Original Article

WTAP-mediated abnormal m6A modification promotes cancer progression by remodeling the tumor microenvironment: bibliometric and database analyses

Yumeng Du[1], Lihua Huang[2], Mao Long[3], Xin Wu[1], Jinglei Miao[1]

[1]Department of Spine Surgery, Third Xiangya Hospital, Central South University, Changsha, China; [2]Center for Experimental Medicine, Third Xiangya Hospital, Central South University, Changsha, China; [3]Department of Renal Medicine, Third Xiangya Hospital, Central South University, Changsha, China

Contributions: (I) Conception and design: Y Du, X Wu; (II) Administrative support: J Miao; (III) Provision of study materials or patients: Y Du, L Huang; (IV) Collection and assembly of data: Y Du, M Long; (V) Data analysis and interpretation: Y Du, X Wu, J Miao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jinglei Miao, MD, PhD; Xin Wu, MD, PhD. Department of Spine Surgery, Third Xiangya Hospital, Central South University, Tongzipo Road, Yinpenling Street, Changsha 410013, China. Email: miaojinglei@126.com; xinwudrxinwu@163.com.

Background: Wilms' tumor 1 associated protein (WTAP) is an essential component of the m6A methyltransferase complex. The research on WTAP has been continuously developed and promoted in recent years. It is needed to make systematic specific bibliometric and database analyses on WTAP, to identify the cooperation and impact of authors, countries, institutions and journals, to evaluate the knowledge base and find the hotspot trends, and to detect the emerging topics regarding WTAP research.

Methods: The related articles and reviews of WTAP in the Web of Science Core Collection from January 1999 to June 2022 were retrieved, and CiteSpace and VOSviewer were used to perform bibliometric and knowledge-map analyses. Multiple databases were used to explore the expression level of WTAP in pan-cancers and its correlation with prognosis and immune infiltration.

Results: In recent years, the number of publications on WTAP research has increased rapidly. Among the journals publishing WTAP research, *Frontiers in Cell and Developmental Biology* had the most papers, while Nature papers were most cited. The country with the highest number of publications on WTAP was China, and China Medical University was the institution with the most publications. The most prominent author was Haruo Sugiyama from Japan. Four main aspects of WTAP research included m^6A modification, tumor association, cancer therapy, and regulatory mechanisms. The research frontiers and hotspots were m^6A modification, methyltransferase, demethylation, tumor microenvironment (TME), and immunotherapy. Bioinformatics analysis showed that the expression of WTAP was up-regulated in a variety of tumors and closely related to TME and survival prognosis.

Conclusions: From the bibliometric and database analyses on the researches on WTAP, it is suggested that up-regulated WTAP in cancers may promote cancer progression by mediating abnormal m^6A modifications to reshape the TME, thereby affecting the survival prognosis of the patients. The information would provide helpful references for scholars focusing on WTAP and provide new insights for WTAP as a prognostic evaluation and immunotherapy for tumors in the future.

Keywords: Wilms' tumor 1 associated protein (WTAP); m^6A; bibliometrics; tumor microenvironment (TME); immune infiltration

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Introduction

Wilms' tumor 1 associated protein (WTAP) is a protein that interacts with the Wilms' tumor 1 (WT1) protein identified in yeast two-hybrid screening, and its gene is located on human chromosome 6q25-27 (1). m^6A modification is a process in which methyltransferase catalyzes the methylation of adenine at the N6 position, which is the most abundant epigenetic modification in eukaryotic mRNA (2) and is involved in many vital processes such as the growth and development of mammals and the occurrence and development of diseases (3). Bokar *et al.* discovered that the methyltransferase complex could catalyze the formation of m^6A in 1994 (4), and the methyltransferase METTL3 was found in 1997 (5). In 2014, Ping *et al.* first identified WTAP as a critical component of the mammalian m^6A methyltransferase complex (6). Since then, the research field of methyltransferase and m^6A modification has been opened and has attracted the interest of many researchers. As an essential regulatory subunit for methyltransferase activity, WTAP plays a crucial role in the occurrence and development of many diseases by regulating m^6A modification (6). In particular, WTAP expression is upregulated in most tumor cells and is associated with poor prognosis. Mechanistically, WTAP mainly affects the expression level of m^6A on the mRNA of target genes, thus regulating the expression of target genes and activating or inhibiting related pathways to affect tumor progression (7). It is worth noting that WTAP-mediated changes in m^6A expression levels showed different regulatory results in different target genes, the molecular mechanism of which requires further study. In addition, WTAP also plays an alternative splicing function to regulate the gene transcription process, which directly or indirectly affects embryonic development (8). The current studies on the mechanism of WTAP-mediated m^6A in different tumors and its biological function, as well as the clinical protocols of WTAP as a potential therapeutic target are of great significance. In recent years, the research interest in m^6A modification has remained high, and the number of relevant papers continues to surge yearly. As a critical protein involved in m^6A modification, WTAP has also received extensive attention from scholars around the world. Comprehensive bibliometric and database analyses of the WTAP research area are needed thereby.

