Trends in metabolomics research: a scientometric analysis (1992–2017)

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The aim of this study is to identify thematic trends, landmark articles, influential scientists and journals of metabolomics by exploring the scientific outputs in this field. This work was based on 66,721 bibliographic records retrieved from the Web of Science Core Collection database during 1992–2017. The results show that the USA was the leading country, and the Chinese Academy of Sciences had the largest number of publications. The Proceedings of the National Academy of Sciences of the United States of America was the most influential journal, meanwhile PLOS ONE had the most number of publications. Nicholson was identified as the most prominent scientist with the most number of articles and the highest co-citation counts. Metabolic syndromes and related diseases, disease biomarkers, novel pathways, as well as system biology association studies in metabolomics research, might be closely observed in the coming years.

Keywords: CiteSpace, metabolomics, scientometrics, visualization analysis.

THE omics, including independent or integrated genomics, transcriptomics, proteomics, and metabolomics, offer new approaches for understanding diverse biological systems through different levels of biomolecular organization and have continued to grow rapidly over the last several years[1]. Metabolomics has become a comprehensive qualitative and quantitative method to analyse all small molecule metabolites in the metabolome[2]. Metabolome is the collection of the complete set of all low molecular weight metabolites (<1500 Daltons) found in a biological system (cell, tissue, organ or biological fluid) exposed to a given set of conditions[3]. A major advantage of metabolome is that it can be seen as the final omics level of biological events, while genome, transcriptome and proteome represent the mediums in the flow of gene expression[4]. In addition, metabolomics has been exploited in various fields, such as medicine discovery, medical science and synthetic biology in human studies, as well as predictive modelling in different species systems[5].

Many names have been used in this new field, including metabolic profile, metabonomics and metabolomics. The metabolic profile terminology[6] was first introduced in the literature in 1971; a new method was applied to describe the different chromatographic patterns of biofluids. Metabonomics was formally defined by Nicholson[7] in 1999, and the term metabolomics was later coined by Fiehn[8] with different meaning and perspectives. Whatever, metabolomics is the term preferred by most scientists, so we use this term throughout this article.

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Today, more and more studies related to metabolomics are being published. However, attempts to systematically collect and analyse data of these publications such as authors, countries, institutions, journals and citations are few. Scientometrics, which can be processed by a useful visualization software named CiteSpace developed by Chen[9], has been utilized to make comprehensive evaluation of the developments in various research fields[10]. CiteSpace, one of the most popular techniques in scientometrics, is written using a JAVA program and is specifically applied to analyse the citations in the scientific literature. It has been exploited in different areas such as schizophrenia research[11], life cycle assessments[12] and so on.

We have used CiteSpace to depict metabolomics studies derived from the Web of Science Core Collection database from 1992 to 2017. The top countries, institutions, journals, authors, subject categories and keywords in metabolomics studies are presented in 'summary of metabolomics researches' section. Furthermore, individual visualization maps have been drawn to make intuitive observations, including landscape, influential scientists and journals of metabolomics which could help achieve a better and deeper understanding of the developments in metabolomics in the period of study.

Methods

Data collection

Bibliographic records were retrieved by a topic search on the Science Citation Index Expanded (SCI-Expanded) of the Thomson Reuters' Web of Science Core Collection on 16 July 2017. The search queries consist of six phrases about metabolomics: ‘metabolomic*’ OR ‘metabonomic*’ OR ‘metabolome*’ OR ‘metabolic profil*’ OR ‘metabolic footprint*’ OR ‘metabolite profil*’. The wildcard ‘*’ captures relevant variations of a word, such as metabolic profile and metabolic profiling. The document types were limited to ‘original research articles’ and ‘review papers’ for two reasons: (i) original research articles could represent the landscape of the field, and (ii) review papers are representative papers selected by domain experts[13]. Encompassing a time span from 1 January 1992 to 16 July 2017, the search retrieved a total of 66,721 records. Full records and cited references were downloaded in text format. After duplicates were removed (no duplicate records found), the data files were imported into the software package CiteSpace, version 5.0.R2.

