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Original Article

Knowledge mapping of interleukin-33: a bibliometric study

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Abstract: Interleukin-33 (IL-33) is a member of the IL-1 family of cytokines. IL-33 is associated with the expression of tissue damage or necrosis after increasing and being released into the cell, it influences the suppression of tumorigenicity 2 (ST2) receptor expression of a variety of immune cells (including mast cells and type 2 congenital lymphocytes). Furthermore, during type 2 innate immune reactions and allergic inflammation IL-33 plays a central role in immune amplification and "alarming"; thus, regulating immune responeses. IL-33 is closely related to inflammation-related diseases such as allergic diseases, autoimmune diseases, infectious diseases, and tumors. It is essential in maintaining tissue homeostasis, eliminating inflammation, and repairing tissue damage. We searched the Web of Science Core Collection (WoSCC) database for relevant publications on IL-33 from 2005 to 2021 and screened them according to specific inclusion criteria. A total of 2626 articles were included in our analysis. Using Microsoft Excel 2019 (Redmond, WA), VOSviewer 1.6.11 (The Centre for Science and Technology Studies, CWTS), and Citespace5.8. R2 (Drexel University, Philadelphia, PA) were used for data processing and visualization. Countries/regions, journals, authors, co-cited references, and keywords were analyzed. We discovered that IL-33 plays an important role as a cytokine in numerous diseases, especially allergic diseases. Studying its mechanism of action is of great importance for developing novel drugs and therapeutics.

Keywords: Citespace, vosviewer, IL-33, visualization, bibliometric analysis, cytokines

Introduction

In 2005, Schmitz et al. discovered interleukin-33 (IL-33) protein and mRNA, a new member of the IL-1 family [1]. Baekkevold et al. later confirmed it to be a nuclear factor of High Endothelial Venules (NF-HEV) [2]. IL-33 is abundantly expressed in the HEV of lymphoid organs.

IL-33 is mainly expressed in endothelial, epithelial, mast, and fibroid cells and tissue [3]. It is widely expressed in immune cells, barrier tissues, and related cells of the central nervous system [1, 4]. IL-33 activates numerous cells involved in type 2 immunity and allergic inflammation, including group 2 innate lymphoid cells (ILC2), mast cells, T helper 2 cells (Th2), eosinophils, basophils, dendritic cells, and alternatively activated macrophages [5-7]. It is also involved in allergy, fibrosis, chronic inflammation, tumorigenesis, metabolism, and homeostasis [8, 9].

The IL-1 family consists of 12 members, and most of the other 10 members (except IL-18 and IL-33) encode genes clustered in the 400Kb region of human chromosome 2. IL-33 differs from other IL-1 family members in that its gene is located on the short arm of chromosome 9 (9p24.1). Moreover, IL-33 has no common ancestor with other members of the IL-1 family [5]. The IL-33 gene is composed of an N-terminal nuclear localization sequence (containing chromatin-binding motifs that bind to histones), a helix-turn-helix motif (involved in the regulation of DNA transcription), and a C-terminal region (homology region of IL-1 family structure) [10]. After transcription and translation, IL-33-related genes are the first to form a precursor protein (IL-33FL), which aggregates in the nucleus as a nuclear factor. This character-

istic enables the dual functions of IL-33. It can aggregate in the nucleus as a nuclear transcription factor that regulates gene expression and it can be released into the extracellular space to act as an alarmin [11].

When the body is exposed to harmful events such as infection, injury, or inflammation, barrier tissue cells such as epithelial cells release IL-33 in response to the external injury. The released IL-33 binds to an isomer composed of ST2L/IL-1RacP, and the Toll/interleukin-1 receptor (TIR) domain of the receptor cytoplasmic segment and recruits the MyD88 complex. Subsequently, IL-33 induces signal transduction through MyD88 adaptor, interleukin 1 Receptor Associated Kinase 1 (IRAK1), interleukin 1 Receptor Associated Kinase 4 (IRAK4), and TNF Receptor Associated Factor 6 (TRAF6), eventually activates mitogen-activated protein kinase (MAPK) and nuclear factor kappa-B (NF-κB) transcription factors, and alerts the innate and adaptive immune system cells, which recruit immune cells to injured or infected tissues and regulate the immune response. However, the mechanism underlying IL-33 release *in vivo* remains unknown. Previous studies have shown that cell and tissue damage in the respiratory tract is an important factor in IL-33 release [1, 7, 12].

Bibliometric research is a qualitative and quantitative scientific discipline. The authors, keywords, institutions, countries, H index, G index, citation volume, publication time, and other aspects of the selected relevant articles can be comprehensively analyzed, and mathematical algorithms can be used to calculate the objective relationship between values. CiteSpace is a bibliometric analysis tool invented by Dr. Chaomei Chen (Drexel University, Philadelphia, PA, USA) and is currently widely used in several fields, including environmental science, education, mathematical statistics, and medicine [13]. Through the Timeline of co-cited references analysis, this algorithm can also predict future hot issues to a large extent. Professor Chaomei Chen published a visual analysis of the emerging research trends in regenerative medicine in Expert Opinions on Biotherapy [14] in May 2012 and predicted that Shinya Yamanaka, a Japanese scholar, would win the Nobel Prize in Physiology or Medicine that year [15]. VOSviewer is a Java-based free software that was developed by Van Eck and Waltman [16] in 2009. It is one of numerous scientific knowledge graph software packages, suggesting that mapping scientific knowledge graphs is based on the relationship between the construction and visual analysis of "network data" (mainly literature knowledge units). It displays the structure, evolution, cooperation, and other relationships in the field of knowledge, and one of its outstanding features is its solid graphical display capacities, which is suitable for large-scale data. The core idea of VOSviewer software design is "co-occurrence clustering", suggesting that two things that appear simultaneously are related. There are numerous types of correlation, and their strength and direction are also different. Different types of communities can be created based on the measurement index clustering of relationship strength and direction. This study used bibliometrics to comprehensively analyze the research status of IL-33 in the medical field using the research results obtained from WoSCC. In addition, we did not find any relevant papers that evaluated the bibliometrics of IL-33. Now, we systematically sorted out the bibliometrics of IL-33 to obtain the development trend of IL-33 and provide a reference for researchers that investigate the roles of IL-33.

Materials and methods

Data source

On July 16, 2022, we searched the relevant literature for IL-33 from WoSCC, with Science Citation Index-Expanded (SCI-E) as the data source.

Data retrieval

The term IL-33 was officially coined in 2005 [1]; thus, the retrieval dates between January 1, 2005, and December 31, 2021 were used. Using WoSCC advanced search with "TI = (IL-33 OR interleukin-33 OR IL 33 OR interleukin 33 OR IL33 OR interleukin33) OR KP = (IL-33 OR interleukin-33 OR IL 33 OR interleukin 33 OR IL33 OR interleukin33)" as the search formula, 2626 articles were retrieved.

Inclusion and exclusion criteria

Only journal articles and reviews were selected, and non-medical studies were excluded. This

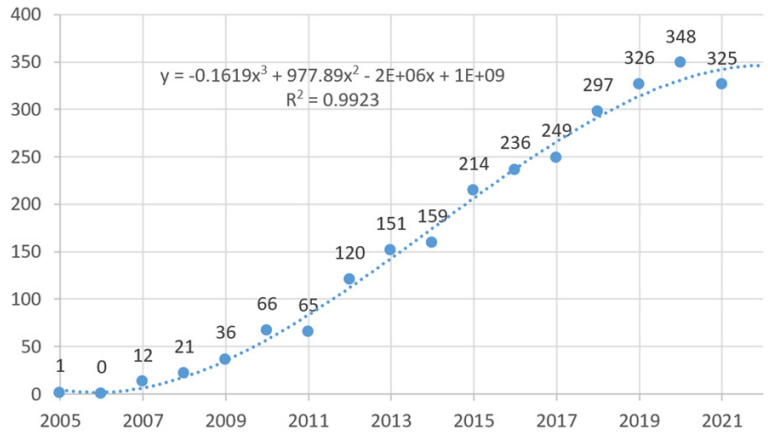

Figure 1. The number of annual publications (WosCC).

process was completed by three experimenters (Yu Xia, Dandan Zhang, and Zhujun Yu). If there was any disagreement among the three authors, the literature was submitted to Professor Zhimin Tan for a final decision.

