Analysis of the evolutionary path and hotspots of innate lymphoid cells based on a knowledge map

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To the Editor: Innate lymphoid cells (ILCs) are a heterogeneous population of lymphocytes that lack specific antigen receptors and yet produce effective cytokines to match the T helper cell subsets.[1] For the past decade, the discovery of these cells and research on this topic have revealed that ILCs are tissue resident cells that have multiple immune roles, such as regulating tissue inflammation, tissue remodeling and metabolic homeostasis, by the effector functions of their subsets and are involved in diseases such as asthma, allergic rhinitis, inflammatory bowel disease, and cancer. Various publications have sorted and summarized the research results in this field, but these reports were descriptive literature reviews and qualitative taxonomic research that cannot fully and objectively reflect the whole picture of ILC research. The purpose of this study to evaluate the development of ILC and explore the future prospects of this research by examining the evolutionary path of hotspots and the distribution of time and geographic region in ILC research.

Bibliometrics is a method to reveal research hotspots and predict future research trends by using knowledge map tools such as CiteSpace, Histcite, and VOSviewer.[2] Therefore, we performed a knowledge map analysis on studies of ILCs published between 2010 and 2019 by CiteSpace V 5.0.R1 SC (Drexel University, Philadelphia, PA, USA). Data were obtained from the Science Citation Index Expanded database of the "Web of Science Core Collection" on August 3, 2019, the search terms were used as follows:= ("innate lymphoid cells") OR= ("natural helper cells") OR = ("nuocytes") OR = ("innate type 2 helper") OR = ("multipotent progenitor type 2") OR= ("IH2 cells") OR = ("mpptype2") OR = ("natural killer 22 cells") OR = ("natural cytotoxicity receptor 22 cells"). Since the nomenclature of ILCs was proposed in 2013, many different names have been used for ILCs and can be found in a search query. The timespan was set between 2010 and 2019, and the document type was set to "article" and "reviews." The search resulted in 3083 papers that met the inclusion criteria.

From 2010 to 2019, 3083 documents related to ILC research were published, and a vast increase in publications occurred, from 12 in 2010 to 660 in 2018. The research on ILCs has rapidly improved since 2014, with 2784 papers published between 2014 and 2019, which was approximately 90.3% of the total over the past 10 years, and the cumulative publication rate also grew rapidly. Only 12 articles were published in 2010, and a large increase in annual output was seen thereafter, demonstrating that ILC research attracted interest and grew rapidly over the past decade.

Figure 1A shows the co-author network knowledge map on the research of ILCs, which describes the co-author relationship among researchers in the field of emerging ILC trends. Andrew N.J. McKenzie ranks first, with 58 articles, followed by David Artis (52 papers), Marco Colonna (37 papers), and Eric Vivier (34 papers). There are collaborative groups of various sizes, most of which are interconnected but not that close. Therefore, academic exchange and research cooperation should be further enhanced in the field of ILCs.

The spatial distribution of the research on ILCs shows the number of published papers, the cooperation and the centrality of the top countries and institutions. There are mainly three clusters of groups published in the ILC field: the United States, France, and China. Based on the number of published papers, the United States (1333 articles), the United Kingdom (367 articles), and China (332 articles) strongly contributed to this field, accounting for 65.9% of the aggregate number of papers, followed by Germany, Japan, and France. Figure 1B reflects the top 50 institutions in the ILC research field. Institut Pasteur ranks first with 92 papers, followed by the Washington University, National Institute of Allergy and Infectious Diseases, Harvard Medical School, while the Chinese Academy of Science ranks 33rd with 26 papers. Many institutions originating from the United States have co-operative relationships with

