consent of publication was obtained from all participants.

Availability of data and material

All data and material is available.

Competing interests

All authors confirmed that they had no competing interests.

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Authors' contributions

Kaicheng Wen, Lin Tao and Siming Zhou were joint first authors. Kaicheng Wen and Yue Zhu contributed to the manuscript design as well as drafting of the manuscript; Siming Zhou and Keda Yang performed the search and collected data; Zhengbo Tao and Wacili Da conducted the data analysis; Lin Tao and Yan Meng contributed to acquisition of data and data analysis. All authors read and approved the final manuscript. Kaicheng Wen, Lin Tao, Siming Zhou contribute equally to this research.

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Tables

Table 1 Countries/regions contributing to the 100 most-cited articles

Rank	Countries/regions	Number of articles	Centrality
1	USA	65	0.69
2	FRANCE	16	0.23
3	BELGIUM	11	0.05
4	ENGLAND	11	0.18
5	GERMANY	11	0.04
6	NETHERLANDS	9	0.01
7	DENMARK	8	0.01
8	CANADA	7	0.06
9	JAPAN	7	0.05
10	SWEDEN	7	0.00
11	FINLAND	6	0.12
12	SPAIN	6	0.06
13	AUSTRALIA	5	0.01
14	IRELAND	5	0.14
15	SINGAPORE	4	0.01
16	PEOPLES R CHINA	3	0.00
17	SWITZERLAND	3	0.00
18	AUSTRIA	2	0.01
19	BRAZIL	2	0.01
20	ISRAEL	2	0.00
21	ITALY	2	0.00
22	VENEZUELA	2	0.00
23	CROATIA	1	0.00
24	LUXEMBOURG	1	0.00
25	MALAWI	1	0.00

Table 2 Institutions contributing to the 100 most-cited articles

Rank	Institutions	Number of articles	Centrality
1	WASHINGTON UNIV	18	0.27
2	UNIV COLORADO	16	0.34
3	HARVARD UNIV	12	0.41
4	UNIV COPENHAGEN	8	0.08
5	INRA	7	0.14
6	NYU	6	0.19
7	STANFORD UNIV	6	0.01
8	UNIV READING	6	0.00
9	UNIV TOKYO	6	0.16
10	CALTECH	5	0.04
11	CATHOLIC UNIV LOUVAIN	5	0.24
12	INST PASTEUR	5	0.21
13	MASSACHUSETTS GEN HOSP	5	0.04
14	UNIV HELSINKI	5	0.16
15	VET AFFAIRS PALO ALTO HLTH CARE SYST	5	0.01
16	BROAD INST MIT HARVARD	4	0.02
17	HOWARD HUGHES MED INST	4	0.04
18	HUMBOLDT UNIV	4	0.07
19	JAPAN SCI TECHNOL AGCY	4	0.04
20	OSAKA UNIV	4	0.04
21	UNIV CALIF BERKELEY	4	0.12
22	WAGENINGEN UNIV	4	0.00
23	BGI SHENZHEN	4	0.01
24	CLEVELAND CLIN	4	0.01
25	CNRS	4	0.12

Table 3 Journals contributing to the 100 most-cited articles

Rank	Journals	Number of articles
1	NATURE	21
2	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	15
3	SCIENCE	15
4	CELL	5
5	LANCET	4
6	CELL HOST MICROBE	3
7	GASTROENTEROLOGY	3
8	DIABETES	2
9	GENOME BIOLOGY	2
10	GUT	2
11	JOURNAL OF LIPID RESEARCH	2
12	NATURE MEDICINE	2
13	NEW ENGLAND JOURNAL OF MEDICINE	2
14	PLOS BIOLOGY	2
15	SCIENCE TRANSLATIONAL MEDICINE	2
16	ANNUAL REVIEW OF IMMUNOLOGY	2
17	BRITISH JOURNAL OF NUTRITION	1
18	DIABETOLOGIA	1
19	EMBO REPORTS	1
20	HEPATOLOGY	1
21	INFECTION AND IMMUNITY	1
22	JOURNAL OF PHYSIOLOGY LONDON	1
23	MOLECULAR MICROBIOLOGY	1
24	NATURE REVIEWS GASTROENTEROLOGY HEPATOLOGY	1