Database establishment

Records in WosCC can simutaneously select up to 500 documents. When downloading documents, the "Plain Text" was selected as file format and "full records and cited references" was selected as record content to export the screened documents in "txt" format from WoS. The exported documents' information included titles, abstracts, keywords, authors, as well as research institutions, and the exported file was renamed "Download number. txt". The files were imported into CiteSpace 5.8.R2 for data conversion to facilitate literature analysis.

Analysis strategy

Data were de-duplicated, analyzed, and visualized using CiteSpace 5.8.R2 (Chen Chaomei, Drexel University, USA), followed by visualization of institutions/organizations' cooperation and co-citation analysis of references. In addition, we explored changes in the direction and trends of research by creating a timeline of co-cited journals. We used CiteSpace to capture keywords and references with intense citation bursts, and constructed visual representations to better identify research hotspots. Therefore, CiteSpace can be used to investigate research trends in a particular topic; for example, the published trend and hot research trends of IL-33 [17]. Microsoft Office Excel 2019 (Microsoft, Redmond, Washington, USA) was used to construct a polynomial regression model (f(x) = p0xn + p1xn - 1 + p2xn - 2 + p3xn - 3 +...+ pn) to predict the number of publications in 2022. The bar charts of the top 10 countries, top 10 authors, top 10 co-cited authors, top 10 journals and magazines, and reference pictures of the top 10 co-cited references were drawn. We used VOSviewer 1.6.11 (The Centre for Science and Technology Studies, CWTS) to explore collaborative networks among authors, countries, and journals as well as derive results on citations among them. Lastly, the collaboration between authors, countries, and journals was visualized. In VOSviewer, nodes represent authors, countries, and journals, and their size depends on their co-occurrence frequencies. ArcGIS 10.7 (Environmental Systems Research Institute, Inc.) was used to plot the distribution of the number of articles published in each country.

CiteSpace parameters are as follows

The following parameters were used: Connection retention coefficient (LRF = 3), time span (2005-2021), time slice (1 year), number of retrospective years (LBY = 8), threshold selection (G-Index K = 25), and minimum duration (MD = 1). Next, keywords, authors, and institutions of the literature origin were analyzed using metrology. Other relevant data were selected as follows: Impact Factor (IF) in 2021, Journal Citation Reports (JCR) in 2021, and Journal Citation Indicator (JCI) in 2021.

Results

Overall

In this study, we identified 2626 articles related to IL-33 published between 2005 to 2021 by searching the WoSCC database. As shown in **Figure 1**, the annual output of publications has steadily increased since 2005 and peaked in 2020 (n = 348, 13.25%), with an average annual publication number of 164 articles. By fitting

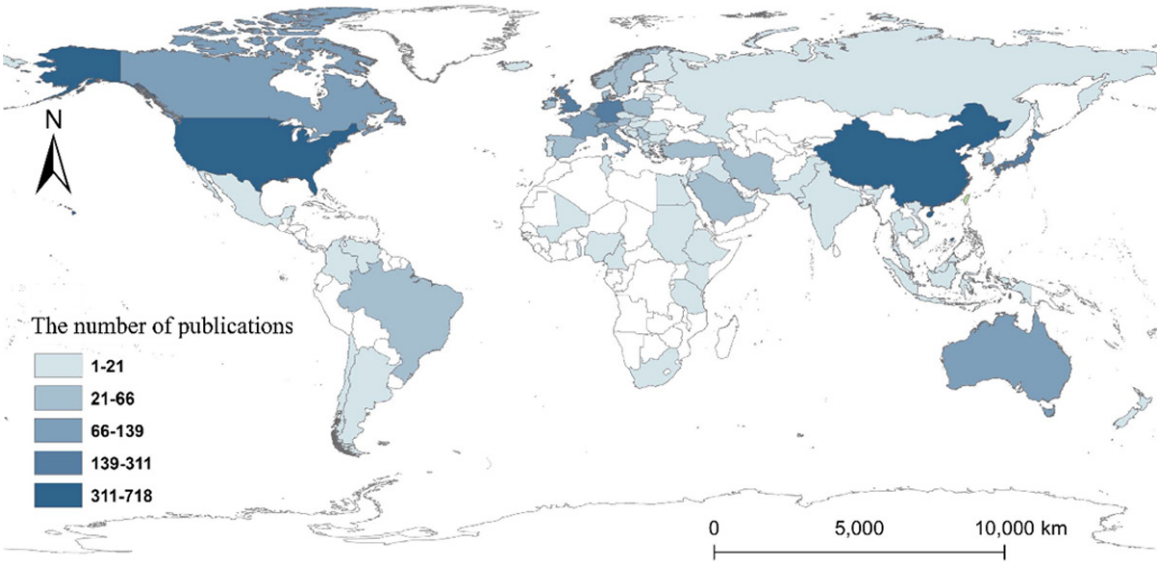

Figure 2. Number of publications published by country/region.

the data curve, we observed a statistically significant relationship between the year and number of publications (R^2 = 0.9923). Only one study on IL-33 was published between 2005 and 2006. The number of publications increased exponentially from 2005 to 2018, peaking in 2020. The number of articles published in 2020 was 348, indicating that IL-33-related research attracted much attention during this period. At the same time, we also fitted the curve to predict the rate of future IL-33-related studies. We expect the number of published papers to reach approximately 350 by 2022. It is worth noting that the output of papers may have been affected by COVID-19, international unrest, and the economic crisis, which might lower the article output. We predict that the number of articles published in 2022 might between 300 and 350. The number of published IL-33 studies has plateaued, and the number of subsequent studies will continue to increase until more IL-33-related breakthroughs are achieved, such as approval of IL-33-related drugs and formal large-scale clinical application.

Schmitz et al. published an article in Immunity in 2005, which introduced IL-33, a new member of the IL-1 family, and revealed the origin of IL-33 as well as its functions in the host defense, immune regulation, and inflammation. This study is fundamental. It is also by far the most frequently cited article [1]. Cayrol and Girard systematically reviewed the underlying mechanisms of IL-33 from its discovery in 2005 to 2018 in an article published in Immunological Reviews (IF = 12.988) [9]. IL-33 has been analyzed in detail, including its molecular characteristics, nuclear localization, biological activity form, cell origin, release mechanism, and protease regulation. More importantly, this study used IL-33-deficient cells.

