

Original Article

The progress and development trends on stress granules in the world and China during the past 35 years



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ABSTRACT

Stress granules (SGs) will be produced when the body is under external stimuli, and SGs play an important role in the pathogenesis of more and more diseases. The study on SGs has generally grown to a comprehensive subject in the past 35 years (from 1988 to 2022). The bibliometric analysis was used to comprehensively analyze the progress and development trend of SGs research. The literature output in the field of peritoneal dialysis showed a fluctuating growth in the past 35 years, and the last five years were the peak period of literature output. Journal of virology was the most widely published journal on SGs. And the most common research category was Biochemistry Molecular Biology. No matter in terms of the number of papers, citation frequency, H-index, or the distribution of journals and funding sources, the United States was far away from leading. With the enhancement of economic and scientific research strength, China has gradually carried out research on SGs. However, the citation frequency and H-index of Chinese papers were relatively low. Research cooperation between research institutions was relatively close, but domestic research institutions had less cooperation with relevant international institutions. The cooperation among authors was relatively scattered, and further exchanges and cooperation between scholars were needed for Chinese scholars. There are more and more reports about SGs, but there was still a big gap between China and the United States in the study of SGs.

1. Introduction

When cells are exposed to various environmental stresses, such as hypoxia, arsenite, and heat shock, the cells themselves could inhibit their transcription, apoptosis and repair stress-induced damage, which induces the accumulation of various RNA particles in the cytoplasm, known as stress granules (SGs) [1]. SGs do not exist under normal growth conditions but are produced in response to environmental stimuli [2].

The formation of SGs is a self-protection mechanism of cells, and SGs are composed of

mRNAs in the translation initiation stage, various translation initiation factors, RNA-binding proteins and many non-RNA-binding proteins. SGs are sites of mRNA sorting, where the complete composition of mRNA can be detected and then determined whether it is restarted translation, degraded, or stored [3].

Studies have shown that SGs affect biological responses mainly in two ways. First, the local high-concentration aggregation of some components disrupts the molecular equilibrium mechanism of the interaction, thereby enhancing the aggregation of SGs and protecting cells. This effect mainly inhibits

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apoptosis by reducing the production of reactive oxygen species [3] and enhances the innate immune response to enhance virus resistance [4]. The second way is that SGs restrict the functions of certain components within the SGs and avoid interactions between components within the particle [5, 6].

In the past more than thirty years, more and more investigations have been conducted on SGs. SGs have been implicated in viral infections [7], inflammatory diseases [8], cancer [9], and various neurological diseases, including spinal muscular atrophy [10], myotonic dystrophy [11], spinocerebellar ataxia [12], Fragile-X syndrome [13], and other pathological processes. Therefore, it is necessary to use professional methods to analyze the relevant literature on SGs research from a global perspective, discuss the development status and trends of SGs research, and provide a reference for the development of SGs [14-16].

Bibliometrics refers to the interdisciplinary science that quantitatively analyzes all knowledge carriers using mathematical and statistical methods. The hot areas of bibliometrics research are determined by the word frequency analysis method, the frontier fields and development trends of bibliometrics research are determined by detecting subject headings with significant changes in word frequency, and information visualization software is used to draw bibliometrics representatives, representative works, The knowledge map of hot fields and research fronts vividly displays the representatives, representative works, research hotspots and frontiers of bibliometrics, so that scholars can understand the research content of bibliometrics more intuitively [14-16]. Bibliometric analysis has been gradually applied in the field of medicine, such as cancer [17], infectious disease [18], digestive disease [19] and other disciplines.

VOS in VOSviewer means “visualization of similarities”. The earliest versions of the software were used only to present visualized results, but as versions of the software have been updated, the capabilities and data types for analysis have been greatly expanded. For

example, the analysis function of RIS document format is added, the visualization function of GML files is added, the file support of Pajek is extended, and the analysis of PubMed topics is supported, etc. At present, the software has almost all the common bibliometric analysis functions. It can use clustering techniques as well as other techniques to build 2d maps. After the maps are generated, three views can be viewed: Network Visualization, Overlay visualization, and Density visualization [20].