Data analysis

We have used CiteSpace to perform co-citation analysis in references, identify the collaborations between co-cited authors/journals and generate networks of all the aforementioned items. The time interval of bibliographic records was set from 1992 to 2017, nearly 26 years. The length of a single time slice was specified as 2 years. The top 100 most cited references per time slice have been used to map the references co-citation network in a standard graph view.

Discussion and results

Summary of metabolomics studies

Figure 1 displays the trends of annual publications and citations from 1991 to 2017. As shown in Figure 1, the total number of metabolomics publications equals 66,721 papers. In 2016, there were 7962 publications in the field of metabolomics, accounting for 11.93% of the total set. During this period, the exponential growth pattern is shown (publications = 5E-105exp$^{0.1235\text{Year}}$, $R^2 = 0.9603$), which indicates the fast growth in metabolomics publications. Figure 1 also shows the trend of citations of papers during 1992–2017. Obviously, the overall trend of citations increased from 168 times in 1992 to 111,860 times in July 2017. The 66,721 publications were cited 1,544,293 times, including 29,074 times of self-citations by 16 July 2017. In addition, the average citations were close to 23, which was a relatively high level of citations, reflecting the numerous interests of scientists in metabolomics.

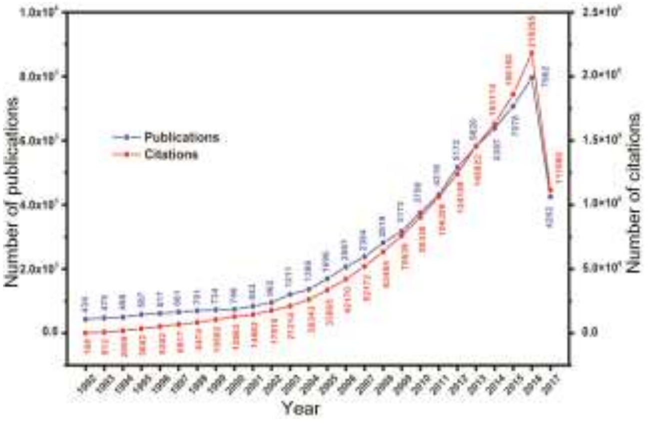

Figure 1. Trends of publications and citations on metabolomics during 1992–2017.

The top 15 countries were ranked by the number of publications in metabolomics per country (Table 1). During the study period, USA greatly exceeded all other countries, with 20,414 publications, followed by China, with 7761 publications and then Germany, with 5689 publications. Two North American countries, four Asian countries, seven European countries, one Oceania country and one South American country were ranked in the top 15 countries that delved in metabolomics. The extensive cooperations between countries/regions could be seen in Supplementary Figure 1. Compared to the analysis of countries, there were slight collaborations between the institutions that contributed to metabolomics (see Supplementary Figure 2). Moreover, Table 1 also exhibits the top 15 most productive institutions that contributed to the evolution of metabolomics. The top 15 institutions, with 8774 published articles, accounted for 13.15% of total publications. The Chinese Academy of Sciences won the first position, followed by Harvard University and Imperial College London.

The top 15 journals with the most number of scientific papers published on metabolomics are displayed in Table 2. Together, these journals published 9818 papers by July 2017, constituting 14.72% of total publications. Among the top 15 journals, the most noteworthy journal was *PLoS ONE*, with 2240 publications, followed by *Metabolomics* with 964 publications; *Analytical Chemistry* was third. Additionally, all impact factors displayed in Table 2 are from 2016. Of the journals that constitute the observed ranking, the *Proceedings of the National Academy of Sciences of the United States of America* (9.661) has the highest impact factor, followed by *Analytical Chemistry* (6.320), and *Journal of Clinical Endocrinology and Metabolism* (5.455). The other journals exhibit impact factors ranging from almost 2.6 to approximately 4.3.

