A bibliometric analysis of the research on hematological tumor microenvironment

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Background: In recent years, the incidence of hematological tumors has increased. The tumor microenvironment (TME) is the local biological environment in the process of tumor occurrence and development and is closely related to hematological malignancies, including lymphoma and leukemia. This study aims to conduct a bibliometric analysis of the research on the hematological TME, reflect the general situation of the research in this field, and remind the focus of future research.

Methods: Search the Science Citation Index Expanded (SCI-E) database on the Web of Science Core Collection (WOSCC). Use subject terms to search tumor microenvironment; the limited search subject is Hematology, and the time range is from 1990 to July 18, 2021. Use CiteSpace software to analyze the number of annual papers published, the number of citations, the distribution of disciplines, the distribution of countries/institutions, the distribution of authors, the distribution of journals, and the frequency of use of keywords and its trend of change.

Results: There were 1,992 related research articles cited 77,213 times. The top 5 countries with the number of published papers in this field are: the United States, Italy, China, Germany, and the United Kingdom; the top 5 centrally ranked countries are the United States, Italy, Spain, France, and Japan. Literature and cooperation are mainly from the United States. The top three researchers with several published papers are Anderson KC, Ansell SM, and Gascoyne RD. Their centrality scores are all low, with only 5 researchers reaching above 0.01, and there is less collaboration between the authors. High-quality papers are from Blood, Cancer Res, P Natl Acad Sci USA, and Nature. Keyword analysis shows that immunotherapy is the current focus of research in this field.

Conclusions: The research on the microenvironment of hematological malignancies is rapidly developing. At present, the main research focus is on targeted immunotherapy.

Keywords: Hematological malignancies; tumor microenvironment (TME); bibliometrics; immunotherapy

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Introduction

In recent years, the incidence of hematological tumors has increased. Statistics show that the number of new cases of non-Hodgkin’s lymphoma, Hodgkin’s lymphoma, and leukemia in 2002 were 300,571, 62,329, and 300,522, respectively. In 2018, they were 758,314, 106,157, and 746,039, respectively. Almost all have doubled, and the number of deaths has also increased significantly (1,2). Analysis of the reasons is mainly related to the pollution of the living environment and the advancement of diagnostic technology (3,4). With the deepening of research, people have a richer understanding of the pathogenesis of hematological malignancies. Ioannides and Whiteside first proposed the tumor microenvironment (TME). It is defined as the local biological environment in the process of tumorigenesis and development, which can provide a scaffold and barrier for the growth of tumor cells and generate immune exempt areas, providing tumors with a “culture base” (5). With the deepening of research on TME, the oncology community is paying increased attention to the role of TME in tumorigenesis and development (6,7). TME mainly plays an important role in three aspects: the most direct role is to provide a growth environment for tumors; certain components in TME can weaken the therapeutic effect of anti-tumor drugs; the local immune response is immunosuppressive, helping tumor cells escape immune surveillance (6,8). Studies have shown that TME is closely related to hematological malignancies, including lymphoma and leukemia (9,10). Generally, hematological TME consists of cells including tumor-associated macrophages, follicular dendritic cells, fibroblastic reticular cells and endothelial cells (11). Bibliometrics is a method of indirect research on developing a certain field that has emerged in recent years. Compared with reviews, by analyzing most literatures on some theme, it can reflect the annual development and change trend of research in the field and the current research focus, especially to sort out important research and research institutions and researchers in this field (12,13). The research results of bibliometrics help researchers grasp this field’s development direction and avoid repeated research (14). A previous bibliometric analysis of TME in oral cancer provided an overview of the research status in oral oncology (15). This study conducts a bibliometric analysis of the research on the hematological TME, reflects the general situation of the research in hematology, and reminds the focus of future research.

Methods

Search objects

We searched the Science Citation Index Expanded (SCI-E) database on the Web of Science Core Collection (WOSCC). The database is the primary data source for bibliometrics research, which can provide subject retrieval and limit the research field, minimize invalid retrievals and make retrieval results more accurate (16).

Retrieval steps

First, use subject terms to search, the search term is tumor microenvironment; then, the search subject is limited to Hematology; the time range is from the earliest document time of the database to the last retrieval time of this research (July 18, 2021); finally, the search results are obtained.

