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A Bibliometric Analysis of the Research about Radical S-Adenosyl-Methionine Enzymes in 1999-2020

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Abstract

This paper aims to clarify the current research status and hot spots, as well as to predict future research trends about radical S-adenosyl-methionine (SAM) enzymes. We conducted this study based on 649 research papers about radical SAM enzymes published in the years of 1999 to 2020 on the Web of Science. Tools like CiteSpace were employed for statistical and visual network analysis of the time of publication, national cooperative relations, core authors, and co-word networks. Our findings include: 1) the number of academic publications in this field has been growing approximately linearly, especially after 2010. Since then, a spike occurred, and the average number of annual publications has grown to somewhere around 50. Besides, the representative keywords have become more diverse, demonstrating a gradual extension of the field into multi-area research. 2) The research papers in this field fall into 44 different disciplines, but only a limited number of journals have been publishing then, among which *Biochemistry* is the journal in which the largest number of papers are published, and the *Journal of the American Chemical Society* leads in the volume of publications and Impact Factor (IF). Both journals serve as the most noteworthy ones in this field. 3) The United States is the dominant country of study origin in the field, ranking first in terms of publication volumes and centrality. Other countries with comparatively high numbers of publications, such as France, England, Japan, Switzerland, Sweden, and Denmark, also indicate high centrality. Despite being a late starter, China has witnessed a rise in the number of published articles recently. 4) Various newly-born research subjects have emerged from classic research topics and expanded to more diverse research areas. In conclusion, this study could be of reference for follow-up researchers to quickly understand the current situation of radical SAM enzymology studies, screen relevant

literature, and develop novel and effective research programs in the future.

Subject Areas

Bioinformatics

Keywords

Radical SAM Enzyme, Bibliometrics, CiteSpace

1. Introduction

With more than 22,000 members, the radical S-adenosylmethionine (rSAM) enzyme superfamily is the largest known enzyme superfamily [1] [2]. rSAM enzymes, believed to be one of the earliest biocatalysts on earth, are found in all three domains of life, and new annotated sequences are continuously being discovered. If a [Fe_4S_4] cluster in rSAM enzymes is reduced by one electron, the enzymes would cleave SAM and become 5'-deoxyadenosyl radical species that could trigger various radical-based reactions. The substrates of rSAM are very diverse, including small organic molecules, proteins, DNA, RNA [3], and inorganic molecules [4]. As rSAM enzymes can catalyze challenging reactions, they have the potential to become catalysts for diverse biotechnological applications [5] [6]. Aside from their relatively simple structures and the chemical reactions they could catalyze, rSAM enzymes are highly abundant in nature, which has attracted early interest in their applications as tools in synthetic biology to deal with difficult and expensive pathways [7].

In recent years, extensive research has been conducted on rSAM enzymes, revealing their benefits and chemical mechanisms for real-world applications. For example, Broderick *et al.* summarised the common features of rSAM enzymes and delved further into the biochemical, spectroscopic, structural, and mechanistic details of the enzymes [3]. Following the extensive review by Drennan *et al.* in 2011 [8], Nicolet reviewed some of the latest developments in the field with a focus on the structure-function relationship of these enzymes and provided some insights into the mechanisms [6]. Besides, rSAM enzymes are also likely to engage in human health and diseases, and Booker *et al.* provided a stimulating review of the research on this aspect. However, few studies have attempted to gather global and systematic data on rSAM enzymes, resulting in unclear development trends, hot spots, and future frontiers in the research about these molecules. Therefore, a comprehensive literature review is needed to provide relevant scholars with information about the current research progress and main research directions, which could benefit their future work.

Bibliometrics takes the system and the characteristics of the literature as its research object and adopts mathematical and statistical methods to analyze the distribution structure, quantitative relationship, and alteration laws of the in-

formation in science literature [9] CiteSpace, which was developed by Chen Chaomei *et al.*, is an information visualization software designed to measure and analyze scientific literature data quantitatively. As an important tool for scientific bibliometric and knowledge network analysis [10] [11], it could assist in analyzing the rationale and tracking down the hottest and most advanced topics, thereby identifying research features and predicting the trends of this field. In this study, we used CiteSpace (5.4.R4) to carry out the statistical and visual network analyses on the global literature from 1999 to 2020 based on their time-series output, national partnerships, core authors, and keyword co-occurrence networks. Moreover, we provided a detailed summary of hot research directions and predicted the future development trend of this field, which could make the life of follow-up researchers easier when screening relevant literature and designing valuable research plans.

2. Data Collection and Processing

The data in this study were derived from the web-version of Web of Science for the Institute for Scientific Information (ISI). The largest and most comprehensive database of academic information and resources, Web of Science is an authoritative citation index database that collects the online version of SCI, SSCI, A-HCI, CPCI-S, and ISSHP databases and literature in numerous disciplines [12]. Several keywords, namely "Radical SAM Enzyme", "Radical SAM", "SAM Radical", "Radical AdoMet" and "AdoMet Radical", were used as the search phrases to screen topics from January 1, 1999, to December 31, 2020. 649 documents were obtained in this study, which is sufficient to reflect the research status in this field to the maximum extent. It is noteworthy that articles originated from Hong Kong, Macau, and Taiwan Province of China were not under the heading "China" in the analysis, and they were listed separately. Articles from England, Scotland, Northern Ireland, and Wales were grouped under the heading "United Kingdom (UK)".

Aspects, namely the chronological order, country, institute, keyword, author, and journal of publication, were all analyzed by Microsoft Excel 2017 to obtain the statistics of relevant literature. Besides, Origin2019 was applied on the aspects to draw graphics and demonstrate the overall trend. Furthermore, these two softwares were employed together with CiteSpace (5.4.R4) for data display, which acted as a clearer demonstration of the cooperative relationship between authors and institutions, as well as the research hot spots, and future research directions.

3. Results and Discussion

3.1. Document Types and Output Trends

Paper output is an important indicator of knowledge accumulation in the field, thereby demonstrating how mature a discipline or research field is [13]. As for the language of publication, all the 616 documents analyzed are written in Eng-

lish, suggesting that English is the most widely used tool for academic exchange in the field. When we consider the document types, 445 articles were published, accounting for 68.567% of all the documents; 134 pieces of literature (20.647%) are reviews, and 57 (8.783%) are conference papers. The first paper in this field can be traced back to 2001 (Figure 1). Over the past 20 years, despite fluctuations in individual years, the number of publications has been rising from 2 papers in 2001 to 77 in 2018, which remains the highest so far.

Furthermore, research regarding rSAM enzymes has caught the attention of scholars from home and abroad, leading to fruitful scientific findings. It turns out that the relationship between the number of publications and the year can be described as a linear equation: $Y = 3.7692$, $X = 7545.5$, $R^2 = 0.9141$, where Y is the number of publications, and X is the year. According to this equation, the year 2025 is expected to see 105 articles published. Growth of rSAM enzyme studies in the past 2 decades can be divided into two stages. The years of 2001-2009 belong to the stage of slow growth, with an average number of annual publications not exceeding 20; the remaining years, 2010-2019, belong to the stage of rapid growth, in which the average number of published papers has been surging to about 50.