Table 4 Authors contributing to the 100 most-cited articles

Rank	Authors	Number of articles
1	GORDON JI	18
2	KNIGHT R	13
3	LEY RE	9
4	TURNBAUGH PJ	8
5	BACKHED F	7
6	CANI PD	6
7	DELZENNE NM	6
8	GIBSON GR	5
9	GUARNER F	5
10	MAZMANIAN SK	5
11	RELMAN DA	5
12	ATARASHI K	4
13	DE VOS WM	4
14	DORE J	4
15	HAMADY M	4
16	HONDA K	4
17	LITTMAN DR	4
18	NEYRINCK AM	4
19	XAVIER RJ	4
20	BATTO JM	3
21	BAUMGART DC	3
22	BRITT EB	3
23	BURCELIN R	3
24	CLEMENTE JC	3
25	DETHLEFSEN L	3

Figures

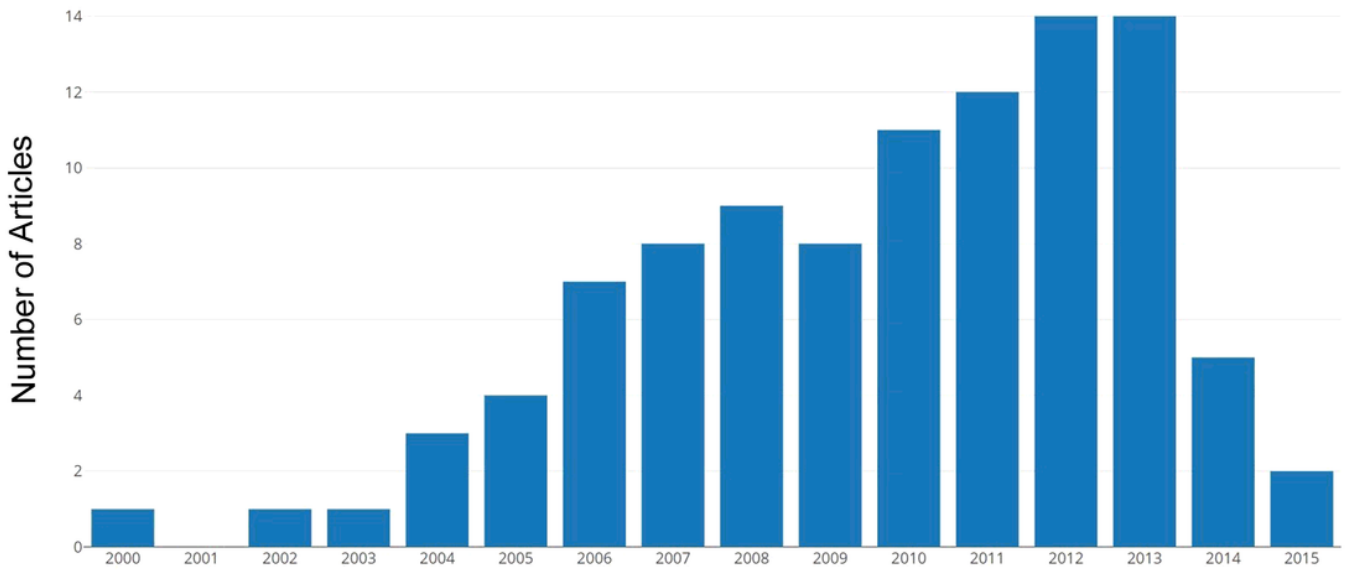

Figure 1

Total number of articles from 2000 to 2015

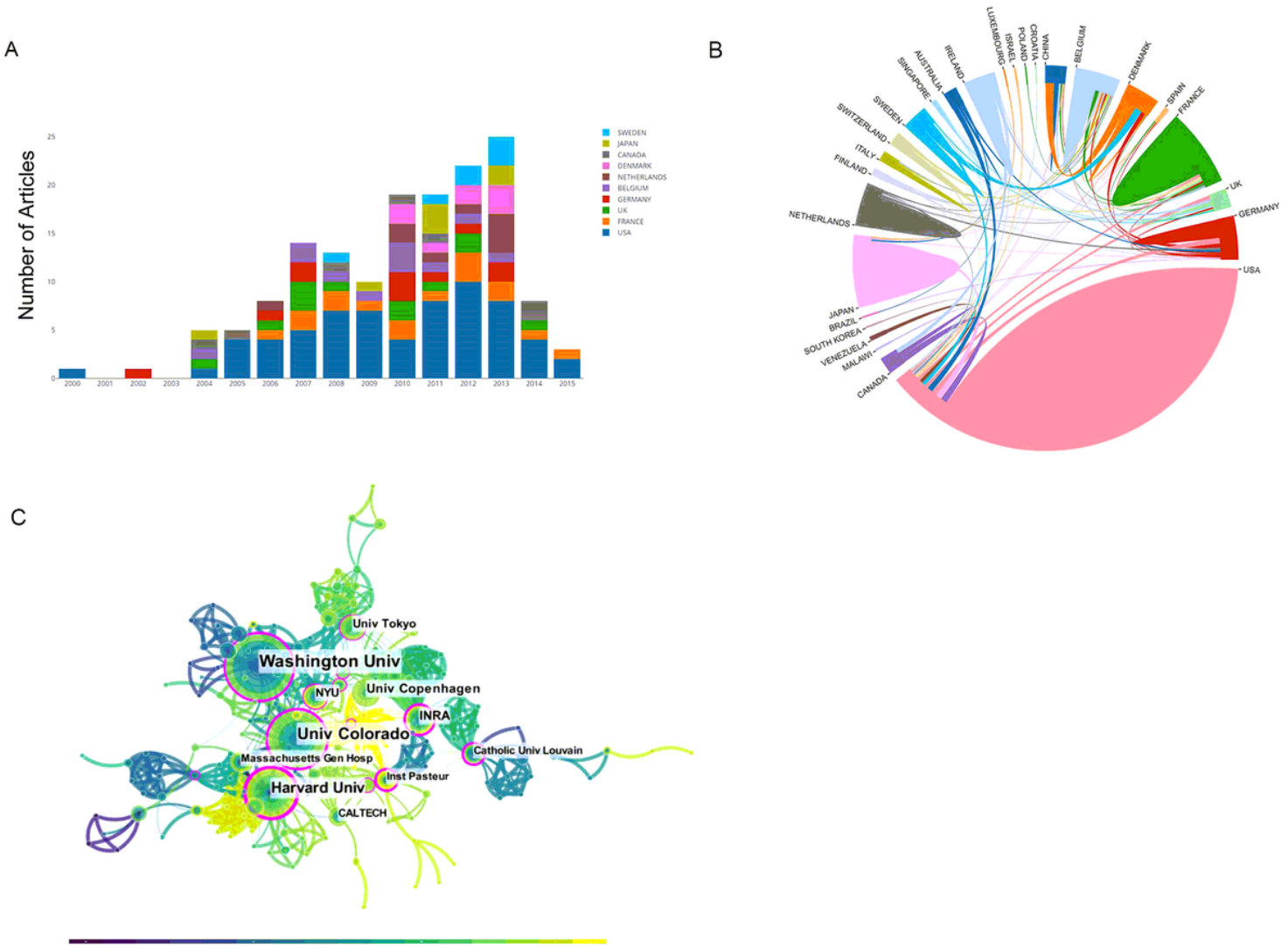

Figure 2

A. Number of studies by year and country B. The network map of countries that involved in this field C. Cooperation of countries/regions