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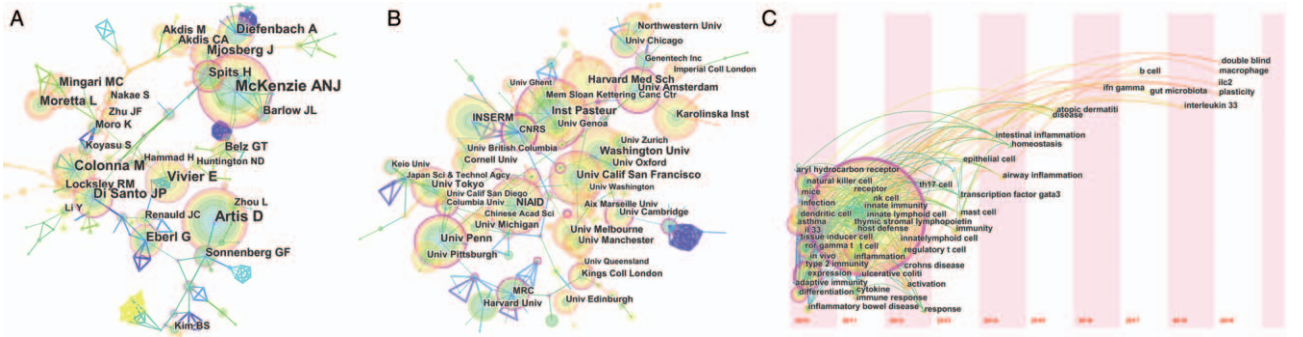

Figure 1: Co-author network in ILC research (A); institutional collaboration network (B); the timeline map of ILC research (C). ILC: Innate lymphoid cells.

different countries, which shows the strong research potential and academic exchange awareness in the research field in ILCs. This result may explain why the United States had the highest research output.

Figure 1C shows the time trend of hot keywords in the research on ILCs for the last 10 years. These keywords were classified into three clusters: "immunity related," "cell biology related," and "disease related." In the immune-related part, the primary keywords were adaptive immunity (168 times), type 2 immunity (223 times) and immune response (174 times), dendritic cells (469 times), and T cells (427 times). In the cluster of cell biology, the top keywords were natural killer cell (594 times), ror gamma t (323 times), cytokines (338 times), and differentiation (315 times). For the disease-related cluster, the primary keywords were inflammation (574 times), asthma (379 times), inflammatory bowel disease (178 times), homeostasis (144 times), and cancer (66 times). Before 2014, in the early stage of ILC research, the most popular keywords were allergic airway inflammation, homeostasis, atopic dermatitis, adipose tissue, adaptive immunity, T helper cells, cytokines and dendritic cells, most of which are still hot topics to date, highlighting the importance of ILCs in inflammation, tissue homeostasis, repair, and metabolism. Some new keywords appeared later: cancer, eosinophil, B cell, macrophage, double blind, heterogeneity, phenotype, and plasticity, which provide insight into the disease mechanism and the cell biology of ILC research. ILCs display phenotypic and functional plasticity to respond to stimuli from the environment, and the plasticity of ILCs directs the heterogeneity of these cells in tissues, which might be important for effective immune responses and may play roles in immune diseases, especially in cancer.[3] For example, in the tumor microenvironment, the nature killer cells can convert into ILC1s to respond to transforming growth factor-β, which promotes tumor growth and metastasis.[4] Keywords such as eosinophils, B cells, and macrophages are immune cells that play important roles in the immune response with ILCs and induce different types of inflammation by secreting cytokines. These new keywords might be a promising research area in the future that reveals the potential application of basic studies of ILC biology, highlights the importance of transcriptional regulatory networks and the immune response of ILCs and helps to develop new treatments for patients with immune disease. In summary, research on ILCs has grown rapidly in the past decade. Research related to ILCs in inflammation, tissue homeostasis, repair, and metabolism is a hot topic, while research on cancer and transcriptional regulatory networks has recently become a new trend.

In conclusion, research on ILCs has grown rapidly in the last decade and will hopefully become a hot topic in immunology in the future. Andrew N.J. McKenzie, David Artis, Marco Colonna, and Eric Vivier are the major contributors in this field, and the co-operation of different collaborative groups should be reinforced. The United States published the majority of the papers through academic exchange and research communication with most of the countries. Institut Pasteur ranks first in the publishing output on ILCs among institutions worldwide. Research related to ILCs in inflammation, tissue homeostasis, repair, and metabolism is a hot topic, and topics related to cancer and transcriptional regulatory networks may be promising research areas in the future.

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Conflicts of interest

None.

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