VOSviewer can choose from two types of import before importing data: one is text corpus, that is, related database exported files for analyzing co-occurrence of words in titles and abstracts; One is data processed by other software, i.e. RIS, EndNote and RefWorks files, which are used to analyze co-citation and coupling relationships of literatures, journals, authors, institutions, etc. The advantage of VOSviewer is that it can process a large amount of data, and the co-occurrence network works normally when there are more nodes. The graph is clear and readable [21].

There is no relevant Bibliometric analysis of SGs research. Therefore, this paper analyzes the development status and frontier hotspots of SGs by systematically searching literatures related to SGs research in the Web of Science (WOS) database in the past 35 years (from 1988 to 2022). Based on this study, it would provide reference and reference for researchers, clinicians and patients engaged in SGs.

2. Methods

2.1. Data source

The search scope is determined to be an internationally recognized database, and the search period is until December 31, 2022. The research literature was searched electronically from 1988 to 2022 in the core collection of the WOS database and the PubMed database. This study is retrospective and does not involve ethical issues. The Impact factors (IF) in the article refer to the latest impact factors of the latest SCI journals in 2022 published on the official website of Clarivate Analytics.

2.2. Retrieval strategy

For searches of the WOS database, the retrieval TOPIC was "Stress Granule" or "Stress Granules". The retrieval Article Type was Article or Review or Meeting Abstract or Editorial Material or Proceedings Paper or Letter. The retrieval Languages is English. The retrieval Databases were SCI-Expanded, CPCI-S, BKCI-S, ESCI, and SSCI. The retrieval TIMESpan is 1988-2022.

For the retrieval of the PubMed database, the set retrieval strategy was "Stress Granule" [MeSH Terms] or "Stress Granule" [All Fields] OR (Stress Granules [MeSH Terms] or "Stress Granules" [All Fields]). The retrieval article type was Books and Documents or Clinical Trial or Meta-Analysis or Randomized Controlled Trial or Review or Systematic Review.

2.3. Bibliometric analysis

In this study, the visualization tool VOSviewer 1.6.16 was used to extract the publication year, journal, country, author, and institution of the retrieved literature, generate a map of author cooperation and institutional cooperation, and analyze the hotspots of high-frequency keywords. VOSviewer is a bibliometric analysis software developed by Nees J. Van Eck and Ludowailman of Leiden University in the Netherlands in 2009 to draw a map of scientific knowledge. Research directions and hotspots [22]. Based on the coupling and co-citation principle of literature, VOS-viewer interprets the visual map based on the size, density, color, and distance between nodes. The size of a node indicates the number or frequency of publications. The larger the number, the greater the number of occurrences. The distance between nodes indicates the closeness and sparsity of the relationship, the shorter the line, the closer the relationship. In the cluster analysis of keywords, each color represents a cluster.

3. Results

3.1. Publications on SGs in worldwide and China

As shown in Figure 1, for the PubMed and WOS databases a total of 2,482 and 3,339

literature on SGs were respectively retrieved from 1988 to 2022 based on the retrieval strategy mentioned above. Due to the different publications included in the two databases, the search results were different.

The results showed that the number of published SGs papers recorded in the two databases showed a trend of increasing year by year ([Supplementary file](#) (Figure 1 and 2)). This indicated that in the past 35 years, scholars' research interest in SGs has increased year by year. At the same time, scholars from 77 countries have participated in related research on SGs. According to the WOS database records, American researchers published the most papers (1410 papers, 42.228%), followed by China (368 papers, 11.021%), Germany (356 papers, 10.662%), Canada (315 papers, 9.434%), and Japan (265 articles, 7.937%) ([Supplementary file](#) (Figure 3)). It is worth noting that the United States and China have relatively more published papers, and the growth rate of concurrent publications is the highest among the top 5 countries with the largest number of publications.