Country/region and institution analysis

The 2626 articles related to IL-33 come from 78 countries. The number of publications is shown in the distribution map by country (**Figure 2**) and in a bar chart (**Figure 3**). According to the distribution map of the number of articles published by countries, China delivered the highest number of studies. However, the publication output is mainly concentrated in the United States, Japan, Canada, Australia, while Europe, and the number of papers published by countries in Africa and the Middle East is relatively small. As the publication of an article is often a multi-country collaboration, the final number of countries counted was 3690. The top three countries/regions in the number of publications were China (n = 718, 19.46%), the United States (n = 709,

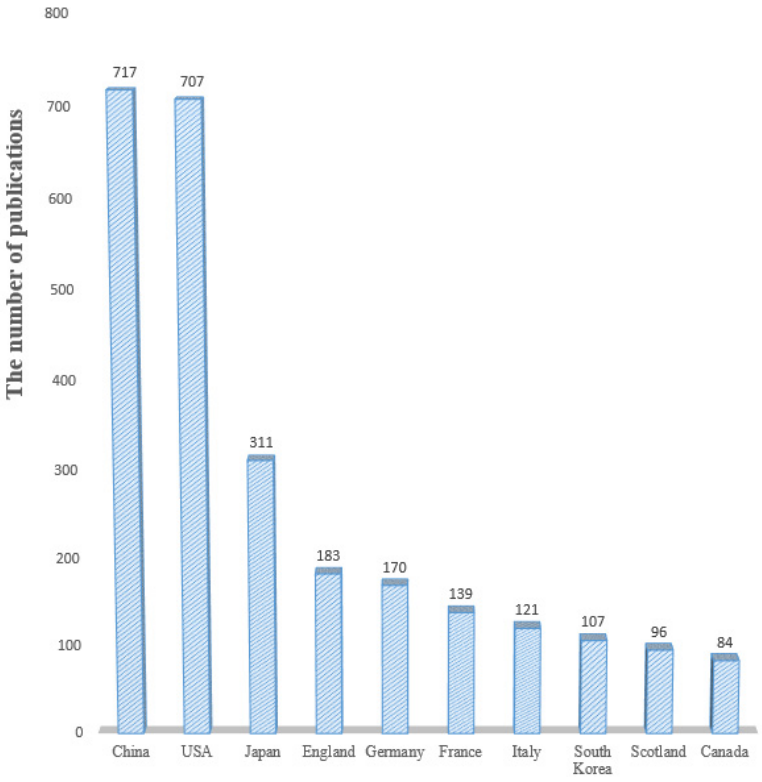

Figure 3. Top 10 countries by the number of publications issued.

19.21%), and Japan (n = 311, 8.43%). In addition, as shown in **Figure 4B**, there was extensive cooperation between countries/regions, especially between China and the United States. The cooperation between several countries and the United States is frequent, and the intermediary centrality of the United States is 0.50, while Germanyand the United Kingdom had a centrality = of 0.17 and 0.14, respectively. This reflects the extensive cooperation between the United States and other countries when it comes to IL-33 research, indicating that the United States plays a key role in the study of IL-33. The 2626 articles were submitted by 2,652 institutions, and the top 10 contributed to 656 articles, accounting for 24.98% of the total number (**Figure 3A**). Regarding the number of institutional publications, the Centre National de la Recherche Scientifique (CNRS) ranked first (n = 88, 3.35%). The Institut National de la Santé et de la recherche médicale (Inserm) (n = 83, 3.16%) and Harvard University (n = 78, 2.97%) ranked second and third, respectively. As shown in **Figure 3B**, cooperation between institutions is extensive and indicates that research institutions that published earlier, drive new research institutions to work together. In terms of co-citation frequency, the University of Glasgow (Count = 69), the University of Tokyo (Count = 59), and Huazhong University of Science and Technology (Count = 54) had the highest co-citation frequency. This shows that these three research institutions have a deep foundation in IL-33 research and have been widely recognized by the industry. In terms of centrality, Harvard University (centrality = 0.43), the U.K. Medical Research Council (MRC) (centrality = 0.37), and France's National Institutes of Health and Medical Research (centrality = 0.20) had strong mediating centralites. This highlights the important contribution and key roles these institutions play in international research. In **Figure 4A**, the circle shows that Chinese institutions have published numerous relevant articles in the past five years. Chinese research institutions such as Huazhong University of Science and Technology, Fudan University, Shanghai Jiao Tong University, Capital Medical University, China Medical University, Zhengzhou University, and Nanjing University have produced widely cited research results overthe last five years, indicating that investments in IL-33 research in Chinese research institutions have accelerated significantly.

The author analysis

The 2626 publications were authored by 15002 authors (**Figure 5**). The top ten productive authors and co-cited authors are listed in **Table 1**. Nakae S. led with 47 articles published, followed by Liew FY. (count = 44) and Li Y. (count = 39). The most frequently cited authors in the field are Schmitz J. (1358 Citations), Liew FY. (767citations), Cayrol C. (678 citations), Moussion C. (557 citations), and Miller AM. (504 citations). However, there was no absolute correlation between the num-

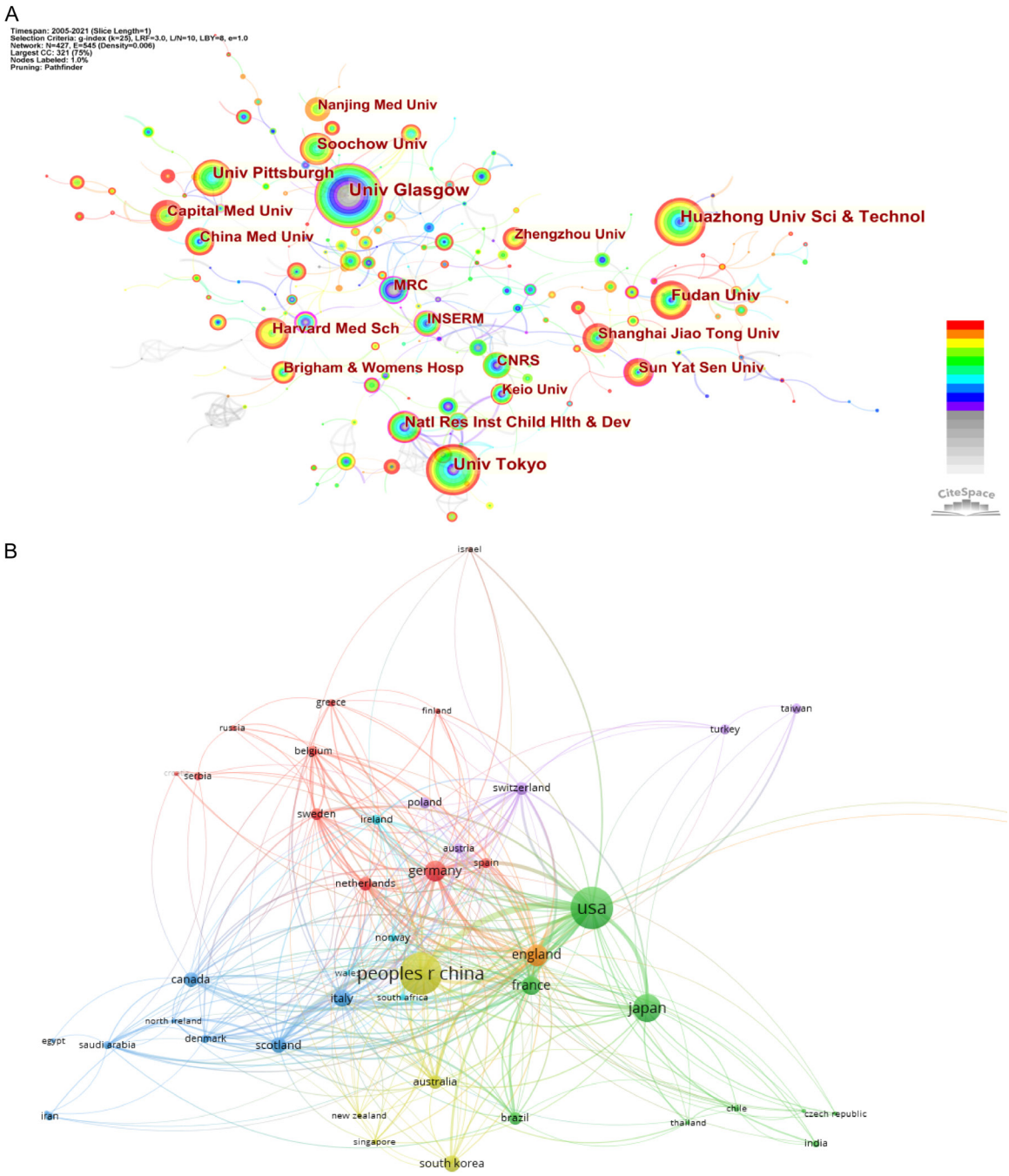

Figure 4. (A) Institutional cooperation. (B) national cooperation. Figure Note: (A) (1) Legend from white to red shows the progression of years. The white to red years are from January 1, 2005, to December 30, 2021. (2) The purple outer circle indicates betweenness centrality, and the darker the color, the higher the betweenness centrality. Centrality indicates the extent to which a node is an "intermediary" to other nodes in the graph, and such nodes play a communication and critical role in the network. (B) The circle size represents the frequency of cooperation with each country; The higher the frequency, the larger the circle. Color classification represents clustering, reflecting the tendency of mutual reference and clustering among countries.