m^6A is the most abundant RNA modification in eukaryotes, and in recent years, more and more evidence has proved that m^6A modification plays an important role in the pathogenesis of tumors such as glioblastoma, hepatocellular carcinoma, renal cell carcinoma, breast cancer, and acute myeloid leukemia, etc. (9-11). m^6A promotes or suppresses tumor cells mainly by regulating the expression of mRNAs of relevant oncogenes or tumor suppressor genes, and the level of expression often directly determines the pathology of tumors. m^6A methylation modification is a double-edged sword. The level of m^6A methylation modification is a double-edged sword, and over-modification or reduction of the modification level may lead to tumor development and progression (12,13). Therefore, the study of m^6A-regulated genes in different cancers and the identification of key m^6A target genes are of great significance to the understanding of cancer pathogenesis and the development of individualized therapeutic plans.

The tumor microenvironment (TME) plays a crucial role in tumor development. It comprises cellular components and an extracellular matrix, in which infiltrating immune cells account for a large proportion (14). Commonly, immune cells recognize and eliminate abnormal tumor cells (15). However, tumor cells can inhibit the anti-tumor effect of the human immune system in various ways to survive and grow (16). The infiltrating immune cells and stromal cells in the TME are associated with angiogenesis, chemotherapy resistance, immunosuppression, and tumor cell migration (17,18). Previous studies have shown that the role of m^6A methylation in TME is not negligible, and m^6A methylation in tumor cells will affect the infiltration, activation, and efficacy of immune cells in TME, and promote the formation of TME and cellular adaptation (19).

Highlight box

Key findings

- Wilms' tumor 1 associated protein (WTAP)-mediated abnormal m^6A modification promotes cancer progression by remodeling the tumor microenvironment.

What is known and what is new?

- The role of m^6A methylation in tumor microenvironment (TME) is not negligible, and m6A methylation in tumor cells will affect the infiltration, activation, and efficacy of immune cells in TME.
- The abnormal modification of m6A mediated by WTAP can affect cancer occurrence, development, and metastasis by reshaping TME.

What is the implication, and what should change now?

- This study would provide helpful references for scholars focusing on WTAP and provide new insights for WTAP as a prognostic evaluation and immunotherapy for tumors in the future.

TME also plays a crucial role in the complex regulatory network of m^{6}A modification. TME can affect the expression of related regulatory factors of m^{6}A modification through hypoxia-inducible factors (HIFs) and other factors, thereby changing the abundance of m^{6}A. In short, m^{6}A and TME are mutually induced and regulated in tumor occurrence and development, both complementing each other and supplementing mutually (20).

Bibliometrics is an interdisciplinary subject that uses mathematical and statistical methods to quantitatively analyze and study the distribution structure, quantitative relationship, and development law of literature with the literature system and bibliometric characteristics as the research object (21). Bibliometric techniques can offer a convenient way to visibly measure researchers' efforts in the investigation of a specific field. With the help of VOSviewer1.6.18 and Citespace5.8R3, we conducted bibliometric analysis on WTAP research, quickly obtained important information from massive data, constructed a visual knowledge map, summarized the research hotspots and development trends in this research field, and looked for new topics and directions (22,23). We also extracted the data of WTAP expression in pan-cancers from the online databases, and analyzed its relationship with survival prognosis of the patients.

Methods

Data collection

The Web of Science Core Collection (WoSCC) database is considered the most influential database, and we chose it because it can provide comprehensive information bibliometric software needs (24). We conducted data retrieval in the WoSCC database. The retrieval time was from the beginning of the database to 6 June 2022. WTAP and its MESH words were used as search terms, the literature types were Article and Review, and the language was limited to English. The search results were deduplicated, and non-representative articles such as conference calls, news, and reviews were deleted. The downloadable search results record reads "Full Record and Cited References". By 6 June 2022, 691 articles were finally selected from the database, including 636 articles and 55 reviews. In addition, we obtained the gene data of various tumors and normal tissues from TCGA and GTEx databases, and performed pan-cancer analysis and immunoassay for WTAP using the Sangerbox 3.0 online tool. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data analysis and visualization

There is currently much auxiliary software for bibliometric analysis, including VOSviewer, CiteSpace, SCI2, NetDraw, HistCite, etc. (25-28). Comparing the characteristics and advantages of each software, we used VOSviewer and CiteSpace to conduct bibliometric analysis and draw the knowledge map (27,29,30). We imported the "download_*.txt" file into CiteSpace 5.8.R3 and selected "Data" to remove duplicated studies. The time span was set as 1999–2022.06 and years per slice. Keywords were merged with the same meaning in the exported data and meaningless keywords were removed. The author keywords were used in VOSviewer1.6.18 for keyword co-occurrence analysis, and the counting methods were all fractional counts (31). Thresholds (T) of items were set based on different situations, which were marked in corresponding tables and figures. Microsoft Office Excel 2019 is used to draw a three-line chart of keywords and co-cited references. Besides, the 2020 journal impact factor (IF) and JCR were obtained from the Web of Science.