According to the results of the VOSViewer software analysis, we found that the cooperative research on SGs among countries was relatively close. Only 46 countries had published more than 5 papers related to SGs. Among them, the United States, India, Ireland, Northern Ireland and Israel had a relatively close relationship in research SGs. Argentina, Brazil, Canada, Chile, Czech Republic, France, Mexico, Portugal and Scotland were also closely related to collaborative research on SGs. South Korea and China were also closely related.

Germany often collaborates with Denmark, Greece, Italy, Spain and Switzerland on SGs. Therefore, it could be seen that cross-border and cross-regional exchanges were very common in the field of SGs research. Combining the growth curve and the cooperative network map shows that the United States was still a world leader in the field of research on SGs. The research on SGs in China was also increasing, seeking more international cooperation, and the research contribution to SGs was also increasing.

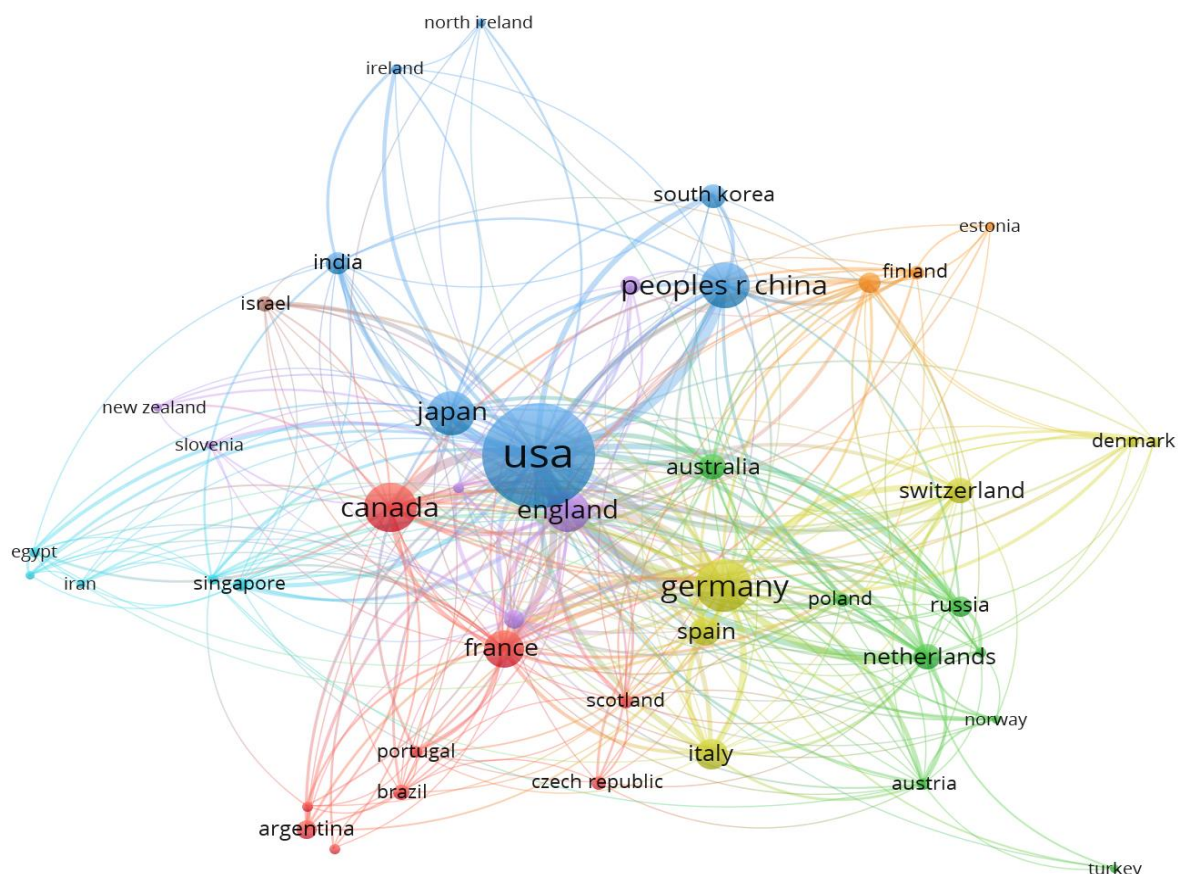


Fig. 1. A network map showing the collaborative relationships between various countries in the field of mitophagy research (Mitophagy-related article overview).