To some extent, the number of published articles per country reflects the development and maturity of rSAM enzyme research internationally. It is noteworthy that the number of published documents has increased significantly since 2010, suggesting rSAM enzymes have been extensively applied and studied internationally in recent years.

In addition to the rising publications, the number of keywords involved has also increased significantly. Only two representative keywords, "Radical" and

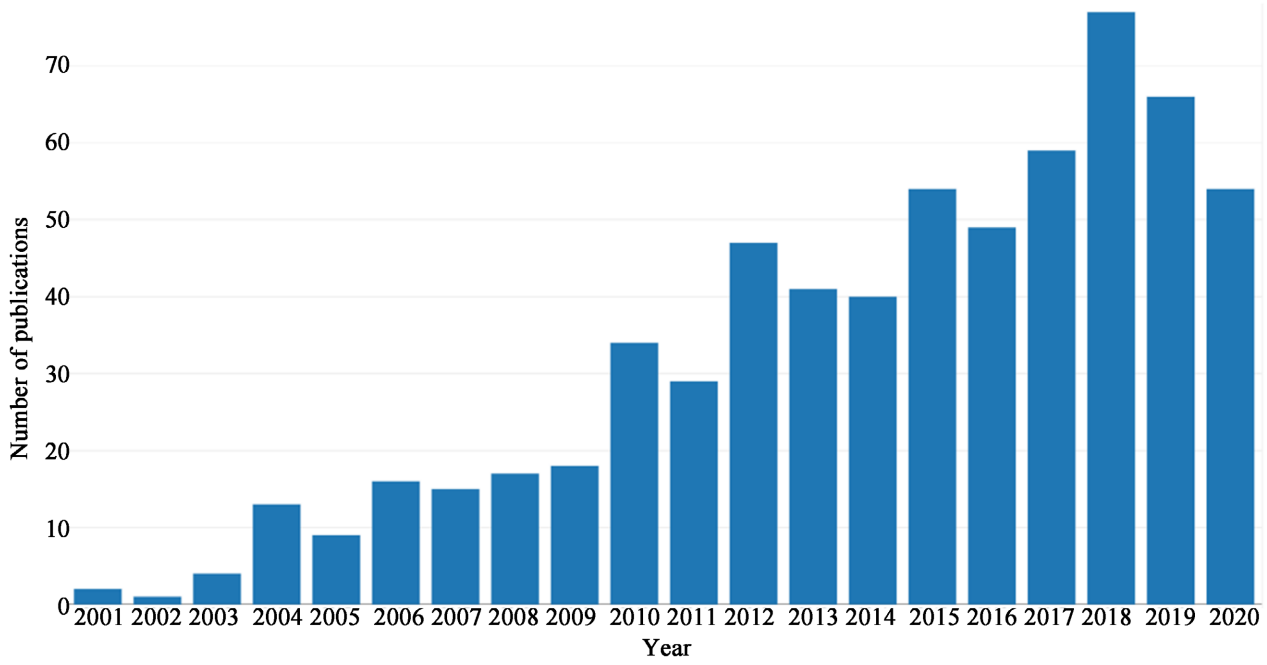

Figure 1. Chart of annual changes in the number of global publications.

"Enzyme Mechanism", were mentioned in 2003. However, in 2019, 16 representative keywords were mentioned, indicating that rSAM enzymes have been gradually applied in more areas (Figure 2).

3.2. Subject Categories and Journals

44 subject categories were identified in this study, and the Top 10 among them were selected for further analysis. The productive subjects are summarized in Table 1, namely, *Biochemistry Molecular Biology*, with 346 related articles published, taking up 53.313%, followed by *Chemistry Multidisciplinary*, *Biophysics*, *Multidisciplinary Sciences*, and *Cell Biology* with high publication volumes. And the proportions they occupied were 24.961%, 10.478%, 9.091%, and 6.934%

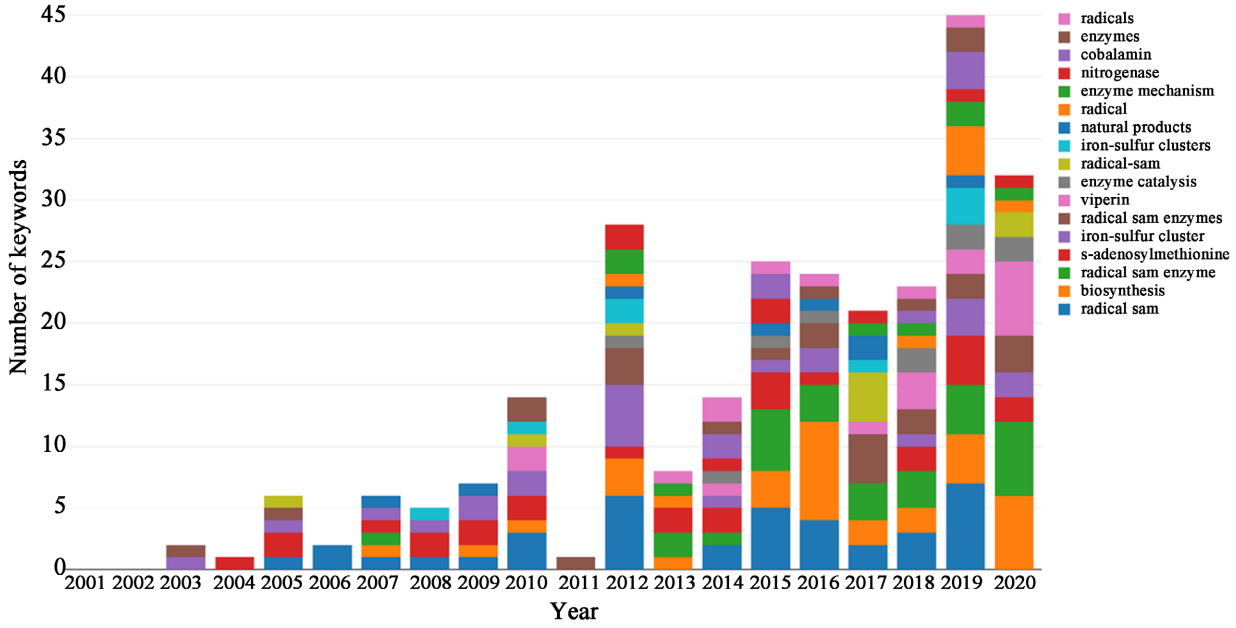

Figure 2. The number of keywords changing over the years.

Table 1. The Top 10 productive subjects.