ber of IL-33-related articles published by authors and their co-citations. Authors with a high number of publications tend not to have high co-citations. Schmitz published three articles on topic between 2005 and March 19, 2022, of which the total number of citations

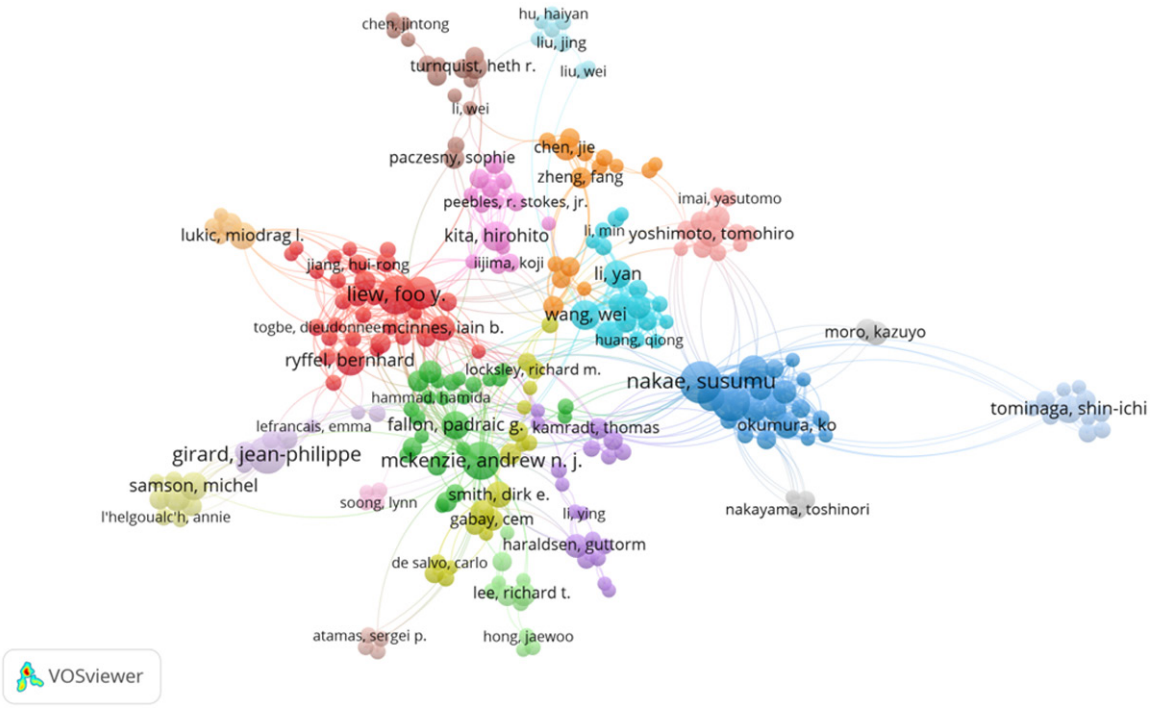

Figure 5. VOSviewer network visualization map of the co-occurring author. Figure Note: Each node represents an author and the size of the circle reflects the number of articles published by the researcher. The lines connecting the circles represent co-occurrence relationships between authors. There was a close co-occurrence relationship between authors and co-cited authors, and high-yielding authors generally co-occur more with other authors. Each color represents a cluster, which can be considered a small group.

Table 1. Top 10 most productive and co-cited authors for IL-33 research

Rank	Author	Count	Rank	Co-cited author	Citation
1	Nakae S	47	1	Schmitz J	1358
2	Liew FY	44	2	Liew FY	767
3	Li Y	39	3	Cayrol C	678
4	Saito H	37	4	Moussion C	557
5	Girard JP	36	5	Miller AM	504
6	Mckenzie ANJ	36	6	Carriere V	501
7	Matsumoto K	28	7	Kurowska-Stolarska, M	459
8	Zhang L	24	8	Xu D	399
9	Kita H	23	9	Oboki K	358
10	Zhang Y	23	10	Ali S	350

was 2618, while the most classic article ("IL-33, an Interleukin-1-like Cytokine that Signals via the IL-1 Receptor-Related Protein ST2 and Induces T Helper Type 2-Associated Cytokines") was cited 2516 times. Liew FY. was the only author in the top 10 in terms of co-citation and high yield. Liew FY. is ranked second among the high-yield and co-cited authors, and can be recognized as an author with a high contribution in this field. Based on ResearchGate, Liew FY. considers his main research fields as Nitric Oxide, Cytokines, Molecular Biology, Rheumatoid Arthritis, and Inflammation. Most scholars recognize his experimental findings regarding IL-33. The aforementioned data show that authors with basic and pioneering research are more likely to be cited than authors with many papers. In terms of countries and universities the top authors were, Liew FY., Kurowska-Stolarska, M., Xu D. from the University of

Glasgow, UK; Schmitz J. and Ali S. from Germany; Cayrol C and Carriere V. from the CNRS, France; and Moussion C. and Miller AM. from the United States. Productive authors Nakae S., Saito H., and Matsumoto K. from Japan; Liew FY. and McKenzie ANJ. from the United Kingdom; Li Y., Zhang L., Zhang Y. from China; Girard JP. from France; and Kita H. from the United States. Most of the high-yield and high-co-citation authors are from developed countries, and Chinese authors make most contributions to the article output; however, Chinese scholars lack prominent achievements in academic co-citation. The University of Glasgow has made outstanding achievements in the research of IL-33, mainly reflected in the study of the molecular mechanism of IL-33 and the relationship between IL-33 and related diseases. Furthermore, the University of Glasgow has been studying IL-33 for the longest time, which may be one of the reasons for its high co-citation. The Liew group has significantly contributed to the IL-33 research performed at The University of Glasgow.

Analysis of journals and co-cited academic journals

A total of 2626 articles on IL-33 were published in 758 academic journals, of which the Journal of Immunology (n = 114, IF 2021= 5.426) ranked first. Allergy (n = 37, IF 2021 = 14.71) had the highest impact factor among the journals with more than 35 articles, followed by Proceedings of The National Academy of Sciences of The United States of America (n = 43, IF 2021 =12.779) and Journal of Allergy and Clinical Immunology (n = 68, IF 2021 = 14.29) (**Table 2**). As shown in **Figure 6**, there is a wide range of citation relationships among different journals, and numerous mutual citations among immunology journals. During the seven years from 2015 to 2021, the IF of IL-33 publications increased (the quality of journals shown in yellow circles was generally higher than that of journals shown in purple circles). Published IL-33-related articles increasingly clustered in the Q1 region of the interquartile category. The results showed that the quality of IL-33 research has significantly improved over the past five years.