Statistical and bibliometrics analysis

Export all records of the search results and cited references in plain text format, and use CiteSpace software to analyze the number of annual papers published, the number of citations, the distribution of disciplines, the distribution of countries/institutions, the distribution of authors, the distribution of journals, the frequency of use of keywords, and the trend of change is analyzed to reflect the research on the microenvironment of hematological malignancies. In this descriptive study, variables were expressed as numbers and percentages. No comparison was conducted; therefore, no P value was set.

Results

Retrieval results

There are 1,992 related research documents, including 1,211 original articles, 500 reviews, 240 meeting abstracts, 40 proceedings papers, 22 editorial materials, 19 book chapters, and 19 early access, 14 letters, 3 corrections, and 2 notes (Tables 1,2, Figure 1). The citation frequency is 77,213 times, the h-index count is 130, and the average number of citations per paper is 38.76 (Figure 2).

Distribution of countries and institutions

We use CiteSpace V software to analyze data and generate national visualization maps (Figure 3) and institutional
Table 1 Document type analysis

| Literatures           | Records | % of 1,992 |
|-----------------------|---------|------------|
| Original articles     | 1,211   | 60.8       |
| Reviews               | 500     | 25.1       |
| Meeting abstracts     | 240     | 12.0       |
| Proceedings papers    | 40      | 2.0        |
| Editorial materials   | 22      | 1.1        |
| Book chapters         | 19      | 1.0        |
| Early access          | 19      | 1.0        |
| Letters               | 14      | 0.7        |
| Corrections           | 3       | 0.2        |
| Notes                 | 2       | 0.1        |

Table 2 Annual distribution of the number of papers in the past 20 years

| Years | Records | % of 1,992 |
|-------|---------|------------|
| 2021  | 44      | 2.2        |
| 2020  | 200     | 10.0       |
| 2019  | 183     | 9.2        |
| 2018  | 156     | 7.8        |
| 2017  | 181     | 9.1        |
| 2016  | 145     | 7.3        |
| 2015  | 123     | 6.2        |
| 2014  | 115     | 5.8        |
| 2013  | 100     | 5.0        |
| 2012  | 91      | 4.6        |
| 2011  | 113     | 5.7        |
| 2010  | 86      | 4.3        |
| 2009  | 80      | 4.0        |
| 2008  | 65      | 3.3        |
| 2007  | 48      | 2.4        |
| 2006  | 37      | 1.9        |
| 2005  | 38      | 1.9        |
| 2004  | 32      | 1.6        |
| 2003  | 25      | 1.3        |
| 2002  | 17      | 0.9        |

visualization maps (Figure 4). The results show the top 5 countries for the number of papers published in this field are the United States, Italy, China, Germany, and the United Kingdom; the top 5 centrally ranked countries are the United States, Italy, Germany, Spain, and France (Tables 3,4). The results suggest that the United States is in a leading position in research in this field. The institutional analysis also shows that institutions that have published many papers and those with more collaborations are also mainly from the United States (Tables 5,6, Figure 4).

Authors

The top three researchers with the number of papers published in this field are Anderson KC, Ansell SM, and Gascoyne RD. However, the centrality scores are all low, and only 5 researchers who reach over 0.01 are: Gascoyne RD, Anderson KC, Gribben JG, Steidl C, and Wilcox RA indicate that although some authors have published more papers, there is less collaboration among authors (Tables 7,8, Figure 5). In terms of paper citations, the top three authors of citations are Burger JA, Hideshima T, and Steidl C, but the top three co-cited centralities (the third had two authors) are Anderson KC, Simmons PJ, Gabriilovich DI, and Bataille R (Tables 9,10), and most of these authors are from the United States. The author's co-cited visualization map (Figure 6) shows that the authors have more intensive mutual citations, reflecting that the main research results in this field are concentrated on these authors.

Journals distribution

Of the 1,992 articles from 184 journals, 22 journals have published over 20 articles, accounting for 1,676 articles, 84.1% of the total literature (Table 11). Regarding the number of published papers, related papers are concentrated in hematology professional journals (Table 11). However, in terms of the number of citations or centrality (Tables 12,13), high-quality papers are still concentrated in authoritative journals, including Blood, Cancer Res, P Natl Acad Sci USA, and Nature (Table 12).