Subjects	Publications	Percentage (%)
Biochemistry Molecular Biology	346	53.313
Chemistry Multidisciplinary	162	24.961
Biophysics	68	10.478
Multidisciplinary Sciences	59	9.091
Cell Biology	45	6.934
Microbiology	36	5.547
Chemistry Inorganic Nuclear	27	4.16
Biochemical Research Methods	26	4.006
Chemistry Medicinal	22	3.39
Biology	20	3.082

respectively. Judging from the table, the research on rSAM enzymes is multidisciplinary.

Table 2 gives the Top 10 journals that published research papers on rSAM enzymes. 317 papers were published in these journals, accounting for 48.844% of all the papers studied. Therefore, these journals are comparably influential in this field. The top-ranked journals include *Journal of the American Chemical Society*, *Biochemistry*, *Journal of Biological Chemistry*, *Abstracts of Papers of the American Chemical Society*, etc. Specifically, *Biochemistry* has the highest number of publications, with an IF of 2.865. *Journal of the American Chemical Society* exhibits a very high IF (14.612) and a high number of publications (59). Judging from the data, these two journals are the most influential in the field of enzymology.

3.3. Authors

Generally speaking, the corresponding authors are more frequently seen than the first authors. Therefore, the corresponding authors can reflect the core representatives of a certain field more accurately than the first authors. In our study, 233 authors worldwide were identified as the corresponding authors, and the numbers of articles they published and citations of their articles are shown in Table 3. Judging from the table, the top high-yield authors are *Broderick JB* (24), *Zhang Q* (20), *Booker SJ* (20), and *Bandarian V* (15) The top 10 authors in total citations include *Drennan L* (549), *Booker SJ* (442), *Frey PA* (385), and *Krebs C* (315). Particularly, *Broderick JB*, *Booker SJ*, *Drennan CL*, *Berteau O*, *Begley TP*, and *Fontecave M* are well renowned for their strong capability and great influence in the field. All of them are among the Top 10 in terms of articles

Table 2. The Top 10 journals of publications.

Journals	Publications	Percentage (%)	IF (2019)
Biochemistry	63	9.707	2.865
Journal of the American Chemical Society	59	9.091	14.612
Journal of Biological Chemistry	46	7.088	4.238
Abstracts of Papers of The American Chemical Society	28	4.314	12.959
Proceedings of the National Academy of Sciences of the United States of America	25	3.852	1.394
Angewandte Chemie International Edition	22	3.39	3.246
Methods in Enzymology	21	3.236	2.371
Journal of Biological Inorganic Chemistry	19	2.928	4.966
Biochimica Et Biophysica Acta Proteins and Proteomics	18	2.773	9.689
Current Opinion on Chemical Biology	16	2.465	3.057

Table 3. The Top 10 corresponding authors in publications and citations.

Ranking	Corresponding author	Country	Total number of citations	Corresponding author	Country	Number of articles
1	Drennan, CL	USA	549	Broderick, JB	USA	24
2	Booker, SJ	USA	442	Zhang, Q	China	20
3	Frey, PA	USA	385	Booker, SJ	USA	20
4	Krebs, C	USA	315	Bandarian, V	USA	15
5	Sofia, HJ	USA	301	Drennan, CL	USA	14
6	Broderick, JB	USA	298	Berteau, O	France	12
7	Fontecave, M	France	258	Begley, TP	USA	12
8	Berteau, O	France	243	Lin, HN	USA	11
9	Begley, TP	USA	164	Fontecave, M	France	11
10	Roach, PL	England	154	Marsh, ENG	USA	10

publications and citations, and *Drennan CL*, a prestigious scientist, is even the most cited author. Furthermore, 7 of the top 10 corresponding authors are from the United States, suggesting that American researchers are decisive and very influential in the research of rSAM enzymes.

The cooperation network of authors can reflect the communication and cooperation between scholars at home and abroad. Social network analysis could reveal the cooperation relationships in the field. The size of the nodes in **Figure 3** represents the number of articles published by the authors, and the width of lines connecting the nodes implies the degree of cooperation between the authors. From the figure, it can be inferred that many scholars in this field cooperate closely when doing research. Most authors cooperate in a scattered way, and a few high-yield authors cooperate with others when doing most of their scientific research. For example, at the lower right corner of the picture, a research team is centered at *Qi Zhang* of Fudan University (*Ji Xinjian* and *Ding Wei* are outstanding Chinese newcomers in this field). Many sub-research teams have been cooperating with them, including Amara's team in Universite Grenoble Alpes (UGA) and another group led by *Deng Zi Xin* from Shanghai Jiao Tong University. Continually, the middle part of the left of the network is mainly composed of *Krebs*, *Carsten*, *Booker*, *Squire J*, *Lanz*, *Nicholas* from Pennsylvania State University and *Grove*, and *Tyler L Albert Einstein College of Medicine*. On the upper left side are *Bandarian*, *Vahe*, *Bruender*, *Nathan A* from the University of Utah, and *Drennan*, *Catherine L.* of the Massachusetts Institute of Technology (MIT). Cross-domain cooperation is more advantageous for researchers in integrating cross-disciplinary knowledge and establishing cross-domain communication, thereby speeding up the research process and enhancing the output of high-quality papers.