3.2. H-Index and citation analysis

As shown in [Supplementary file](#) (Figure 3 and 7), the research institutions that analyzed the published literature found that the Howard Hughes Medical Institute, Harvard University, the University of California System, Centre National De La Recherche Scientifique (CNRS), and Udice French Research Universities were among the top five institutions in the world for the number of SGs published. Among them, Howard Hughes Medical Institute published SGs papers with the highest H-index (81) and the most total citations (30,153) and was a world leader in the field of SGs research.

The paper "Biomolecular condensates: organizers of cellular biochemistry" written by Banani *et al.* [23] and published in 2017 had a total of 2076 citations. As shown in Figure 2C-2D, the Chinese Academy of Sciences, University of Chinese Academy of Sciences Cas, Shanghai Institutes for Biological Sciences Cas, Tsinghua University, and Central South University were the top five Chinese

research institutions that studied SGs and published related papers. The Chinese Academy of Sciences had published a total of 68 papers, with the highest H-index (23) and the most total citations (1,757), and was a leading institution in the field of SGs research. The paper "Nucleolar stress and impaired stress granule formation contribute to C9orf72 RAN translation-induced cytotoxicity" published by Tao *et al.* [24] in 2015 received 163 total citations. Although the growth rate of the number of SGs papers published by Chinese research institutions was relatively high, there was still a considerable gap between these institutions and the top institutions in other countries in the world.

Through the analysis of VOSViewer software, it was found that there were about 309 institutions that had published more than 5 papers related to SGs and about 53 institutions that had published more than 20 papers related to SGs. As shown in Figure 2F and [Supplementary file](#) (Figure 8), it could be

seen from the co-occurrence chart that Brigham and Women's Hospital often cooperate with some other American university institutions to study SGs, and the closest cooperation was Harvard University in the United States. The Brigham and Women's Hospital had close cooperation with some Chinese research institutions. The most closely cooperated were the Chinese Academy of Sciences and the University of the Chinese

Academy of Sciences. As could be seen from the coverage visualization chart, research institutions from the United States were the leaders in the field of SGs research. China cooperation with other countries on SGs research, but there was still a big gap between the number of cooperation and the amount of cooperation between the United States and other countries.