Table 3 shows the top 15 authors of metabolomics according to the publication numbers. Nicholson was the most active author involved in this area, publishing 333 papers. Next in the ranking was Wang with 322 publications, followed by Holmes. The collaboration relationship of authors is demonstrated in Figure 2 *a*. It is worth noting that Nicholson and Holmes appeared closely with Lindon, because they did similar studies in Imperial

Table 1. The top 15 countries and institutions contributed to publications on metabolomics

Rank	Country	Count	Institution	Count
1	USA	20,414	Chinese Acad. Sci.	1257
2	China	7761	Harvard Univ.	884
3	Germany	5689	Univ. London Imperial Coll. Sci. Technol. Med.	803
4	England	5508	Univ. Calif. Davis	673
5	Italy	4224	INRA	591
6	Japan	3486	Univ Copenhagen	522
7	Canada	3450	Univ. Sao Paulo	511
8	France	3413	Leiden Univ.	475
9	Spain	3255	Shanghai Jiao Tong Univ.	464
10	Netherlands	2782	Univ. Washington	455
11	Australia	2191	Univ. Calif San Diego	453
12	Brazil	1938	Univ. Cambridge	430
13	South Korea	1882	CNR	421
14	India	1877	Univ. Alberta	419
15	Switzerland	1725	Tech. Univ. Munich	416

Table 2. The top 15 journals with the most number of publications on metabolomics

Rank	Journal	Count	Per cent (%)	IF2016
1	*PLOS ONE*	2240	3.357	2.806
2	*Metabolomics*	964	1.445	3.692
3	*Anal. Chem.*	800	1.199	6.320
4	*J. Proteome Res.*	788	1.181	4.268
5	*Sci. Rep.*	693	1.039	4.259
6	*J. Agric. Food Chem.*	633	0.949	3.154
7	*Drug Metab. Dispos.*	507	0.760	4.242
8	*J. Pharm. Biomed. Anal.*	479	0.718	3.255
9	*BMC Genomics*	439	0.658	3.729
10	*J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.*	420	0.629	2.603
11	*J. Clin. Endocr. Metab.*	390	0.585	5.455
12	*Anal. Bioanal. Chem.*	384	0.576	3.431
13	*J. Chromatogr. A*	379	0.568	3.981
14	*J. Biol. Chem.*	354	0.531	4.125
15	*P. Natl. Acad. Sci. USA*	348	0.522	9.661

College London. In addition, Nicholson, Holmes and Lindon were close collaborators of many highly cited articles in the field of metabolomics[14].

Depending on the content classification of the Web of Science database, the study of metabolomics was distributed across 178 specific subject categories. Only those with 2 or more bibliographic records were calculated. The top 15 subject categories were ranked based on the publications of metabolomics (see Supplementary Figure 3). Clearly, the field of metabolomics was interdisciplinary and showed a variety of applications in several fields of knowledge and research. The categories of subjects with the most records were pharmacology and pharmacy (7809 records, 11.7%), biochemistry and molecular biology (7168 records, 10.7%) and endocrinology and metabolism (6459 records, 9.7%), followed by other categories with less than 6000 publications.

Supplementary Figure 4 reveals keywords that occurred in the 66,721 papers of metabolomics. Among those keywords, the top 15 keywords with the highest frequency were particularly inserted in Table 4. The most common keywords were metabolomics (7476 records), insulin resistance (4987 records) and metabolic syndrome (4760 records). Herein, research hot spots in these years were extracted by frequently occurring keywords, with a reasonable description in CiteSpace. Based on the listed keywords, we have inferred that the hot spots of metabolomics research mainly consist of functional genomics, metabolic syndromes and related diseases. In biological systems, metabolomics is developing as a functional genomics methodology that contributes to a better understanding of the complicated molecular interactions[15]. Besides, at systems level, metabolomics can be regarded as the logical process from extensive analysis of RNA and proteins[16]. Moreover, there is a potential in the metabolomics, applied in metabolic syndromes and related diseases research, i.e. diabetes, cardiovascular disease, hyperlipidemia and obesity[5]. The major purpose for its use in metabolic syndromes is exploring disease status or biomarkers. Biomarkers, or, more precisely,