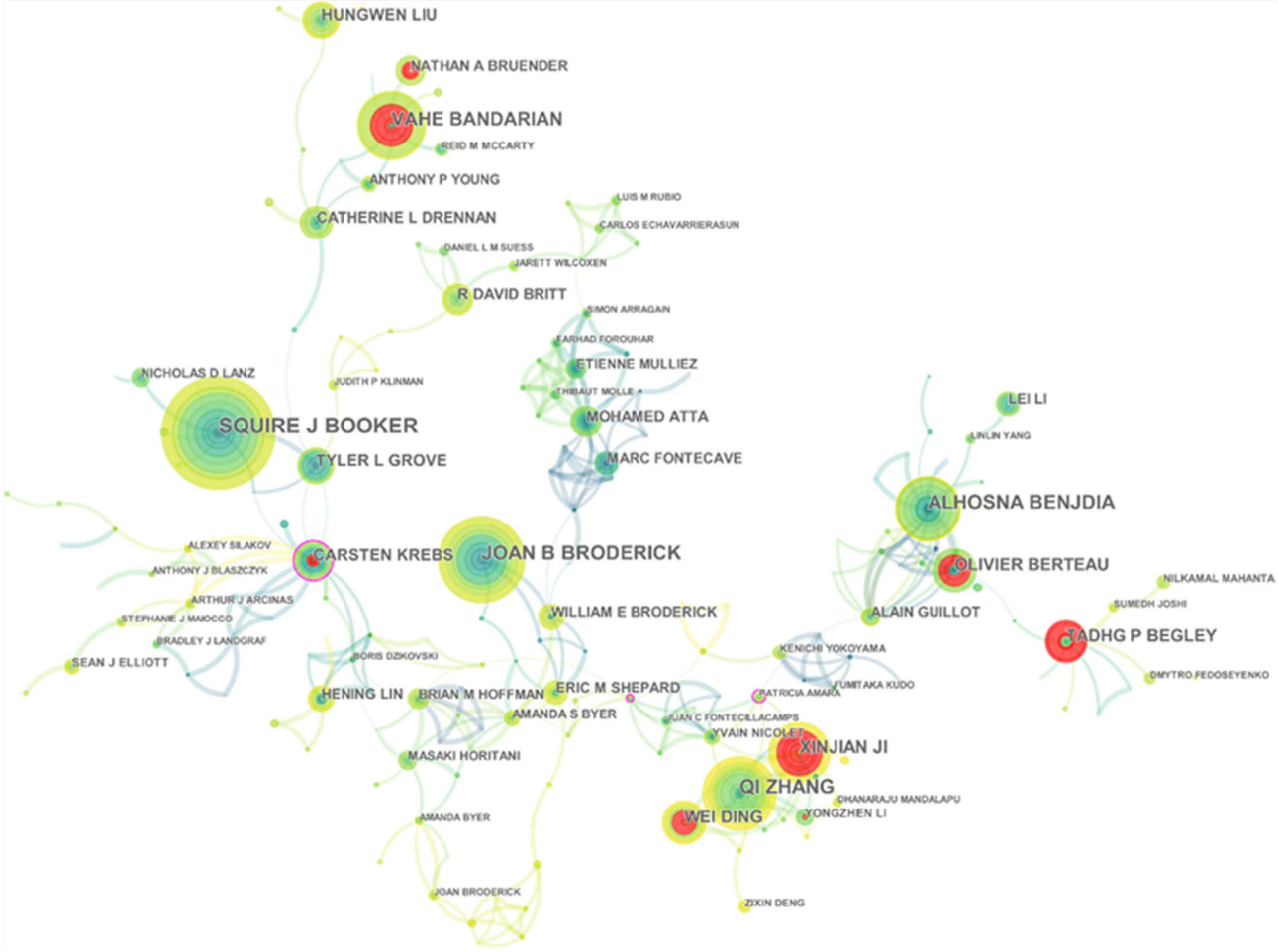

Figure 3. Co-authorship analysis map.

3.4. Regions and Institutions of Issuance

A network diagram of inter-institutional collaboration could be used to illustrate the cooperative relationships among agencies. In **Figure 4**, the size of nodes and tags in the network is proportional to the number of publications, and the width of lines connecting the nodes reflects the frequency of cooperation between agencies. Judging from the figure, publications related to rSAM enzymes are mainly authored by researchers from universities and scientific institutions. The Top 10 institutions in the number of publications are *Penn State Univ.*, *Montana State Univ.*, *MIT*, *Fudan Univ.*, *Univ. Calif. Irvine*, *Univ. Illinois*, *Univ. Texas Austin*, *Texas A&M Univ.*, *Northwestern Univ.*, and *Univ. Utah* (in the descending order of papers published), and 9 of them are American. Meanwhile, these organizations are also the most active international cooperator, suggesting that international cooperation is vital in the development of rSAM enzyme researches.

As for the centrality of publications, the Top 10 research institutions are *Univ. Grenoble Alpes*, *MIT*, *Univ. Michigan*, *INRA*, *Univ. Calif. Davis*, *Texas A&M Univ.*, *Penn State Univ.*, *Fudan Univ.*, *Agro Paris Tech.*, *Max Planck Inst. Med. Res.* (**Table 4**), and 5 of them are in the United States. However, this set of institutions

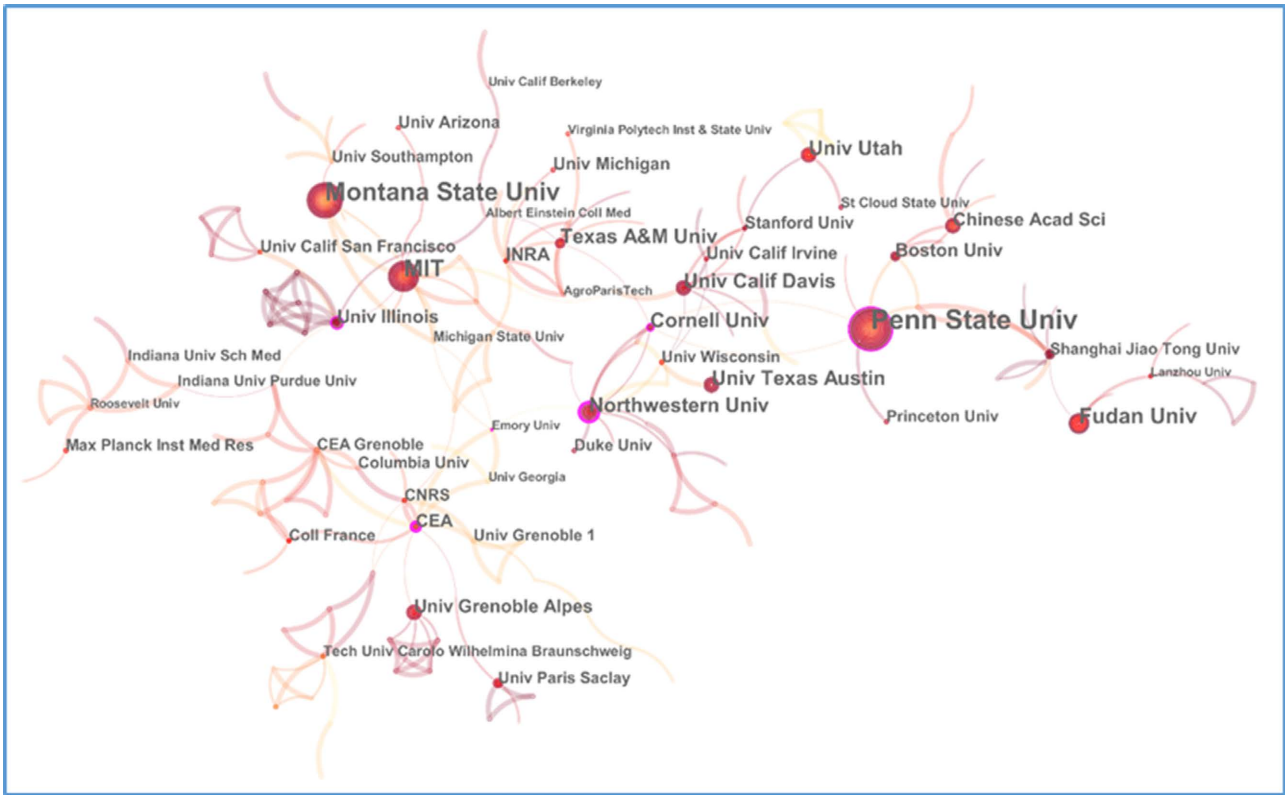

Figure 4. Network diagram of inter-institutional collaboration.