Results

Annual growth trend of the papers on WTAP research

A total of 691 articles were included, including 636 articles and 55 reviews. As can be seen from *Figure 1A*, since 1999, the annual publication volume and citation frequency of WTAP-related research in journals showed a steady upward trend, especially in the four years from 2017 to 2021, which almost showed a fold surge. *Figure 1B* is the annual publication volume trend chart of each country drawn on the bibliometrics online analysis platform, which can more intuitively show the differences in publication volume of different countries at different time points. Colors in the figure represent different countries, among which China, represented by blue, is the country with the most significant number of publications and the fastest trend growth in recent years.

Countries/regions and institutions in WTAP research

The top five countries in the number of WTAP research papers were China (n=288), the United States (n=191),

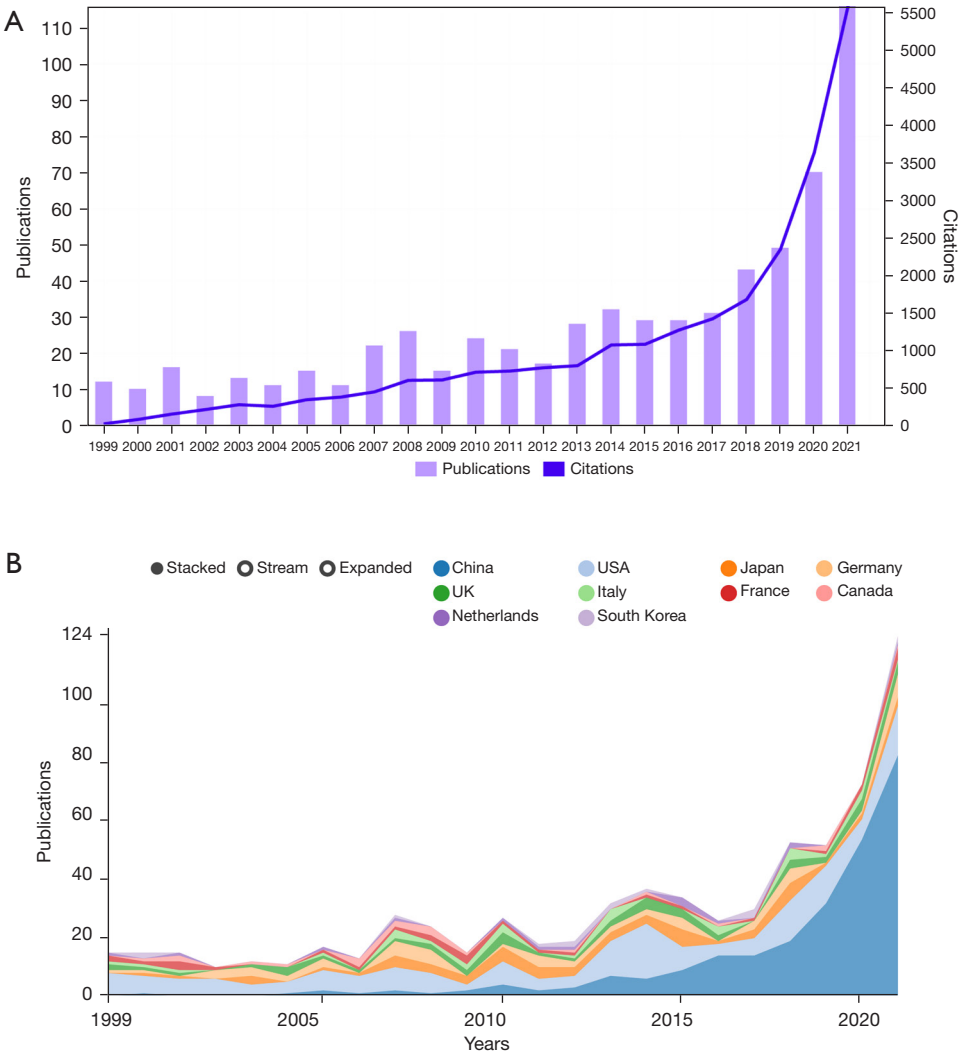


Figure 1 Growth trend of the papers on WTAP research. (A) Annual publication number and citation frequency of WTAP-related research. (B) The composition ratio of the top 10 countries by the publication number, with different colors representing different countries. WTAP, Wilms' tumor 1 associated protein.