Table 3. The top 15 active authors and co-cited authors in the field of metabolomics

Rank	Author	Count	Co-cited author	Frequency	Centrality
1	J. K. Nicholson	333	J. K. Nicholson	3668	0.13
2	Y. Wang	322	O. Fiehn	2613	0.14
3	E. Holmes	292	D. S. Wishart	2265	0.05
4	Y. Zhang	255	J. C. Lindon	1700	0.02
5	A. R.Fernie	242	D. R. Matthews	1636	0.30
6	Y. Li	220	M. Kanehisa	1626	0.04
7	J. Li	217	W. B. Dunn	1623	0.03
8	J. Wang	203	E. Holmes	1443	0.03
9	Y. Liu	199	S. M. Grundy	1439	0.02
10	L. Zhang	191	Y. Benjamini	1438	0.02
11	J. Zhang	172	C. A. Smith	1359	0.01
12	L. Li	172	J. G. Xia	1238	0.01
13	K. Saito	170	M. M. Bradford	1176	0.01
14	L. Wang	165	W. T. Friedewald	1173	0.03
15	O. Fiehn	165	K. G. M. M. Alberti	1123	0.01

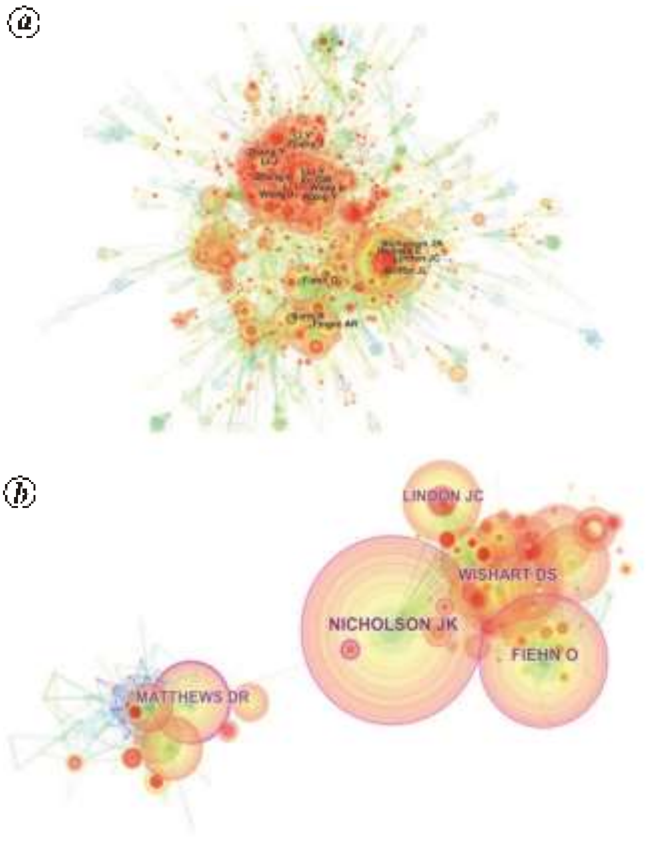

Figure 2. Collaborative network of authors (***a***) and co-cited authors (***b***) contributed to publications on metabolomics.

biological parameters, have been used as indicators of clinical responses (for example, therapeutic effects and toxicity)[17].