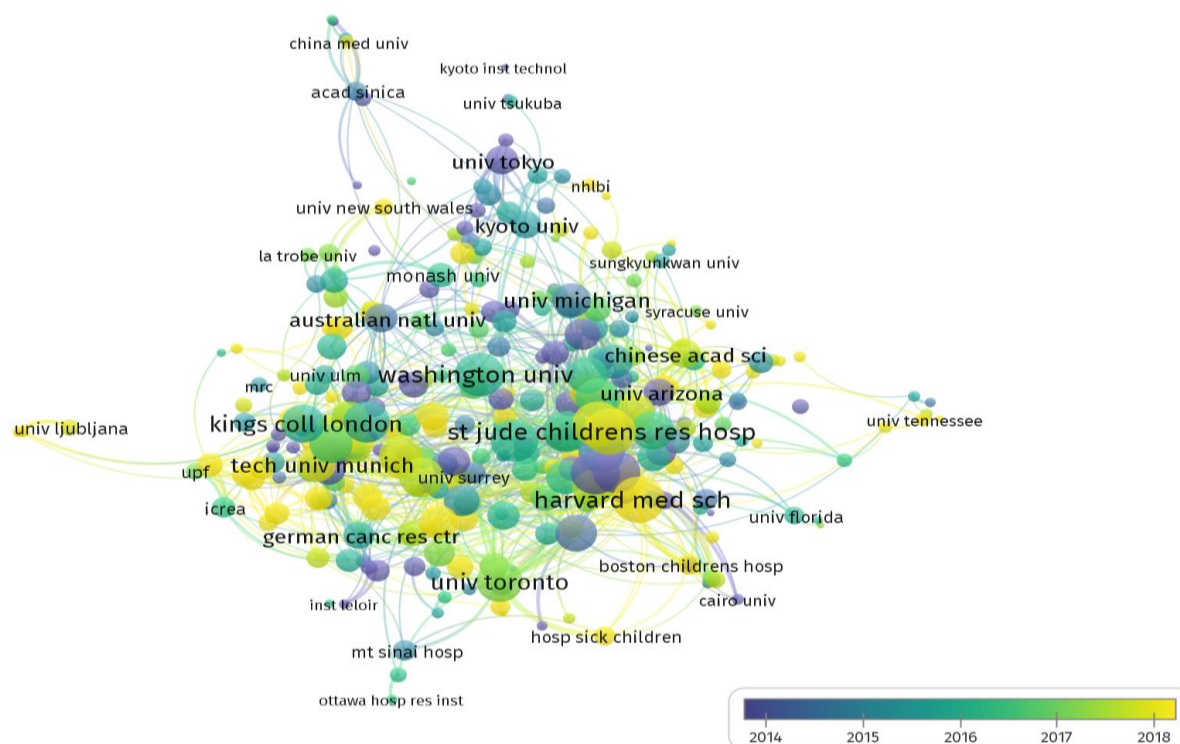


Fig. 2. A density map showing the collaborative relationships between various institutions in the field of SGs research (Citations of related papers and H-index analysis).

3.3. Research direction in SGs and distribution of journals

As shown in [Supplementary file](#) (Figure 9 and 10), scholars around the world published the most papers on SGs in the Journal of Virology (120 Papers, 3.593%), Followed by the Journal of Biological Chemistry (111 Papers, 3.324%) And Plos One (95 Papers, 2.845%). The Scholars in China Published the Most Papers on SGs in the Journal of Virology (10 Papers, 2.717%), Followed By Nature Communications (9 Papers, 2.446%) And Frontiers in Immunology (8 Papers, 2.174%).

According to the journal impact factor ranking displayed by the Journal Citation Reports 2022, most of the top ten journals published by SGs were not the world's top

journals. The impact factor ranking of journals published by Chinese scholars had a similar situation.

As shown in [Supplementary file](#) (Figure 10 and 12), the research fields related to SGs by scholars around the world mainly include Biochemistry Molecular Biology, Cell Biology, Neurosciences, Multidisciplinary Sciences, Virology, Genetics Heredity, Biophysics, Biology, Microbiology and Oncology. China's research fields related to SGs mainly include Biochemistry Molecular Biology, Cell Biology, Multidisciplinary Sciences, Neurosciences, Virology, Immunology, Genetics Heredity, Oncology, Biophysics, and Microbiology.

3.4. Top 10 most cited SGs articles published by scholars worldwide and in China

As shown in Tables 1 and 2, the most cited SG-related papers published by scholars around the world and in China were through the database built in the WOS database. The 2017 paper "Biomolecular condensates: organizers of cellular biochemistry" by Banani *et al.* [23] had been cited 2076 times over the past 35 years. It was by far the most cited article published on SGs internationally. This article was a review that systematically introduced biomolecular polymers exemplified by SGs, which were aggregated in eukaryotic cells in micron-scale regions that lack membrane structures, but which included proteins and nucleic acids in many biomolecules. This article described in detail the various biological processes involved in SGs including RNA metabolism, ribosome biogenesis, DNA damage response and signal transduction. It was worth noting that the key mechanism of SGs formation was also mediated by the liquid-liquid phase separation driven by multivalent macromolecular interactions, and the physical properties, biochemical functions and other processes of SGs were also based on this principle.

The research of Chinese institutions in the field of SGs started relatively late, and the number of published articles was therefore relatively small. The paper "Cell-free Formation of RNA Granules: Low Complexity Sequence Domains Form Dynamic Fibers within Hydrogels" was published in CELL by Kato *et al.* [25] was the most cited paper.