Regarding JCI, Nature ranked first, with a total of 1189 citations and eighth contribution. The JCI of Nature Reviews Immunology and Immunity ranks second and third, respectively. The JCI reflects the influence of a journal and the number of citations. The higher the JCI value, the greater is the impact and number of citations. Among the top 10 journals, six were in Q1 (top 25% of IF distribution), three were in Q2 (25-50% of IF distribution), and one was in Q3 (50-75% of IF distribution). Through a partition analysis of the journals, it can be concluded that research on IL-33 remains a hot spot. In terms of academic journal co-citation, the top three were the Journal of Immunology (Citations = 2070, IF 2021 = 5.426), Immunity (Citations = 1985, IF 2021 = 43.474), and Proceedings of the National Academy of Sciences of the United States of America (Citations = 1818, IF 2021 = 12.779). In the top 10 co-cited journals, seven journals were in the Immunology Division. Additionally, seven journals were distributed in Q1 and the remaining three were distributed in Q2 (**Table 2**). **Table 3** shows that the top journals were still the main subjects of co-citation. Of the top 10 co-citations, six were from the U.S., three from the U.K., and one from Germany, all founded in developed countries.

A total of 1131 co-cited references were visualized using CiteSpace, with the time slice set as a year and the period from 2005 to 2021 (**Figure 7B**). **Table 3** lists the top 10 most co-cited references related to IL-33 levels. Liew FY. published an article titled “Interleukin-33 in Health and Disease (DOI:10.1038/nRI.2016.95)” with 293 total citations. Six of the top 10 co-cited articles were reviews and five were articles (“DOI: 10.1016/j.i mmuni. 2009.05.007” and “DOI: 10.1038/ni. 3370” are tied for the tenth in number of co-citations). CiteSpace was used to construct the co-cited reference network. Further, we generated a timeline of co-cited references (**Figure 7B**). The Modularity Q value (0.6672) and Mean Silhouette value (0.862) were more significant than 0.5. It is commonly agreed that a Modularity Q value > 0.3 means that the cluster structure is substantial. Silhouette (S): Cluster average contour values greater than 0.5 are considered to represent reasonable clustering, while S values > 0.7 represent convincing clustering. A timeline view is a method for visualizing data that combines clustering and temporal slicing techniques. Cluster labels were sorted according to their early or late occurrence after

Table 2. Top 10 most productive journals and co-cited journals for IL-33 research

Rank	Journal	Count (N)	Percentage (N/2626)	IF (2021)	JCI (2021)	Quartile Score
1	Journal of Immunology	114	4.34	5.426	0.92	Q2[a]
2	Frontiers in Immunology	105	4.00	8.786	1.01	Q1[a]
3	Plos One	69	2.63	3.752	0.88	Q2[b]
4	Journal of Allergy and Clinical Immunology	68	2.59	14.29	2.17	Q1[a,c]
5	Scientific Reports	62	2.36	4.996	1.05	Q1[b]
6	International Journal of Molecular Sciences	45	1.71	6.208	0.7	Q1[d]
						Q2[e]
7	Cytokine	43	1.64	3.926	0.63	Q3[a,d,f]
7	Proceedings of The National Academy of Sciences of The United States of America	43	1.64	12.779	2.61	Q1[b]
9	European Journal of Immunology	39	1.49	6.68	0.85	Q2[a]
10	Allergy	37	1.41	14.71	2.16	Q1[a,c]
Rank	Co-cited Journal	Co-citation	Country	IF (2021)	JCI (2021)	Quartile in category
1	Journal of Immunology	2070	United States	5.426	0.92	Q2[a]
2	Immunity	1985	United States	43.474	5.63	Q1[a]
3	Proceedings of The National Academy of Sciences of The United States of America	1818	United States	12.779	2.61	Q1[b]
4	Plos One	1439	United States	3.752	0.88	Q2[b]
5	Journal of Experimental Medicine	1363	United States	17.579	3.18	Q1[a]
6	Journal of Allergy and Clinical Immunology	1338	United States	14.29	2.17	Q1[a,c]
7	Nature Reviews Immunology	1275	United Kingdom	108.555	7.56	Q1[a]
8	Nature	1189	United Kingdom	69.504	10.88	Q1[b]
9	Nature Immunology	1165	United Kingdom	31.25	4.55	Q1[a]
10	European Journal of Immunology	1159	Germany	6.688	0.85	Q2[a]

a, Immunology; b, Multidisciplinary sciences; c, Allergy; d, Biochemistry and Molecular Biology; e, Chemistry, Multidisciplinary; f, Cell Biology. Note: Each node in the tablerepresents an author, and the size of the circle reflects the number of articles published by the researcher. The lines connecting the circles represent co-occurrence relationships between authors. There was a close co-occurrence relationship between authors and co-cited authors, and high-yielding authors generally co-occur more with other authors. Each color represents a cluster, which can be considered a small group.

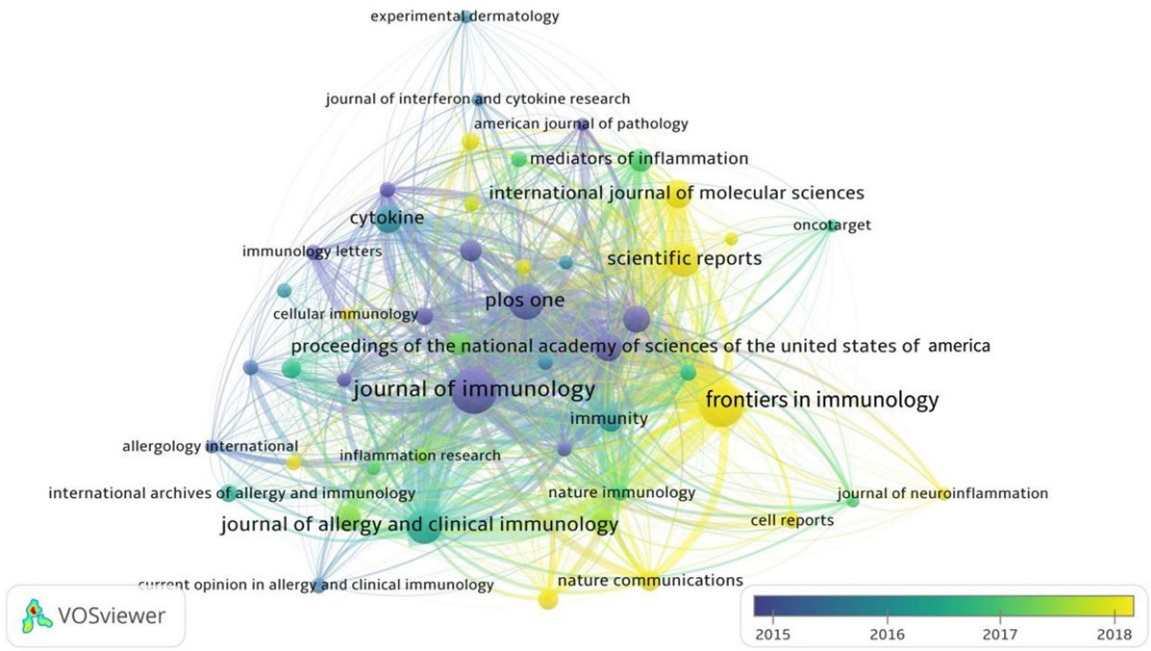

Figure 6. Analysis of co-citation between publications related to IL-33.