Keywords analysis

We used CiteSpace V software to generate a keyword
Figure 1 Annual changes in the number of papers published.

Figure 2 Annual changes of the citation frequency.

Figure 3 A visual map of countries.
Figure 4 Visualization map of institutions.

| Rank | Countries  | Records |
|------|------------|---------|
| 1    | USA        | 864     |
| 2    | Italy      | 221     |
| 3    | China      | 185     |
| 4    | Germany    | 175     |
| 5    | England    | 140     |
| 6    | France     | 123     |
| 7    | Canada     | 98      |
| 8    | Japan      | 92      |
| 9    | Spain      | 75      |
| 10   | Australia  | 61      |

Table 3 Top 10 countries in terms of publication

| Rank | Countries | Centrality |
|------|-----------|------------|
| 1    | USA       | 0.82       |
| 2    | Italy     | 0.39       |
| 3    | Germany   | 0.15       |
| 4    | Spain     | 0.14       |
| 5    | France    | 0.13       |
| 6    | Japan     | 0.10       |
| 7    | Australia | 0.10       |
| 8    | England   | 0.09       |
| 9    | Canada    | 0.07       |
| 10   | Netherlands | 0.05     |
Table 5 Top 10 institutions in terms of number of papers published

| Rank | Institutions                              | Records |
|------|-------------------------------------------|---------|
| 1    | Mayo Clin                                 | 70      |
| 2    | Dana Farber Canc Inst                     | 69      |
| 3    | Univ Texas MD Anderson Canc Ctr           | 67      |
| 4    | Harvard Univ                              | 62      |
| 5    | Harvard Med Sch                           | 36      |
| 6    | NCI                                       | 34      |
| 7    | Karolinska Inst                           | 31      |
| 8    | Massachusetts Gen Hosp                    | 16      |
| 9    | Mem Sloan Kettering Canc Ctr              | 15      |
| 10   | British Columbia Canc Agency              | 15      |

Table 6 Top 10 institutions in terms of centrality

| Rank | Institutions                       | Centrality |
|------|------------------------------------|------------|
| 1    | Dana Farber Canc Inst              | 0.16       |
| 2    | Mayo Clin                          | 0.14       |
| 3    | NCI                                | 0.11       |
| 4    | Univ Texas MD Anderson Canc Ctr    | 0.07       |
| 5    | Harvard Univ                       | 0.05       |
| 6    | Harvard Med Sch                    | 0.05       |
| 7    | German Canc Res Ctr                | 0.04       |
| 8    | Columbia Univ                      | 0.04       |
| 9    | Karolinska Inst                    | 0.03       |
| 10   | British Columbia Canc Agency       | 0.03       |

Table 7 Top 5 authors in the number of papers published

| Rank | Authors           | Records |
|------|-------------------|---------|
| 1    | Anderson KC       | 34      |
| 2    | Ansell SM         | 25      |
| 3    | Gascoyne RD       | 16      |
| 4    | Steidl C          | 15      |
| 5    | Richardson PG     | 15      |

Table 8 Top 5 authors of centrality

| Rank | Authors         | Centrality |
|------|-----------------|------------|
| 1    | Gascoyne RD     | 0.02       |
| 2    | Anderson KC     | 0.01       |
| 3    | Gribben JG      | 0.01       |
| 4    | Steidl C        | 0.01       |
| 5    | Wilcox RA       | 0.01       |

co-occurrence map (Figure 7). The top 10 keywords in terms of frequency of use and centrality are listed in Tables 14 and 15. For keywords with high frequency, we use CiteSpace to perform burst detection on keywords (Figure 8). We can observe the transformation of colony stimulus factors, growth factors, cytokines, tumor necrosis factors at the beginning into currently commonly used drugs, immunotherapy. This reflects the gradual transformation of research in this field, from the initial analysis of microenvironmental components to immunotherapy. It is also a typical process of medical research, the evolution from potential mechanism research to clinical intervention.