Mapping and analysis on references

Analyses of references were applied to analyse the accompanying references cited by a great deal of published papers. Furthermore, the analysis of references is critical to scientometrics, due to the importance of corresponding papers and authors[18]. In this section, the comprehensive research landscape of metabolomics is shown by the references' co-citation network (Figure 3). 1088 references were obtained based on the top 100 most cited references per time slice during 1992–2017. As shown in Figure 3, the node represents cited articles by metabolomics research. In addition, references with citation bursts were described with red rings. According to the interconnectivity of nodes, 282 clusters were generated in the total network. These clusters were labelled by index terms derived from citing articles.

Supplementary Table 1 reveals the top 5 largest clusters in the metabolomics domain. The silhouette scores are all over 0.7, suggesting that the quality of these clusters is relatively reliable. Mean year represents the average year of publication date of member references. The largest cluster (#0) is labelled as *novel pathway*, followed by the second largest cluster (#1), labelled as *mass spectrometry*, and the third largest cluster (#2), labelled as *selective serotonin reuptake inhibitor*.

The thematic trends can be analysed by papers receiving citation burst. A citation burst shows the possibility that the related scientific community has paid special attention to the highly cited publications[19]. In our study, 27 references were summarized with the strongest citation burst in the group of articles that started to burst at the same time (Table 5). It is worthy to note that review papers did not affect emerging trends and thematic patterns in the domain. Therefore, we did not consider review papers with citation bursts. Additionally, references about omics analysis approach and database in metabolite profiling were also excluded in our survey. Papers related to omics analysis approach and database were coloured in grey in the table. Based on the research characteristics, 27 high citation burst references could be divided into 4 different categories.

From 1992 to 1998, the significant background of metabolomics was founded. As shown in Table 5, the root of metabolomics can be traced back to the effects of antihypertensive drugs on glucose and lipid metabolism in patients with hypertension[20]. The episode of burst started in 1992 and ended in 1997. The strongest burst starting from 1998 was correlated with a 1996 paper by Considine *et al.*[21]. This paper depicted a correlation between serum leptin concentrations and the percentage of body fat in humans.

From 1999 to 2002, metabolomics had an initial development. Nicholson *et al.*[7] proposed a new concept named metabonomics, or rather a NMR-based metabonomics, which is defined as 'the quantitative measurement of the dynamic multiparametric metabolic response of biological systems to genetic modification or pathophysiological stimuli'[7]. The citation burst of the article lasted for 8 years from 2000 to 2007. The strongest burst from 2001 was due to the paper written by Fiehn, which achieved the highest burst strength of all references. This article described a new tool of plant functional genomics – metabolite profiling, which helped to find out that different metabolic profiles can be processed by a distinct genotype, implying that this approach has immense potential in confirming the phenotype directly[22].

From 2003 to 2006, metabolomics studies were in a rapid development stage. The citation burst starting in 2004 was led by the article of Soga *et al.*[23]. They proposed a new approach for metabolome analysis by capillary electrophoresis mass spectrometry (CE-MS)[23]. Hence, a number of methodologies had been developed for quantitative metabolome analysis, such as gas chromatography mass spectrometry (GC-MS), nuclear magnetic resonance spectroscopy (NMR), Fourier transform ion cyclotron resonance mass spectrometry (FT-ICRMS) and electrospray ionization mass spectrometry (ESI-MS). The strongest burst starting from 2005 was associated with a 2004 paper by Hirai *et al.*[24]. They presented the first report of research for gene-to-metabolite networks regulating primary and secondary metabolism in *Arabidopsis*, with integration of transcriptomics and metabolomics[24].

Benefiting from the advance in the technologies in the past 10 years, more and more applications of metabolomics have been developed in medical studies. The research frontier of medical metabolomics is to explore biomarkers related to various diseases, such as diabetes[25], prostate cancer[26] and cardiovascular disease[27]. Furthermore, in order to acquire a better understanding of systems biology, metabolomics as the final response part of gene expression, was integrated with upstream omics including genomics, transcriptomics and proteomics.