It was worth noting that the first author and corresponding author of this paper were not scholars from Chinese research institutions, but only Chinese scholars from Chinese institutions participated. The main author of the paper was the University of Texas System. This article investigated the polymerization conditions of SGs, where hundreds of RNA-binding proteins were precipitated in cells when they were exposed to external stimuli.

The components of these proteins were extremely similar to SGs, and certain

sequences in these proteins were essential for the aggregation of SGs caused by external chemical stimulation. In the absence of chemical stimulation, the domains of these proteins were in a hydrogel state. By observing the microstructure of these proteins, it was found that the proteins in the hydrogel state were composed of homogeneously aggregated amyloid fibrils. Unlike pathogenic fibers, the state of the protein sequence aggregates here was dynamic.

3.5. Comparison of co-occurring keywords in the field of SGs

By using the function of co-occurring keywords in VOSViewer software, the changes and connections of keywords in SG-related research in the past 35 years were analyzed. The keyword threshold in the VOSViewer software was set to 50 times, that is, a certain keyword appears in 50 or more published articles, and this keyword would be identified and included in this part of the study. As shown in Figure 3, there were 107 keywords in all articles about SGs in the world that met the above threshold settings. The top four keywords in terms of occurrence were "stress granules", "messenger-RNA", "translation", and "amyotrophic-lateral-sclerosis". As shown in [Supplementary file](#) (Figure 13), in the literature on SGs published by Chinese scholars, only three keywords met the above threshold settings. Ranked by the number of occurrences, they were "messenger-RNA", "stress granules", and "phosphorylation", respectively. In order to further refine the keywords in the field of SGs, most of the research on SGs had been published in the past five years. Therefore, we divided the research on SGs into two phases: the recent five-year research (2017-2022) and the early (1988-2016) research. As shown in [Supplementary file](#) (Figure 14 and 15), research on SGs had slightly changed the types of keywords, and the number of keywords had also increased. In the early study, 44 keywords met the above thresholds, and the top four keywords were "stress granules", "messenger-RNA", "p-bodies", and "translation" in order. In the past six years, 20 keywords met the above thresholds, and the top four keywords were "stress granules", "messenger-RNA", "amyotrophic-lateral-

sclerosis" and "phase-separation" in order. Therefore, there had been fewer high-frequency keywords in the past five years,

which meant that the research field on SGs has become more extensive than before.

Table 1. The top 10 most cited articles on Stress Granules research in the world

Title	Authors	Total citations	Average per year	Source title	Publication date
Biomolecular condensates: organizers of cellular biochemistry	Banani, Salman F, et al.	2076	296.57	Nature reviews molecular cell biology	MAY 2017
N-6-methyladenosine Modulates Messenger RNA Translation Efficiency	Wang, Xiao, et al.	1634	181.56	Cell	4 JUN 2015
Liquid phase condensation in cell physiology and disease	Shin, Yongdae, et al.	1541	220.14	Science	22 SEP 2017
Liquid-Liquid Phase Separation in Biology	Hyman, Anthony A, et al.	1400	140	Annual review of cell and developmental biology, vol 30	2014
A Liquid-to-Solid Phase Transition of the ALS Protein FUS Accelerated by Disease Mutation	Patel, Avinash, et al.	1346	151.89	Cell	27 AUG 2015
Phase Separation by Low Complexity Domains Promotes Stress Granule Assembly and Drives Pathological Fibrillization	Molliex, Amandine, et al.	1337	148.56	Cell	24 SEP 2015
Cell-free Formation of RNA Granules: Low Complexity Sequence Domains Form Dynamic Fibers within Hydrogels	Kato, Masato, et al.	1260	105	Cell	11 MAY 2012
A census of human RNA-binding proteins	Gerstberger, S, et al.	1046	104.6	Nature reviews genetics	DEC 2014
Stress granules and processing bodies are dynamically linked sites of mRNP remodeling	Kedersha, N, et al.	1016	53.47	Journal of cell biology	20 JUN 2005
Converging Mechanisms in ALS and FTD: Disrupted RNA and Protein Homeostasis	Ling, Shuo-Chien, et al.	1013	92.09	Neuron	7 AUG 2013