Discussion

This study analyzed the microenvironmental research literature related to hematological malignancies and found that the research in this field is concentrated in several large medical research institutions in the United States. Although researchers often quote documents from each other, the cooperation between them is few. Most papers are published in professional journals on the blood system, and high-level research is published in authoritative, comprehensive journals. Keyword analysis shows that current research focuses on tumor immunotherapy. Taken together these findings, we provided an overview of studies on hematological TME.

Many molecular therapeutic targets for hematological malignancies have been discovered with the deepening of molecular biology research and technological advancement (9,17-20). The drugs developed in this way delay the progression of the disease to a significant extent and significantly improve the patient’s disease-free survival (DFS) and quality of life (21-23). However, some authors believe it has not helped complete the eradication of tumors (9). However, several recent studies have shown that targeted therapy based on the TME can significantly improve DFS (23,24). This study shows that the research in this field has experienced a typical process, from primary
to clinical. Initially, it was mainly experimental research to deeply analyze the expression characteristics and mechanism of various factors in the microenvironment of tumor cells (25), changes in matrix composition in the bone marrow and other tissues (26). It gradually shifts to the relationship between the specific tumor and the microenvironment (27) until the vital research of immunotherapy in recent years (28). Of course, researchers are still deeply studying the relationship between numerous factors and cells in the TME and lymphoma, leukemia, and myeloma. Related research results are also published continuously, but these studies have been accumulated for a long time in the early stage. Further exploration based on work also explains why most research is concentrated on a few medical research institutions in the United States.

The real rapid development of TME research was in the 1970s. New biomedical research technologies continued to appear, which technically solved the research difficulties. For example, Folkman et al. discovered factors closely related to tumor angiogenesis (29). Researchers have gradually realized that inhibiting angiogenesis can effectively treat cancer, and subsequently, the vascular endothelial growth factor has gradually become an effective target for cancer treatment (30). Based on this, related drugs have been developed and used clinically (31,32). Therefore, more and more studies have confirmed that cell composition, various factors, and local physical properties in the TME all play a direct role in the efficacy of anti-tumor therapy (33). After over 50 years of continuous efforts, many research results of the TME have been continuously transformed into clinical treatment of tumors, and a large number of satisfactory results have been achieved (8).
Table 9 The top 10 most cited authors

| Rank | Authors     | Citations |
|------|-------------|-----------|
| 1    | Burger JA   | 139       |
| 2    | Hideshima T | 123       |
| 3    | Steidl C    | 122       |
| 4    | Hanahan D   | 119       |
| 5    | Ansell SM   | 109       |
| 6    | Dave SS     | 101       |
| 7    | Swerdlow SH | 88        |
| 8    | Mantovani A | 84        |
| 9    | Green MR    | 79        |
| 10   | Chauhan D   | 76        |

Table 10 Top 10 authors of centrality in co-citation

| Rank | Authors          | Centrality |
|------|------------------|------------|
| 1    | Anderson KC      | 0.29       |
| 2    | Simmons PJ       | 0.26       |
| 3    | Gabrilovich DI   | 0.21       |
| 4    | Bataille R       | 0.21       |
| 5    | Abboud SL        | 0.20       |
| 6    | Hideshima T      | 0.12       |
| 7    | Steidl C         | 0.12       |
| 8    | Ribatti D        | 0.12       |
| 9    | Broxmeyer HE     | 0.12       |
| 10   | Liesveld JL      | 0.12       |

Figure 6 The author’s co-cited visualization map.
Table 11  Top 22 journals by publications