Table 4. The Top 10 institutes based on centrality and publication.

Research Institutions	Country	Centrality	Research Institutions	Country	Number of Articles
Univ Grenoble Alpes	France	0.26	Penn State Univ	USA	52
MIT	USA	0.25	Montana State Univ	USA	42
Univ Michigan	USA	0.2	MIT	USA	32
INRA	France	0.16	Fudan Univ	China	23
Univ Calif Davis	USA	0.15	Univ Calif Irvine	USA	23
Texas A&M Univ	France	0.15	Univ Illinois	USA	21
Penn State Univ	USA	0.13	Univ Texas Austin	USA	21
Fudan Univ	China	0.13	Texas A&M Univ	USA	20
AgroParisTech	France	0.13	Northwestern Univ	USA	19
Max Planck Inst Med Res	Germany	0.12	Univ Utah	USA	19

is not identical with that in terms of publication volumes, probably due to insufficient influence and unsatisfactory paper quality of some of these institutions in this field. Generally speaking, American institutions are dominant in publications and centrality.

Under the context of globalization, international cooperation in academic research has become very common in various fields. No matter what country the

research originates from, international cooperation could usually improve the quality of papers, thereby boosting the status and worldwide recognition of a certain institution.

The Top 10 countries of publication are *the United States*, *France*, *Germany*, *China*, *England*, *Japan*, *Switzerland*, *Sweden*, *Canada*, and *Spain* (Figure 5). Most of these countries are located in Europe and North America. Moreover, researchers from countries with a high number of published papers tend to cooperate with others to complete their research programs and contact more with their peers from other regions. US scholars work with French ones the most closely, while they have been increasingly cooperating with Chinese peers. Besides,

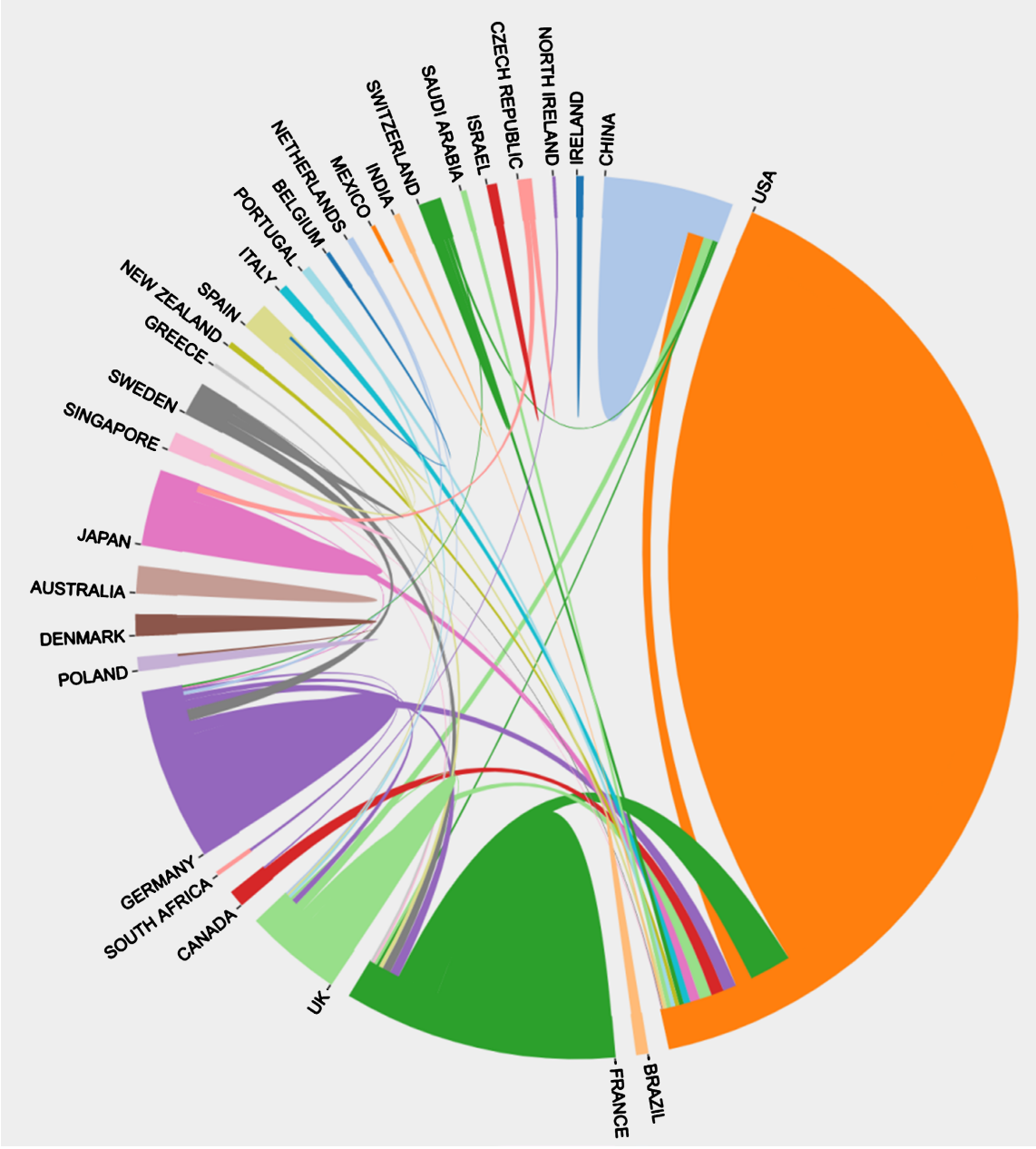

Figure 5. Cooperation networks of countries.

countries with more studies published, such as *the United States*, *France*, *Germany*, *England*, and *Spain*, also exhibit high centrality (Table 5). These countries are predominant in the cooperation network, and they cooperate closely with each other. Such phenomena could be derived from the early beginning of these countries in studying rSAM enzymes. Moreover, these countries attach great importance to and invest a lot in the research, assuring the high volumes of publications.

As for the chronological variations of the number of published articles by country, *the United States* is the first country to study rSAM enzymes and publish relevant research papers in 2001. Then, the efforts of US scholars were followed by copious academic output. In contrast, *China* started late, but it has produced many published articles recently, and the number of annual publications has grown rapidly from 4 in 2008 to 46 in 2019. Therefore, *China*'s efforts in this field may foster its influence in the future (Figure 6).

3.5. Research Hot Spots and Directions

472 keywords were obtained from 616 SCI papers by CiteSpace with g-index as the standard, and the keyword co-occurrence network acquired is shown as Figure 7, where the larger the node, the higher the term frequency. Besides, if two keywords co-occur, they would be connected by lines. The length and width of the lines represent how close the relationship and how strong the co-occurrence between two keywords are, respectively.