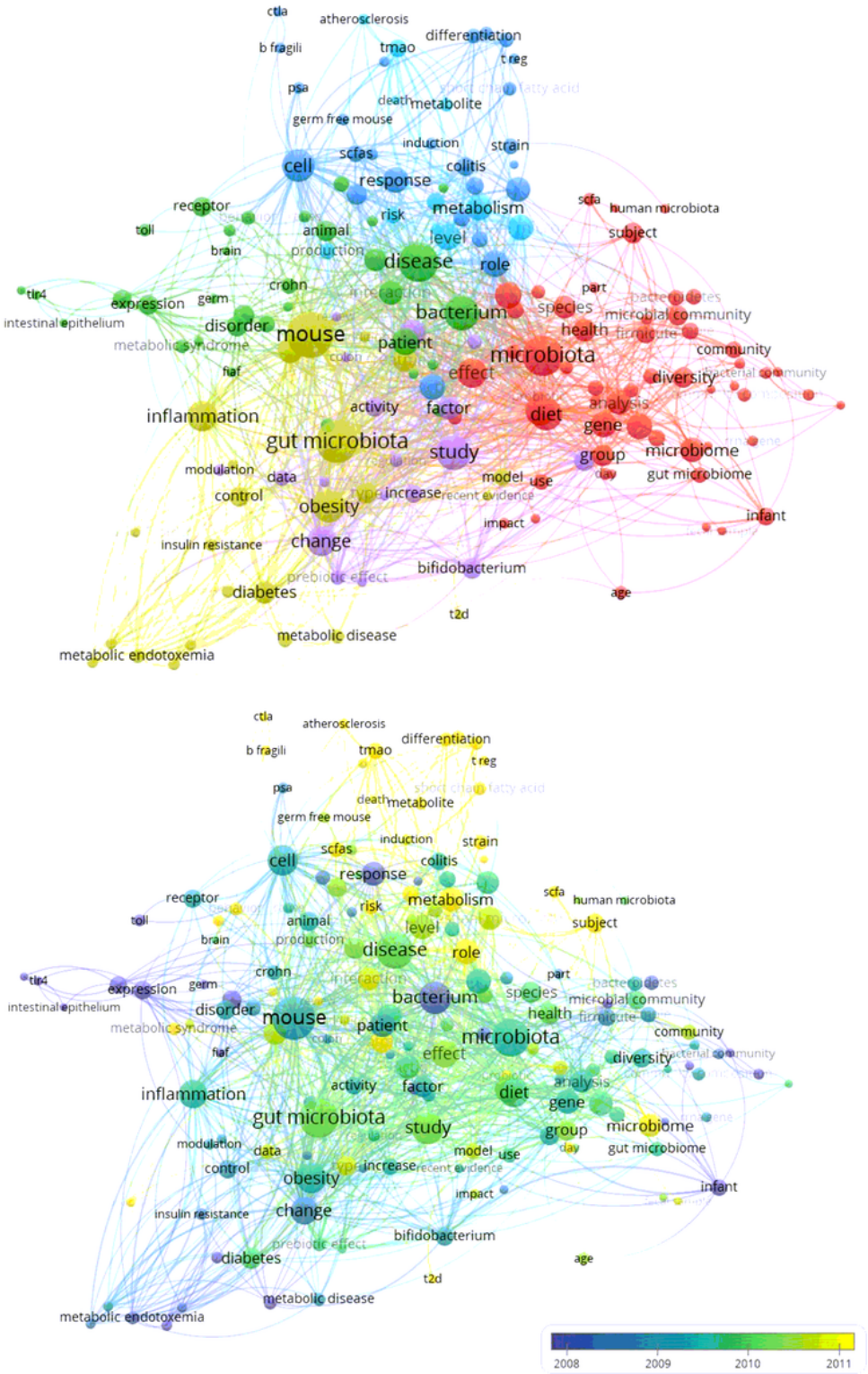

Figure 3

Network visualization using words from the titles and abstracts of the 100 most-cited articles.

Supplementary Files

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- TableS1.xls
- TableS2.xlsx