| Rank | Journals                               | Papers | Percentage |
|------|----------------------------------------|--------|------------|
| 1    | Blood                                  | 457    | 22.9       |
| 2    | Leukemia                               | 133    | 6.7        |
| 3    | Leukemia Lymphoma                      | 125    | 6.3        |
| 4    | Journal of Leukocyte Biology           | 116    | 5.8        |
| 5    | Journal of Hematology Oncology         | 107    | 5.4        |
| 6    | British Journal of Haematology         | 103    | 5.2        |
| 7    | Haematologica                          | 94     | 4.7        |
| 8    | Stem Cells                             | 89     | 4.5        |
| 9    | Critical Reviews in Oncology Hematology| 81     | 4.1        |
| 10   | Experimental Hematology                | 41     | 2.1        |
| 11   | Clinical Lymphoma Myeloma Leukemia     | 40     | 2.0        |
| 12   | Leukemia Research                      | 39     | 2.0        |
| 13   | Blood Advances                         | 31     | 1.6        |
| 14   | Stem Cells and Development             | 31     | 1.6        |
| 15   | Pediatric Blood Cancer                 | 30     | 1.5        |
| 16   | Blood Cancer Journal                   | 27     | 1.4        |
| 17   | Cytotherapy                            | 24     | 1.2        |
| 18   | International Journal of Hematology    | 24     | 1.2        |
| 19   | Annals of Hematology                   | 22     | 1.1        |
| 20   | American Journal of Hematology         | 21     | 1.1        |
| 21   | Current Opinion in Hematology          | 21     | 1.1        |
| 22   | Hematological Oncology                 | 20     | 1.0        |

Table 12  Top 10 journals cited

| Rank | Journals   | Citations |
|------|------------|-----------|
| 1    | Blood      | 1,510     |
| 2    | Cancer Res | 1,176     |
| 3    | P Natl Acad Sci USA | 1,092   |
| 4    | Nature     | 1,011     |
| 5    | Clin Cancer Res | 970     |
| 6    | New Engl J Med | 913     |
| 7    | J Immunol  | 882       |
| 8    | Leukemia   | 874       |
| 9    | J Clin Invest | 856    |
| 10   | J Clin Oncol | 842     |

Table 13  Top 10 journals of centrality in citation

| Rank | Journals            | Centrality |
|------|---------------------|------------|
| 1    | Biochem Bioph Res Co | 0.08      |
| 2    | Brit J Cancer       | 0.07      |
| 3    | J Cell Physiol      | 0.07      |
| 4    | Int J Cancer        | 0.06      |
| 5    | Carcinogenesis      | 0.06      |
| 6    | J Clin Invest       | 0.05      |
| 7    | Embo J              | 0.05      |
| 8    | Nat Cell Biol       | 0.05      |
| 9    | J Cell Biol         | 0.05      |
| 10   | J Immunother        | 0.05      |
Figure 7 Keyword co-occurrence map. Identified in the figure are keywords that often appear together.

| Table 14 Top 10 most used keywords | Table 15 Top 10 keywords for centrality |
|-----------------------------------|--------------------------------------|
| Rank | Keywords | Frequency | Rank | Keywords | Centrality |
|------|----------|-----------|------|----------|------------|
| 1    | expression | 383       | 1    | microenvironment | 0.17 |
| 2    | microenvironment | 325       | 2    | expression | 0.16 |
| 3    | cancer   | 245       | 3    | bone marrow | 0.12 |
| 4    | tumor microenvironment | 216      | 4    | cell       | 0.09 |
| 5    | multiple myeloma | 203      | 5    | cytokine   | 0.09 |
| 6    | survival | 192       | 6    | cancer     | 0.08 |
| 7    | bone marrow | 159      | 7    | colony stimulating factor | 0.07 |
| 8    | t cell   | 153       | 8    | survival   | 0.06 |
| 9    | activation | 153      | 9    | in vitro   | 0.06 |
| 10   | in vitro | 134       | 10   | apoptosis  | 0.06 |
Compared with other TME studies, the microenvironment research of hematological malignancies has been carried out a little later. However, according to our analysis results, it can be seen that in this field, the process of transformation from basic to clinical is faster. However, as mentioned earlier, related research is concentrated on the United States, and there is little cooperation. This makes it necessary to be more cautious in promoting related research results to various people. Future research can appropriately observe different regions and races (34). Besides, we suggest more research to be carried out on the effect of PD-1/L1 inhibitor or CAR-T therapy on TME.

**The limitations of this study**

The search literature of this study is limited to “hematology”, and a small amount of related literature may be missed. However, this study only discusses hematological malignancies. Therefore, for the mechanism studies that may be missed in this part, researchers can search for related papers by other methods to further understand.

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**Footnote**

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-3924). The authors have no conflicts of interest to declare.

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