Table 2. The top 10 most cited articles on Stress Granules research in China

Title	Authors	Total citations	Average per year	Source title	Publication date
Cell-free Formation of RNA Granules: Low Complexity Sequence Domains Form Dynamic Fibers within Hydrogels	Kato, Masato, et al.	1260	105	CELL	11 MAY 2012
Nuclear-Import Receptors Reverse Aberrant Phase Transitions of RNA-Binding Proteins with Prion-like Domains	Guo, Lin, et al.	247	41.17	CELL	19 APR 2018
The role of FUS gene variants in neurodegenerative diseases	Deng, Hao, et al.	183	18.3	NATURE REVIEWS NEUROLOGY	JUN 2014
The LC3-conjugation machinery specifies the loading of RNA-binding proteins into extracellular vesicles	Leidal, Andrew M, et al.	176	44	NATURE CELL BIOLOGY	FEB 2020
Nucleolar stress and impaired stress granule formation contribute to C9orf72 RAN translation-induced cytotoxicity	Tao, Zhouteng, et al.	163	18.11	HUMAN MOLECULAR GENETICS	1 MAY 2015
Long non-coding RNA gadd7 interacts with TDP-43 and regulates Cdk6 mRNA decay	Liu, Xuefeng, et al.	143	11.92	EMBO JOURNAL	28 NOV 2012
The SARS-CoV-2 nucleocapsid phosphoprotein forms mutually exclusive condensates with RNA and the membrane-associated M protein	Lu, S, et al.	126	42	NATURE COMMUNICATIONS	21 Jan 2021
PARYlation regulates stress granule dynamics, phase separation, and neurotoxicity of disease-related RNA-binding proteins	Duan, YJ, et al.	111	22.2	CELL RESEARCH	Mar 2019
mTOR Regulates Phase Separation of PGL Granules to Modulate Their Autophagic Degradation	Zhang, GM, et al.	111	18.5	CELL	6 Sep 2018
Intrinsically Disordered Proteome of Human Membrane-Less Organelles	Darling, April L, et al.	89	17.8	PROTEOMICS	MAR 2018

focus on the practicality and benefit of human health.

Based on these studies and results, keywords on SGs have also changed. For example, "autophagy", which got the 2016 Nobel Prize in Physiology and Medicine, is a new keyword in this field. Autophagy, a lysosome-mediated degradation system, is an evolutionarily conserved pathway for recycling cellular contents and removing aggregated proteins, damaged organelles, and invading pathogens (such as viruses and bacteria), to maintain normal cellular function and homeostasis[26]. Some scholars have found that the autophagy-inducing kinase ULK1/ULK2 agonist LYN-1604 can complete the depolymerization of stress granules by phosphorylating VCP/p97 to alleviate multisystem proteinopathy (MSP) [27].

The autophagy-related gene 5 (ATG5) can alleviate the stimulation of chronic oxidative stress on senescent cells by promoting the formation of SGs, which provides ideas for the treatment of age-related neurodegenerative diseases [28]. Moreover, the autophagy protein ATG16L1 is required for anti-standbys virus through inducing eIF2 α phosphorylation and SGs formation subsequently[29]. The complex of C9ORF72 and p62 could use arginine methylation to eliminate SGs by autophagy in the process of amyotrophic lateral sclerosis (ALS) [30].