clustering. Cluster labels illustrate the topic distribution in the field and show the trends and inter-relationships of research topics over time. The first tag cluster on the knowledge graph was "#0 interleukin-1 family". The second cluster was "#1 asthma". The third was clustered as "#2 innate lymphoid cells". In the timeline view, nodes with different colors in the same row represent different years. The nodes on the left represent older references, whereas those on the right represent newer references. A straight line at the same horizontal position represents the set of all cluster references. The cluster label was located at the far right end of the line. The clusters closest to the present time on the timeline were "#2 innate lymphoid cells", "#3 regulatory T cells", "#5 tumor microenvironment " and "#7 mast cells". These four clusters currently represent research topics associated with high interest. Cluster "#7 mast cells" contained articles addressing allergic diseases such as asthma, allergic rhinitis, allergic dermatitis, conjunctivitis, cough, and other diseases. Cluster "#3 regulatory T cells" contained articles addressing autoimmune diseases. Cluster "#5 tumor microenvironment" included articles addressing tumor-related diseases and more precisely investigating tumor growth and the apoptotic microenvironment. Cluster "#2 innate lymphoid cells" contained articles addressing a variety of diseases, all related to innate lymphocytes. CiteSpace was used to evaluate the references with high citation bursts. Citation bursts indicate that the reference has been widely cited over time, and that the findings of the references are well known in the field (**Figure 7B**). Among the top 15 references with the strongest citation outbreak, "Liew et al., 2016, Nat Rev Immunol, V16, P676, DOI: 10.1038/nRI.2016.95" (2018-2021, strength 92.34) and "Cayrol et al., 2018, Immunol Rev, V281, P154, DOI: 10.1111/IMR.12619" (2019-2021, strength 70.92) were the most cited references that appeared in the past five years. In one of the aforementioned studies, Liew et al. [7] mainly elaborated on the relationship between IL-33 and various diseases and health aspects, as well as the role of IL-33 in tissue and metabolic homeostasis, infection, inflammation, cancer, and central nervous system diseases. The potential therapeutic implications of these findings in humans mainly focus on IL-33 and related diseases. Cayrol et al. primarily elaborated on the discovery of the IL-33 protein, including its molecular characteristics, nuclear localization, bioactive form, cell source, release mechanism, and regulation of protease, focusing on the IL-33 protein itself [9]. One article focused on revealing the relationship between IL-33 and diseases,

Table 3. Top 10 most co-cited articles related to IL-33

Rank	Co-citation	Centrality	Author	Type	Title
1	293	0.00	Liew FY (2016)	Review	Interleukin-33 in health and disease (DOI:10.1038/nri.2016.95)
2	223	0.00	Liew FY (2010)	Review	Disease-associated functions of IL-33: the new kid in the IL-1 family (DOI:10.1038/nri2692)
3	197	0.01	Schiering C (2014)	Article	The alarmin IL-33 promotes regulatory T-cell function in the intestine (DOI:10.1038/nature13577)
4	179	0.00	Cayrol C (2018)	Review	Interleukin-33 (IL-33): a nuclear cytokine from the IL-1 family (DOI:10.1111/imr.12619)
5	169	0.00	Cayrol C (2014)	Review	IL-33: an alarmin cytokine with crucial roles in innate Immunity, inflammation and allergy (DOI:10.1016/j.coi.2014.09.004)
6	160	0.01	Locksley R.M. (2015)	Review	Interleukin-33 in tissue homeostasis, injury, and inflammation (DOI:10.1016/j.immuni.2015.06.006)
7	158	0.03	Carriere V (2007)	Article	IL-33, the IL-1-like cytokine ligand for ST2 receptor, is a chromatin-associated nuclear factor in vivo (DOI:10.1073/pnas.0606854104)
7	158	0.00	Moussion C (2008)	Article	The IL-1-Like Cytokine IL-33 Is constitutively expressed in the nucleus of endothelial cells and epithelial cells in vivo: a novel 'alarmin'? (DOI:10.1371/journal.pone.0003331)
9	156	0.01	Cayrol C (2009)	Article	The IL-1-like cytokine IL-33 is inactivated after maturation by caspase-1 (DOI:10.1073/pnas.0812690106)
10	146	0.01	Luthi AU (2009)	Article	Suppression of interleukin-33 bioactivity through proteolysis by apoptotic caspases (DOI:10.1016/j.immuni.2009.05.007)
10	146	0.01	Martin NT (2016)	Review	Interleukin 33 is a guardian of barriers and a local alarmin (DOI:10.1038/ni.3370)

and the other focused on explaining the characteristics of IL-33 as a cytokine.

In terms of research hotspots, "#2 innate lymphoid cells", "#3 regulatory T cells", and "#5 tumor microenvironment" are worthy of attention.

In the past decade, the discovery and functional study of ILC shave greatly improved our understanding of immune regulation in mucosal tissues. In "#2 innate lymphoid cells", studies addressing the mechanisms of allergic diseases involving related cells and downstream cytokines were included. As an important factor in the ILC2 family, IL-33 has been widely studied. ILCs have been frequently studied in association with allergic, helminthiasis, and inflammatory diseases. For instance, ILC2-deficient mice have been shown to echibit a significantly reduced ability to clear helminthiases compared to that of wild-type mice, which is associated with Interleukin-13 (IL-13), a downstream factor of IL-33 [18]. IL-33 levels correlate considerably with the severity of allergic rhinitis and prognosis after immunotherapy [19, 20].

As a central part of the"#3 regulatory T cells" cluster, Treg play an immunosuppressive role, maintaining immune tolerance and preventing autoimmune reactions. The IL-33/ST2 signal can transform $CD4^+$ FOXP3-T cells into Treg cells expressing Foxp3; therefore, IL-33/ST2 signaling is crucial for maintaining the stability and function of Treg cells. Furthermore, Treg cells inhibit astrogliosis and enhance nerve function through amphiregulin (Areg), which provides a therapeutic opportunity for neuronal protection during stroke and neuroinflammatory diseases [21]. IL-33 signaling in lung Treg cells induces Areg production, which can effectively prevent tissue damage [22]. In the CT26 adenocarcinoma model, administration of re-

A

Top 15 references with the strongest citation bursts

References	Year	Strength	Begin	End	2005 - 2021
Schmitz J, 2005, IMMUNITY, V23, P479, DOI 10.1016/j.immuni.2005.09.015, DOI	2005	73.33	2007	2010	
Carriere V, 2007, P NATL ACAD SCI USA, V104, P282, DOI 10.1073/pnas.0606854104, DOI	2007	72.73	2007	2012	
Allakhverdi Z, 2007, J IMMUNOL, V179, P2051, DOI 10.4049/jimmunol.179.4.2051, DOI	2007	47.25	2007	2012	
Iikura M, 2007, LAB INVEST, V87, P971, DOI 10.1038/labinvest.3700663, DOI	2007	44.02	2007	2012	
Chackerian AA, 2007, J IMMUNOL, V179, P2551, DOI 10.4049/jimmunol.179.4.2551, DOI	2007	49.56	2008	2012	
Moussion C, 2008, PLOS ONE, V3, P0, DOI 10.1371/journal.pone.0003331, DOI	2008	59.57	2009	2013	
Cayrol C, 2009, P NATL ACAD SCI USA, V106, P9021, DOI 10.1073/pnas.0812690106, DOI	2009	47.75	2009	2014	
Smithgall MD, 2008, INT IMMUNOL, V20, P1019, DOI 10.1093/intimm/dxn060, DOI	2008	45.63	2009	2013	
Xu D, 2008, P NATL ACAD SCI USA, V105, P10913, DOI 10.1073/pnas.0801898105, DOI	2008	44.38	2009	2013	
Luthi AU, 2009, IMMUNITY, V31, P84, DOI 10.1016/j.immuni.2009.05.007, DOI	2009	45.62	2010	2014	
Liew FY, 2010, NAT REV IMMUNOL, V10, P103, DOI 10.1038/nri2692, DOI	2010	55.41	2011	2015	
Schiering C, 2014, NATURE, V513, P564, DOI 10.1038/nature13577, DOI	2014	48.54	2016	2019	
Cayrol C, 2014, CURR OPIN IMMUNOL, V31, P31, DOI 10.1016/j.coi.2014.09.004, DOI	2014	45.89	2016	2019	
Liew FY, 2016, NAT REV IMMUNOL, V16, P676, DOI 10.1038/nri.2016.95, DOI	2016	92.34	2018	2021	
Cayrol C, 2018, IMMUNOL REV, V281, P154, DOI 10.1111/imr.12619, DOI	2018	70.92	2019	2021	