Mapping and analysis on authors

The collaboration between co-cited authors was illustrated in a network map (Figure 2 *b*). It can be seen that four authors named Nicholson, Wishart, Lindon and

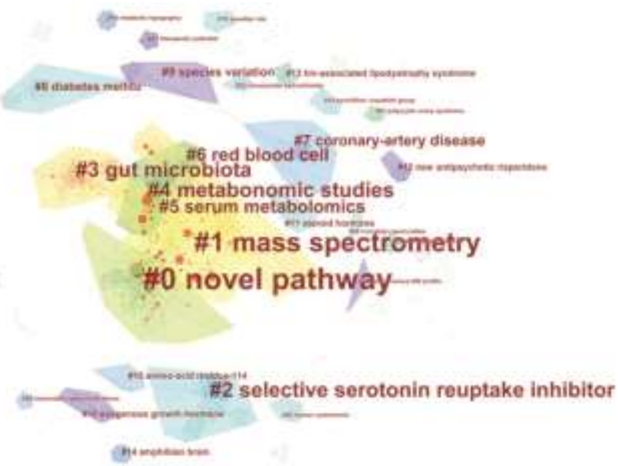

Figure 3. References co-citation network of publications on metabolomics.

Table 4. The top 15 keywords in the field of metabolomics

Rank	Keyword	Count
1	Metabolomics	7476
2	Insulin resistance	4987
3	Metabolic syndrome	4760
4	Metabolism	4616
5	Mass spectrometry	4490
6	Identification	4246
7	Gene expression	4112
8	Expression	3863
9	Obesity	3548
10	Metabolite	3299
11	Disease	3059
12	Oxidative stress	2696
13	Rat	2626
14	Cardiovascular disease	2502
15	Biomarker	2282

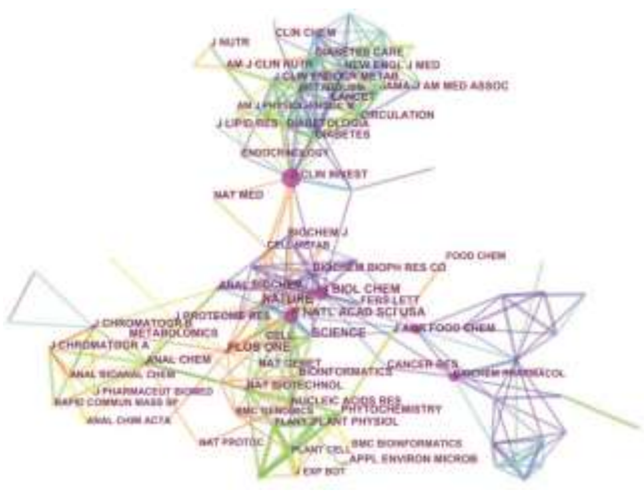

Figure 4. Collaborative network of co-cited journals in metabolomics.

Table 5. References with the strongest citation bursts every year

Reference	Begin	End	1992–2017
T. Pollare[20]	1992	1997	
P. Chomczynski[28]	1994	1995	
J. P. Despres[29]	1996	2003	
H. Shamoon[30]	1997	2001	
R. V. Considine[21]	1998	2003	
R. C. Turner[31]	1999	2005	
J. K. Nicholson[7]	2000	2007	
O. Fiehn[22]	2001	2008	
U. Roessner[32]	2002	2009	
J. T. Brindle[33]	2003	2010	
T. Soga[23]	2004	2011	
M. Y. Hirai[24]	2005	2011	
O. Cloarec[34]	2006	2013	
J. Kopka[35]	2007	2013	
T. A. Clayton[36]	2007	2012	
D. S. Wishart[37]	2008	2015	
A. Subramanian[38]	2008	2013	
C. A. Smith[39]	2009	2014	
E. Holmes[27]	2009	2014	
A. Sreekumar[26]	2010	2014	
D. S. Wishart[40]	2011	2014	
W. R. Wikoff[41]	2011	2017	
T. J. Wang[25]	2012	2017	
A. Mortazavi[42]	2013	2017	
D. S. Wishart[43]	2014	2017	
M. G. Grabherr[44]	2014	2017	
M. Kanehisa[45]	2015	2017	