Recently, histone deacetylase 6 (HDAC6) has received more and more mention in the field of SGs. As an important component of SGs, HDAC6 is involved in the formation of SGs [31]. HDAC6 interacts with the stress granule nucleator G3BP1 (Ras-GAP (GTPase-activating protein) SH3 (Src homology 3) domain-binding protein-1) and decreases SGs formation [31]. HDAC6/G3BP1 complex is dependent on the catalytic domain of HDAC6 and the acidic-rich domain of G3BP1[31]. Stress can lead to the assembly of SGs by inducing dephosphorylation of G3BP1 at phosphoserine 149 [32]. Notably, HDAC6 has a higher binding affinity for dephosphorylated G3BP1 compared with phosphorylated G3BP1[31]. In addition to direct binding, HDAC6 also regulates G3BP1 by deacetylation at Lysine-376 to prevent the disassembly of

SGs [33]. Meanwhile, HDAC6 could regulate DDX3X through deacetylation, promoting phase separation and dynamics of the SGs, and allowing maturation of the SGs [34]. In the coxsackievirus A16 infected cells, HDAC6 was recognized by p62/sequestosome 1 and mediates the repression of the type I interferon response, causing the degradation of SGs through autophagy [35].

Using keyword co-occurrence analysis, we found that many studies have focused on "amyotrophic-lateral-sclerosis" over the years. Interestingly, SGs have the most research published in the virus journal "Journal of Virology". This means that the research of SGs in diseases is mainly focused on neurodegenerative diseases, and the research is relatively mature[36]. Although research on SGs related to viruses has continued for many years, most studies have focused on basic research. Moreover, the wide variety of viruses limits the aggregation of SGs and viral infectious disease research. At the same time, in recent years, the focus of research has also shifted to cancer[37, 38], aging-associated diseases[39], and bacterial infection[40].

With the rapid growth of China's economic strength and the increase of the Chinese government's investment in basic scientific research, scholars from Chinese research institutions have made great progress in the research of SG-related fields, especially in the past five years. From the bibliometric research in this paper, it is found that although the number of SG-related papers published by scholars from Chinese institutions has increased significantly, the total number of citations and H-index of the papers are still far behind those of the world's top research institutions.

By analyzing the journals in which Chinese scholars published SGs papers, many papers were published in world-renowned journals such as Nature Communications. But most of these journals are not journals founded by Chinese institutions themselves. Therefore, if Chinese scholars want to expand their influence in the field of SGs research, it is a good choice to start a high-level SGs journal. By establishing high-level journals recognized

by international peers, more high-level domestic scholars can be attracted to SGs research, and there will be more opportunities for international cooperation.

5. Conclusion

This paper selects the WOS database to search, conducts bibliometric analysis on the number of SGs, countries (regions), journals, etc., and analyzes the cooperation network, co-occurrence network, and co-citation network of the literature through VOSviewer. The results showed that the literature output in the field of peritoneal dialysis showed a fluctuating growth in the past 34 years, and the last five years were the peak period of literature output. Journal of Virology is the most popular journal for publishing most studies on SGs. And the most common research category is Biochemistry Molecular Biology.

No matter in terms of the number of papers, citation frequency, H-index, or the distribution of journals and funding sources, the United States is far away from Leading, which is closely related to the economic strength and scientific research level of the United States. With the enhancement of economic and scientific research strength, China has gradually carried out research on SGs. However, the citation frequency and H-index of Chinese papers are relatively low, and the research quality needs to be improved. Research cooperation between research institutions is relatively close, but domestic research institutions have less cooperation with relevant international institutions.

From the perspective of the author's cooperation network, the cooperation among authors is relatively scattered, and further exchanges and cooperation between scholars are needed. Institutions of higher learning occupy an important position in SGs research and are leaders in scientific research in this field. However, this paper also has limitations. There is subjectivity in the selection of highly cited documents and keyword thresholds. In addition, only using the SCI database of WOS to search for SGs documents may have limitations of missed selection, resulting in an incomplete analysis.

Conflict of Interest

The authors hereby declare that they have no conflict of interest.

Author's contributions

Y.W., and W.L. conceived and supervised the study. W.L. and Y.W., data collection and graphing. W.L., wrote the manuscript. Y.W. edited the manuscript.

Ethics approval and consent to participate

The authors declare no conflicts of interest in financial or any other sphere. This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publications

All authors have read and approved the final manuscript for publication.

Availability of data and material

The data used to support the findings of this study are available from the corresponding author upon request.

Informed Consent

The authors declare not used any patients in this research.

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