B

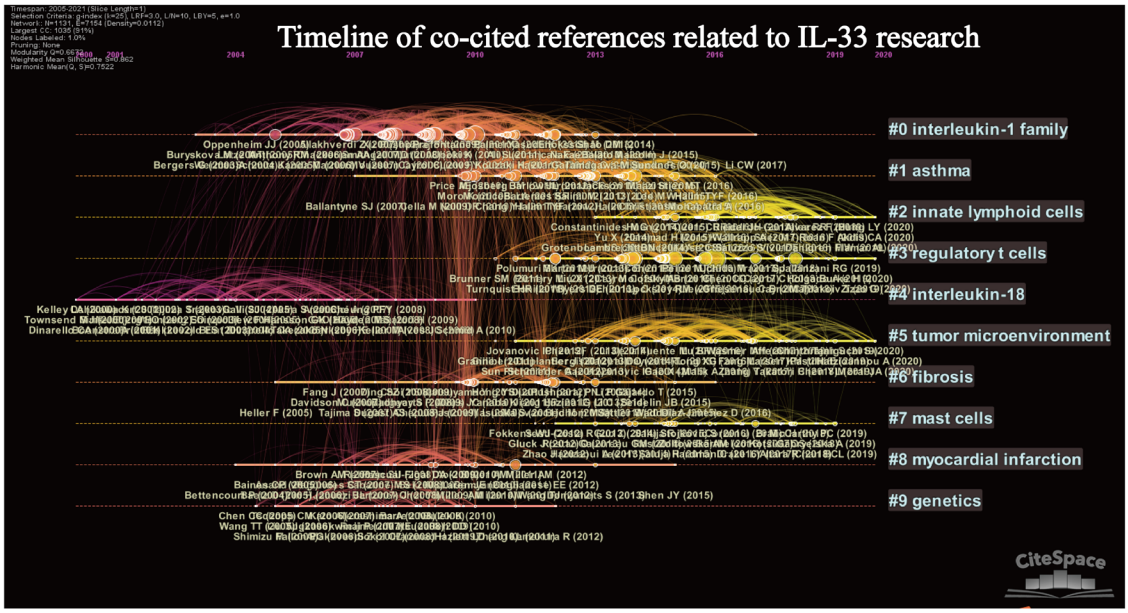

Figure 7. A. Top 15 references with the Strongest Citation Bursts. B. Timeline of co-cited references related to IL-33.

combinant IL-33 to tumor-bearing mice promoted the proliferation of ST2$^+$ Treg cells in the tumor tissue and spleen, while blocking IL-33 reduced their proliferation [23]. IL-33 can aggravate autoimmune encephalitis in C57BL/6 mice, whereas blocking IL-33 treatment can inhibit the production of IL-17and IFN-γ [24].

Lastly, the "#5 Tumor microenvironment" cluster mainly contains literature related to tumor research. In patients with tongue squamous cell carcinoma, high expression of IL-33 or ST2 was associated with a poor prognosis. Increased IL-33 levels in these tumors are also associated with micro-vessels in the stroma [25]. Compared to with normal breast tissue, the expression of IL-33 and ST2 in human breast cancer tissue is increased [26, 27]. IL-33 plays has a complex dual role in tumor development. On one hand, it is related to tumor occurrence, proliferation, and malignant metastasis. On the other hand, it can activate the immune effector mechanism of the body to inhibit tumor growth [28, 29].

Keyword analysis

The keyword network was constructed using CiteSpace (**Figure 8**), where circles represent the common citation frequency of keywords, and the larger the circle, the higher the frequency. The legend from gray to red represents the time slice from 2005 to 2021, and each color represents one year. The top 35 keywords with explosive citation strength were determined using CiteSpace (**Table 4**). In **Table 4**, the green line represents the period from 2005 to 2021, while the period of each burst keyword is represented by the red line. After 2019, the Strength values of "Risk", "Health", and "Role" were 7.09, 6.44, and 5.69, respectively. These results indicate that the current research direction is shifting from micro research (single diseases) to macro analysis (overall health). Among the top 35 most explosive keywords, the highest strength value was "*in vivo*", and the keyword with the longest duration was "Antigen". These two keywords indicate that the study of immune antigen *in vivo* was the focus of IL-33 research.

Discussion

By reviewing the literature, we concluded that the critical point at this stage is to reveal the intracellular and extracellular mechanisms of IL-33, the role of IL-33 in various diseases, and, more importantly, the drug development and potential therapeutic targets for IL-33-related illnesses.

In terms of intracellular and extracellular mechanisms of action, Gautier and Cayrol et al. used a global proteomic approach based on high-resolution mass spectrometry to compare the extracellular and intracellular effects of IL-33 in primary human endothelial cells and discovered that IL-33 acts as a cytokine rather than as a nuclear factor that regulates gene expression in endothelial cells [30]. These findings negate the possibility that IL-33 has a dual-function as proposed by Carriere et al. in 2007 [31]. At the same time, the hypothesis that IL-33 can act inside the cell as a nuclear factor that regulates transcription and outside the cell is rejected. According to Lefrancais et al. [32], in a model of acute lung injury associated with alveolar epithelial damage and neutrophil accumulation in the alveolar wall, it was shown that IL-33FL and the cleaved form of IL-33 were released in bronchoalveolar lavage liquid (BAL) two hours after injury. Kearley et al. [33] showed that viral infection can induce lung epithelial damage and trigger the release of IL-33 from primary bronchial epithelial cells following influenza virus, rhinovirus, or respiratory syncytial virus infection. Although the mechanism of IL-33 release *in vivo* remains elusive, it has been shown that cell damage and tissue damage are essential for the release of IL-33. This sheds some light on the intracellular and extracellular mechanisms of IL-33;however, the cytoplasmic localization of IL-33 and the essential bioactive forms of IL-33 *in vivo* require further investigation.

An outstanding remaining question is 'What role does IL-33 play in disease and health'? Liew et al. [7] suggested that the functional role of IL-33 has expanded from infection to inflammation, metabolic diseases, and tumors. Despite current evidence that IL-33 is a tissue-produced cytokine, the relative importance of IL-33 production by epithelial cells, endothelial cells, fibroblasts, or other cell types during homeostasis and disease remains to be determined using cell-specific knockdown approaches. Due to its pleiotropic function, IL-33 might act as 'a double-edged sword' in diseases, by playing both a protective role as well as promoting disease progression. For example, IL-33 is a critical factor in the progression of allergic diseases, such as asthma, allergic rhinitis, and atopic dermatitis, which can aggravate allergic diseases by inducing the production of pro-inflammatory cytokines and the activation of Th2-type immune cells [34, 35]. Moreover, IL-33 neutralization can inhibit the development of allergic diseases. IL-33 has been shown to exert a protective effect in experimental autoimmune encephalomyelitis (EAE). Knockout of IL-33 in mice aggravated the severity of EAE, which was shown to be accompanied by more severe demyelination [36]. Therefore, the roles of IL-33 in different diseases are not the same.