Table 6. The top 15 co-cited journals in the field of metabolomics

Rank	Frequency	Centrality	Source	Year	Half-life	IF2016
1	23,728	0.46	*P. Natl. Acad. Sci. USA*	1992	21	9.661
2	20,273	0.58	*J. Biol. Chem.*	1992	20	4.125
3	19,240	0.15	*Nature*	1992	21	40.137
4	16,977	0.09	*Science*	1992	20	37.205
5	15,769	0.17	*PLOS ONE*	2010	5	2.806
6	12,254	0.08	*New. Engl. J. Med.*	1992	20	72.406
7	11,884	0.15	*Anal. Chem.*	2002	11	6.320
8	10,909	0.03	*Lancet*	1992	20	47.831
9	10,247	0.14	*Nucleic Acids Res.*	2002	12	10.162
10	9790	0.61	*J. Clin. Invest.*	1992	20	12.784
11	8934	0.07	*Diabetes*	1992	20	8.684
12	8823	0.04	*J. Clin. Endocr. Metab.*	1992	20	5.455
13	8783	0.05	*Circulation*	1992	20	19.309
14	8279	0.07	*J. Proteome Res.*	2008	6	4.268
15	8116	0.01	*Biochem. Bioph. Res. Co.*	1992	20	2.466

Fiehn have relatively tight connections. According to the top 15 co-cited authors (Table 3), Nicholson ranked first in the metabolomics field. His study has been widely cited by other scientists with the frequency of 3668. The second was Fiehn (2613 citations), followed by Wishart (2265 citations). On the other hand, Matthews led the first research echelon of metabolomics owing to the highest centrality of his work. The second-ranked author was Fiehn, followed by Nicholson. Compared with the top 15 prolific authors, three authors, Nicholson, Fiehn and Holmes are included in the list of the top 15 co-cited authors, suggesting that the above authors have made remarkable contribution to the employing and spreading of metabolomics research.

Supplementary Table 2 shows the top 15 authors with the strongest citation bursts. The top ranked author by bursts was Nicholson and followed by Lindon and then Holmes.

Mapping and analysis on journals

CiteSpace was used to detect the co-cited journals on metabolomics studies. Table 6 exhibits the top 15 co-cited journals in the field of metabolomics. All journals had a cited frequency of over 8000. As shown in Table 6, the top ranked item by citation count was *Proceedings of the National Academy of Sciences of the United States of America* with a citation count of 23,728. The second was *Journal of Biological Chemistry* (20,273 citations), followed by *Nature* (19,240 citations).

The network map of journals in the metabolomics area is shown in Figure 4. There was a tight connection among some journals such as *Proceedings of the National Academy of Sciences of the United States of America*, *Journal of Biological Chemistry* and *Nature*. Based on the categories of the journals, it is apparent that fields like multidisciplinary sciences, metabolic syndromes and related diseases, peripheral vascular disease, biochemistry and analytical chemistry were the major application fields of research on metabolomics.

Conclusion

The trend of development in metabolomics research was analysed in this paper. The fast development of metabolomics was confirmed by the exponential growth in metabolomics publications in the study period between 1991 and 2017. USA contributed the largest number of publications and the Chinese Academy of Sciences was the leading institution. *PLoS ONE* contributed to the most number of publications and *Proceedings of the National Academy of Sciences of the United States of America* was the most influential journal. Nicholson was the most prominent scholar in metabolomics area who published most papers with the highest co-citation counts. The largest co-citation cluster was in novel pathway. Functional genomics, metabolic syndromes and related diseases were the research hot spots in this field. Diseases biomarkers and systems biology might be the frontiers of metabolomics research in the coming years.

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