The most frequent keywords in the field are *Escherichia coli* (169), *S-adenosylmethionine* (141), *crystal structure* (133), *biosynthesis* (129), *radical SAM* (116), *mechanism* (89), *protein* (79), *enzyme* (67), *radical SAM enzyme* (65), *pyruvate formate lyase* (59), *identification* (57), and *biotin synthase* (55). Research with these keywords is very mature, and these researches generally show classic

Table 5. The Top 10 countries based on centrality and publication.

Central Top 10 countries		Top 10 countries in terms of number of articles sent	
Country	Centrality	Country	Number of articles
USA	0.85	USA	406
France	0.31	France	80
Germany	0.3	Germany	65
England	0.27	China	60
Spain	0.16	England	43
Japan	0.15	Japan	33
Denmark	0.15	Switzerland	12
Australia	0.08	Sweden	10
India	0.08	Canada	9
Peoples R China	0.04	Spain	9

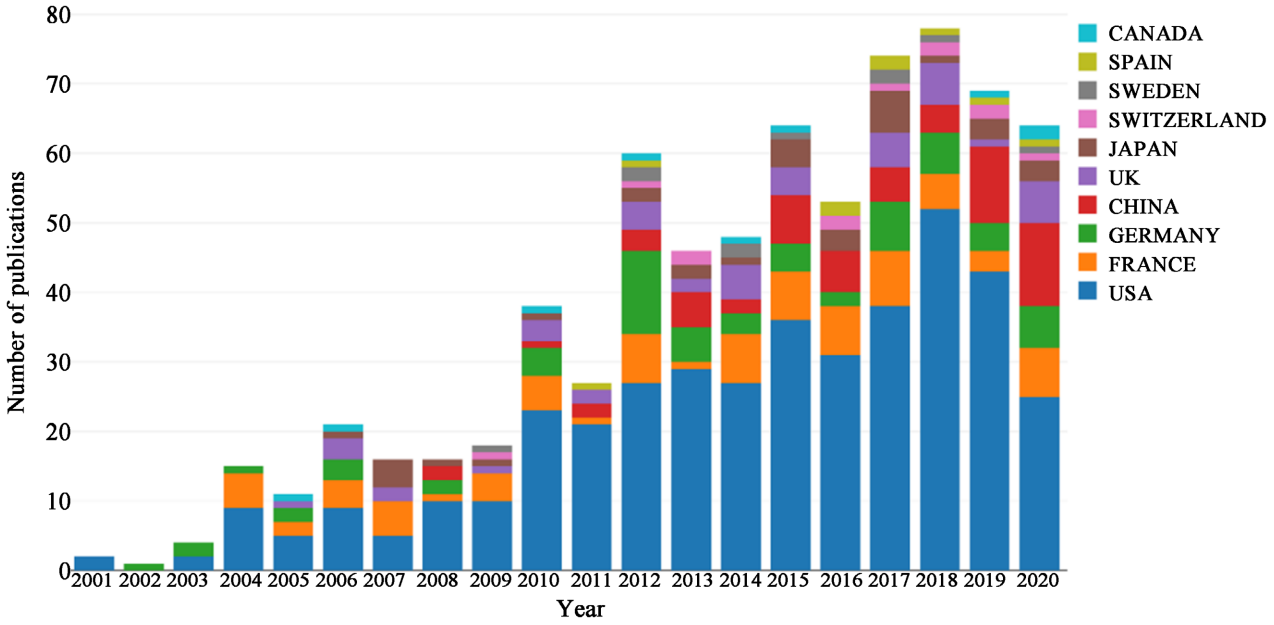

Figure 6. The annual publications of countries.

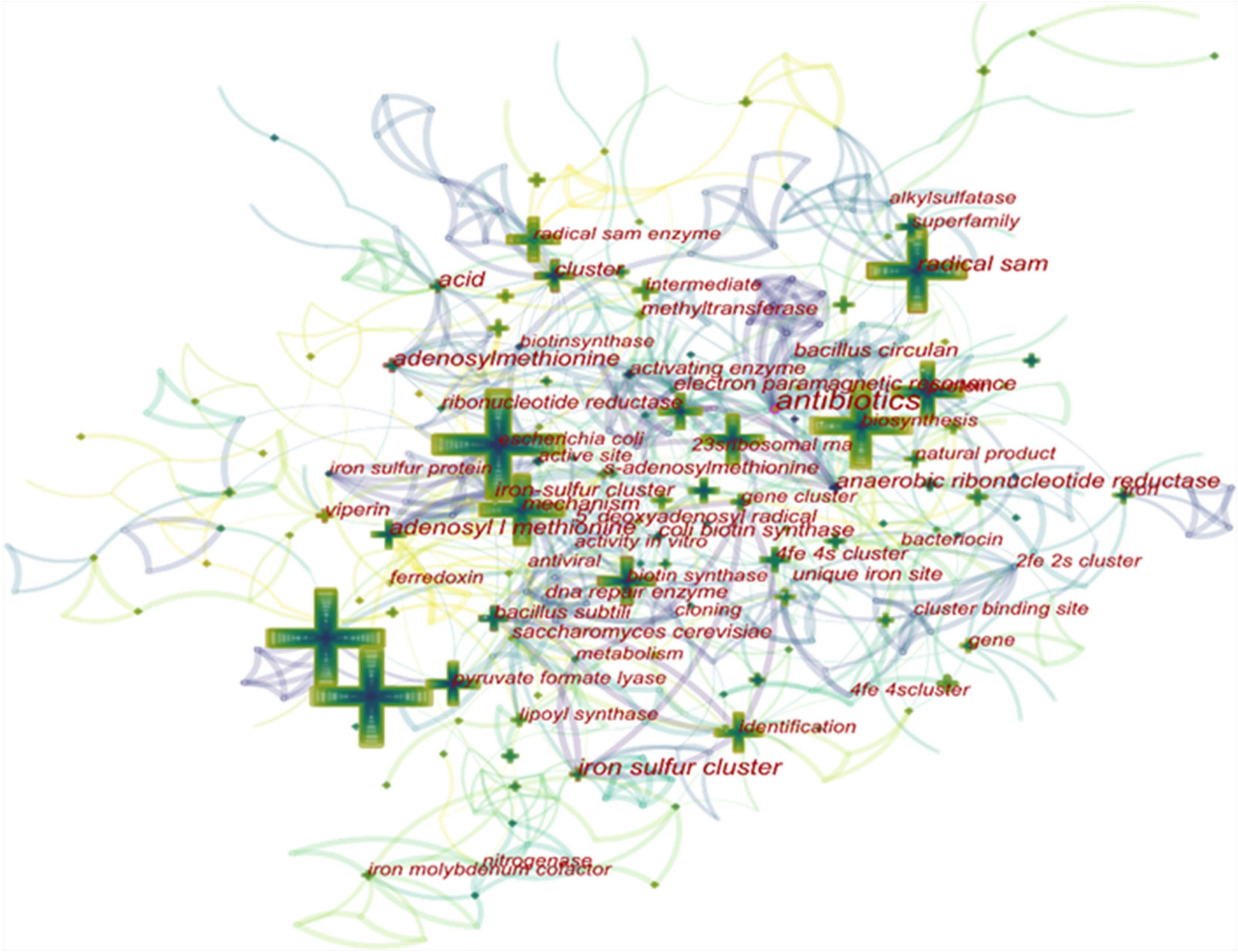

Figure 7. Keyword co-occurrence.

research topics, methods, and hot spots.