Currently, there are drugs that inhibit IL-33 production, and medicines that promote IL-33 production. Using drugs that inhibit IL-33, several pharmaceutical companies attempt to develop asthma and atopic dermatitis therapeutics. For example, ANB020, a monoclonal antibody drug developed by AnaptysBio, targets IL-33 and has

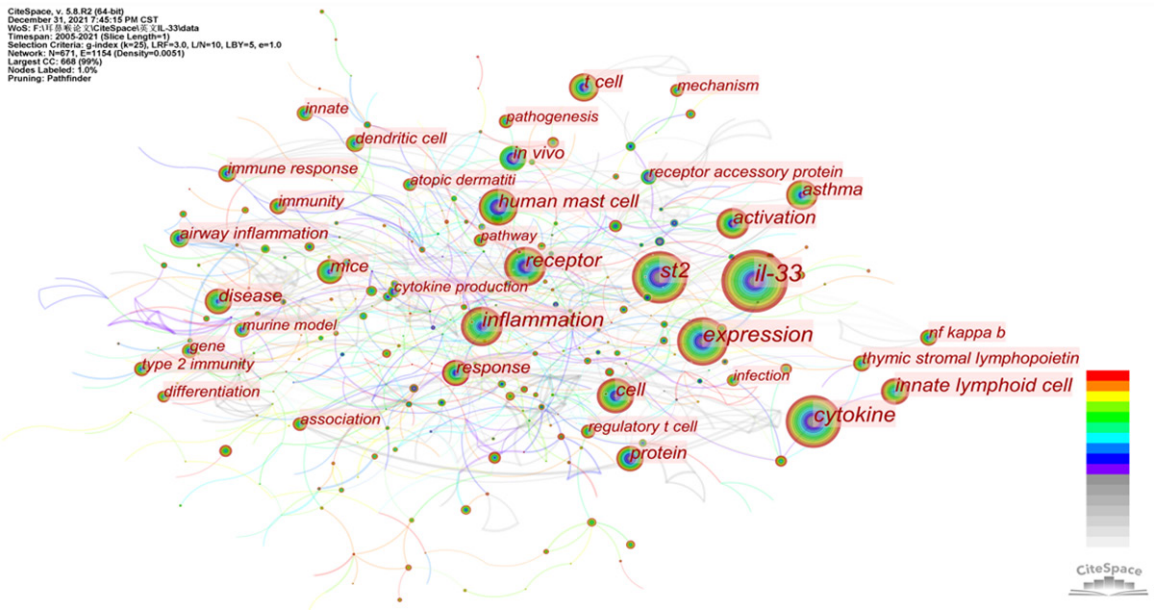

Figure 8. Analysis of keyword co-occurrence.

been used to treat atopic dermatitis in phase II clinical studies [37]. Clinical trials using antibodies targeting IL-33 have been initiated in asthma treatment studies. REGN3500, an IL-33 antibody developed by the French pharmaceutical giant Sanofi and its partner Regeneron, reached the primary endpoint in a phase II clinical trial for treating asthma. It has shown promising efficacy in improving asthma symptoms [38, 39]. CNTO 7160, a monoclonal antibody drug targeting IL-33 developed by GSK, can regulate inflammatory cells in patients by blocking the interaction between IL-33 and ST2 receptors; thus, alleviating asthma and atopic dermatitis symptoms. CNTO 7160 has shown controllable safety and definite efficacy in human experiments [40]. IL-33 monoclonal antibodies-based treatments may be helpful in treating other diseases. However, monoclonal antibodies also have shortcomings. First, the high price of monoclonal antibodies makes their popularization challenging. Second, not all patients respond to treatment with monoclonal antibody drugs. It has been shown that commonly used clinical drugs can also promote the production of IL-33. For example, in a diet-induced obesity mouse model, empagliflozin increased the level of the anti-inflammatory cytokine IL-33 [41]. Statins (fluvastatin/lovastatin) can increase the expression of IL-33 in human cardiomyocytes and fibroblasts by inhibiting activation of the mevalonate pathway *in vitro*, and IL-33 knockout can significantly aggravate cardiac remodeling and impair cardiac function [42, 43]. The aforementioned studies have confirmed that one of the possible targets of statins in the myocardium is IL-33. Therefore, a better understanding of the mode of action, regulation, and function of IL-33 will further promote the development of therapies for the treatment of human diseases associated with IL-33-ST2 signaling. The direct and indirect effects of IL-33 on ILC2, Treg cells,dendritic cells, M2 macrophages, and non-hematopoietic cells are important for our understanding of IL-33-mediated regulation and have profound therapeutic implications. The regulatory effects of IL-33 on various target cells and their roles in disease progression indicate its therapeutic potential. However, mature drugs targeting IL-33 are not available, a limited number of monoclonal antibodies have entered clinical trials for limited indications, and their effectiveness requires further scrutiny. Some natural products, such as Chinese herbal medicines, deserve attention because of their multi-target effects. Some drugs, such as metformin and methotrexate, as well as a variety of natural products with multipotent activity, such as baicalin, Provide II, and quercetin, have been shown to inhibit the production or action of IL-33. Thus, they are expected to become candidate drugs for the treatment of IL-33-mediated diseases. However, the evidence that

Table 4. Top 35 burst keywords in articles related to IL-33

Top 35 Keywords with the Strongest Citation Bursts					
Keywords	Year	Strength	Begin	End	2005-2021
st2	2005	6.35	2005	2009	
interleukin 1 receptor	2005	16.14	2007	2012	
cytokine production	2005	8.29	2007	2012	
protein	2005	6.51	2007	2013	
type 2	2005	5.19	2007	2013	
collagen induced arthritis	2005	5.01	2007	2010	
receptor accessory protein	2005	27.1	2008	2012	
human mast cell	2005	24.83	2008	2012	
th2 cell	2005	11.09	2008	2013	
soluble st2 protein	2005	6.78	2008	2012	
st2 comprise	2005	6.55	2008	2013	
cutting edge	2005	6.12	2008	2012	
cd4(+) t cell	2005	5.2	2008	2011	
antigen	2005	4.82	2008	2016	
in vivo	2005	24.94	2009	2012	
human basophil	2005	15.18	2009	2013	
ligand	2005	9	2009	2014	
human eosinophil	2005	7.47	2009	2013	
myocardial infarction	2005	5.05	2009	2013	
family member	2005	13.03	2010	2015	
maturation	2005	8.11	2010	2014	
induced arthritis	2005	5.34	2010	2014	
family	2005	4.76	2011	2015	
endothelial cell	2005	5.16	2012	2016	
inhibition	2005	4.52	2012	2014	
lung inflammation	2005	4.9	2014	2016	
alarmin	2005	5.46	2015	2017	
cd8 (+) t	2005	4.97	2016	2017	
metastasis	2005	5.82	2018	2021	
poor prognosis	2005	5.01	2018	2019	
progression	2005	4.92	2018	2021	
tuft cell	2005	4.67	2018	2021	
risk	2005	7.09	2019	2021	
health	2005	6.44	2019	2021	
role	2005	5.69	2019	2021	

these drugs have regulatory effects on IL-33 is derived mostly from observational studies or experimental animal data, and the extent to which these findings apply to humans remains unclear. Whether these drugs can be further developed as usable drugs to regulate IL-33 requires further research and clinical trial evaluation [44, 45].

Our study provides the first systematic analysis of IL-33-related publications and their trends. This can provide popular research directions and advanced research results for clinicians and scholars in this field. Simultaneously, we used multiple versions of bibliometric software to investigate research hotspots and obtain more comprehensive as well as multi-dimensional accurate data. However, this study has certain limitations. The selection of articles is inevitably biased because of the influence of language and academic level. The selected papers only included data from WoSCC, while

from other search engines (PubMed, Embase, and Ovid) were not considered. Although these limitations may have led to a slight deviation in the analysis, we attempted to ensure objectivity under given circumstances.

Conclusion

IL-33 is closely associated with allergic diseases. Studying its mechanism of action is crucial for the development off new drugs, and it represents a potential therapeutic target. Research on IL-33 has progressed from laboratory tests to clinical trials. Future studies should pay more attention to human IL-33-related receptors and IL-33 release mechanisms, rather than animal disease models. The development of IL-33 monoclonal antibody drugs is accelerating, and clinical trials are exploring both from single disease therapeutics as well as multiple diseases therapeutics. The emergence of monoclonal antibodies has accelerated the application of precision therapy. The multi-target therapeutic effect of monoclonal antibodies remains the focus of subsequent development, and the interaction between two or more different monoclonal antibodies should also be considered in future research.

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Disclosure of conflict of interest

None.

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