As for the research topics, all the keywords were categorized into 17 clusters (Figure 8). Particularly, 4 clusters contain more than 31 members, suggesting that they are the current research hot spots. Based on the centrality of each cluster, 4 representative clusters are tagged as *Antibiotics*, *Escherichia coli*, *Protein*, and *Biotin Synthase*.

To further understand the evolution of research topics, keywords were placed in their corresponding time zones of the first appearance to obtain the time distribution network (Figure 9). The first appearances of classic keywords are generally earlier, and these keywords are located on the left side in Figure 9. On the other hand, the emerging keywords appeared later, which are located on the right side.

1) The classic themes that appeared in 1999-2005 include Activating Enzyme, Gene Cluster, Iron Sulfur Cluster, Antibiotic, Adenosylmethionine, Anaerobic Ribonucleotide Reductase, etc.;

2) The main themes that appeared during 2006-2010 include Bacillus, Transmethylase, Bacteriocin, Amino-p-hydroxybenzoic Acid, etc.;

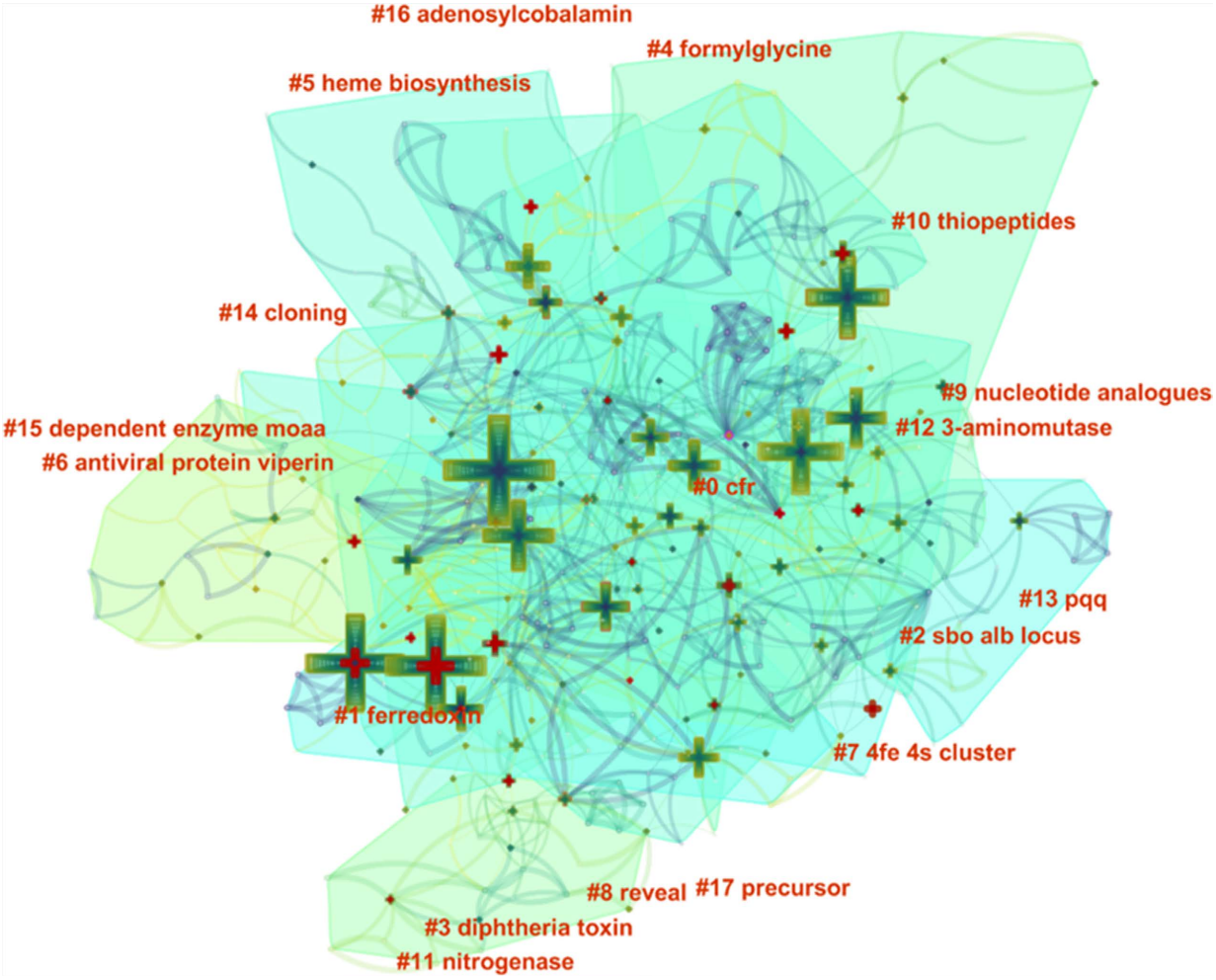

Figure 8. Keyword clusters.

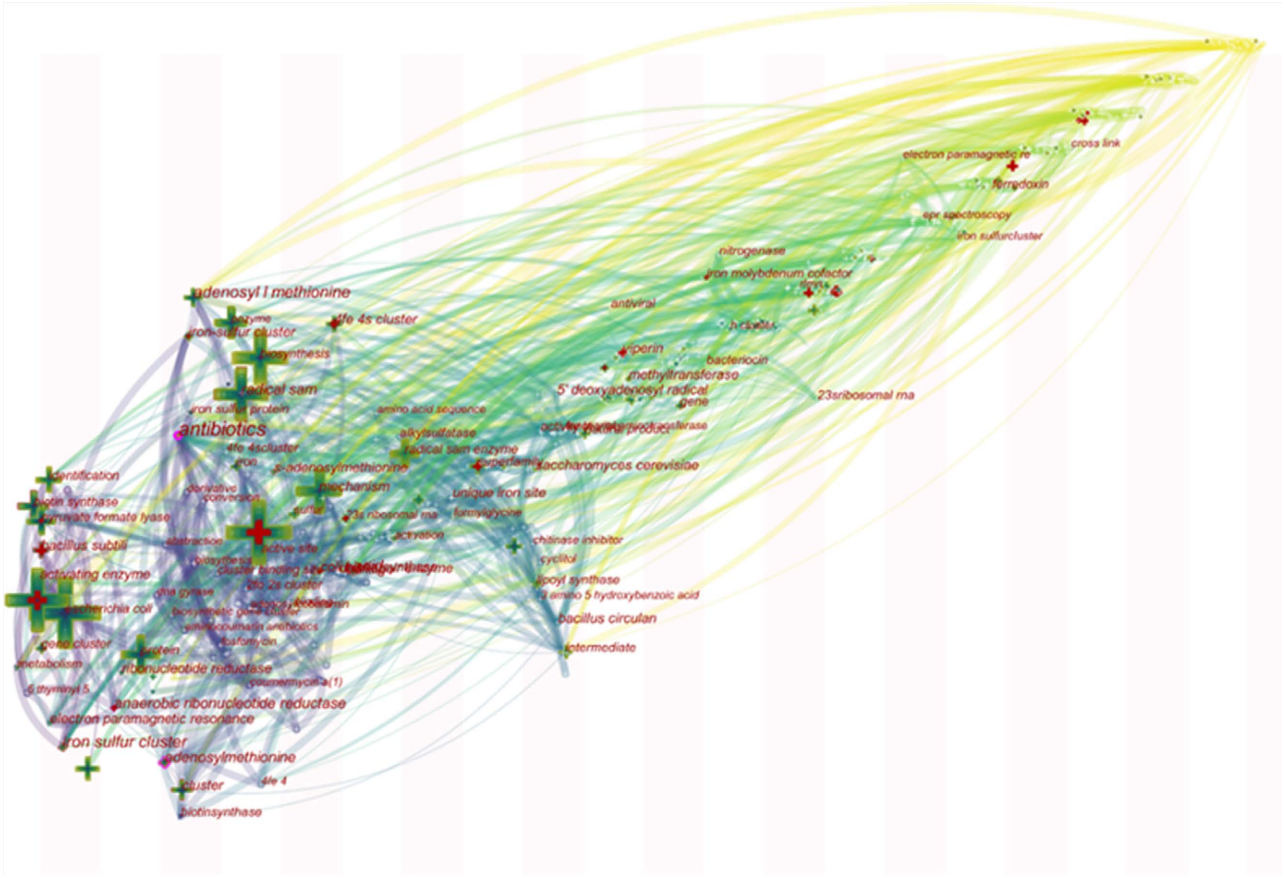

Figure 9. Keyword time zone distribution.

3) The emerging themes were Cross Link, Ferredoxin, Electron Paramagnetic Resonance Spectroscopy, Nitrogenase, Iron Molybdenum Cofactor, etc. between 2011 and 2020.

The subject frontier demonstrates the hot spots and development trends in the discipline, which helps researchers to understand the evolution of this discipline and diversify their research ideas. Kleinberg's burst detection analysis has unique advantages in detecting the subject frontier, and its results can be used to identify a sudden increase in research interest.

In this study, burst detection on keywords was performed on CiteSpace, and the results are shown in Figure 10, where the red line stands for the burst time of a certain topic. Topics with their red lines on the right may represent the frontiers and development directions. It can be inferred that the years 2001 to 2005 belong to the first stage of development, where topics like *anaerobic ribonucleotide reductase*, *pyruvate formate lyase*, *activating enzyme*, *cluster binding site*, and *s-adenosylmethionine* were predominant. The period of 2006-2016 belongs to the second stage, where keywords such as *coli biotin synthase*, *iron-sulfur cluster*, *bacillus subtili*, and 23*s ribosomal RNA* became the hottest topics. The last stage resides in the period of 2017-2018, where keywords like *methyl transfer*, *iron sulfur*, *peptide*, and *viperine* were suddenly highly addressed.

Top 23 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1999 - 2020
anaerobic ribonucleotide reductase	1999	4.9167	2001	2008	
pyruvate formate lyase	1999	5.7027	2001	2005	
activating enzyme	1999	3.8861	2001	2007	
crystal structure	1999	5.7522	2004	2010	
cluster binding site	1999	3.2262	2004	2009	
s adenosylmethionine	1999	4.0809	2005	2010	
coli biotin synthase	1999	3.257	2007	2009	
iron-sulfur cluster	1999	4.674	2008	2012	
superfamily	1999	6.2416	2008	2013	
sam	1999	4.1054	2010	2011	
bacillus subtili	1999	4.1325	2010	2014	
23s ribosomal rna	1999	3.3754	2011	2015	
4fe 4s cluster	1999	3.2607	2011	2013	
cofactor	1999	4.3107	2014	2016	
iron molybdenum cofactor	1999	3.6158	2014	2017	
sam enzyme	1999	6.0535	2015	2018	
s adenosylmethionine enzyme	1999	7.3473	2016	2018	
catalysis	1999	5.2118	2016	2020	
methyl transfer	1999	3.4107	2017	2018	
iron sulfur	1999	4.4922	2017	2020	
expression	1999	3.3634	2017	2020	
peptide	1999	3.4655	2018	2020	
viperin	1999	3.6845	2018	2020	

Figure 10. Keyword burst detection.

4. Conclusions and Outlook

This paper is focused on 616 published articles in the field of rSAM enzymes from 1999 to 2020 in the core database of the Web of Science. Bibliometric methods were employed to obtain the time series output, national partnerships, core authors, and keywords of the documents and to analyze the co-occurrence network. In this way, this work aims to reveal the development and research hot spots in this field, and we draw the conclusions as follows:

Firstly, the number of research papers is growing approximately linearly over the years. Particularly, it has witnessed a rapid development after 2010, and the number of average annual publications increased to about 50, suggesting extensive international application and great research significance of rSAM enzymes in recent years. Meanwhile, the number of representative keywords has also grown rapidly from 3 in 2003 to 16 in 2019, indicating that rSAM enzyme research has gradually developed into a multi-disciplinary direction.

Secondly, the research papers in this field belong to 44 different subject categories. *Journal of the American Chemical Society* exhibits both a high number of publications and high IF, while *Biochemistry* ranks second in terms of the number of publications. The two journals are the most predominant in this field.

Thirdly, papers from the United States are dominant in this field with outstanding volumes and centrality. Meanwhile, countries with a high number of publications, such as France, Germany, England, and Spain, also share relatively

high centrality. All these countries are significant in the research and development of this field. Besides, the Top 10 organizations in terms of issued documents are also the most active in international cooperation, especially those located in the United States.

Fourthly, although China is a late starter, publications from Chinese institutions have rocketed in recent years, suggesting that China's investment and efforts in this field bring it great potential for more results in the future.

Following that, various research hot spots in this field have emerged in different periods, and a general tendency is to integrate with more research fields. Consequently, more fresh research results are expected to be obtained in the future.

Acknowledgements

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Conflicts of Interest

The authors declare no conflicts of interest.

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