Japan (n=58), Germany (n=55) and the United Kingdom (n=40). China had the largest number of documents, accounting for about 41.68%, but the betweenness centrality is only 0.05, while that of the United States (0.4) is the highest among all countries. Betweenness centrality (≥0.10) is usually regarded as the important turning point that may lead to transformative discoveries and acts as a bridge (32). *Figure 2A* contains 49 nodes and 164 links, with a density of 0.1395, indicating active collaborations among different countries/regions.

The top 10 institutions with the most significant number of articles include 8 from China, 1 from Japan and 1 from the United States. Among them, China Medical University is the institution with the most significant number of articles (n=19), accounting for about 2.75% of the total, followed by Zhejiang University in China (n=18), University of the Chinese Academy of Sciences (n=16), Zhengzhou University (n=15), and Osaka University in Japan (n=14). Close cooperation between different institutions can be observed (*Figure 2B*).

Journals and co-cited journals publishing WTAP research

VOSviewer was used for visual analysis of journals and

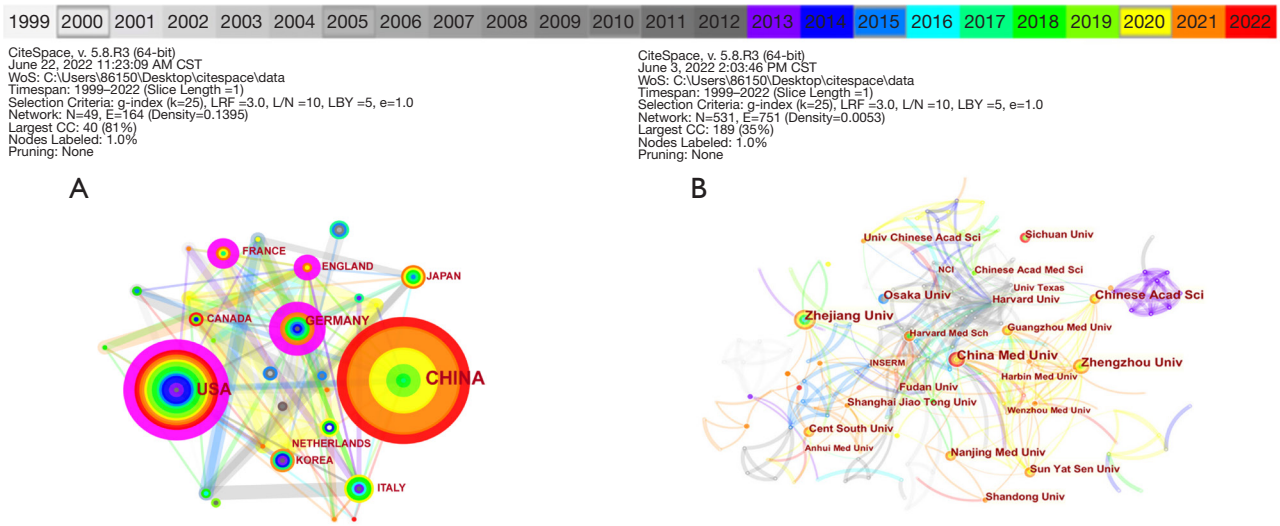


Figure 2 The co-occurrence map of countries/regions (A) and institutions (B) in WTAP research. The node's size reflects the co-occurrence frequencies, and the links indicate the co-occurrence relationships. The color of the node and line represent different years. Colors vary from gray to red as time goes from 1999 to 2022, and a node with a purple round means high betweenness centrality (>0.1). WTAP, Wilms' tumor 1 associated protein.

co-cited journals which published the WTAP research. Among the 371 academic journals, *Frontiers in Cell and Developmental Biology* was the journal with the most significant number of articles (n=11), followed by *Journal of the American Society of Neurology* (n=10), *Frontiers in Oncology* (n=9), *Journal of Biological Chemistry* (n=9), and *Human Molecular Genetics* (n=9). Five of the top 10 journals were in Q1, the IFs of 9 journals were above 5, and most of them were from the United States (n=4) and the United Kingdom (n=3). These journals were the most influential core journals in the field of WTAP research.

Among the 2,933 co-cited journals, 10 journals had citations over 496. *Nature* had the most co-citations (n=1,256, 5.55%), followed by *Cell*, *Journal of Biological Chemistry*, and *Proc Natl Acad Sci USA*. Among the top 10 co-cited Journals, 9 were distributed in Q1, and IFs of 8 journals were more than 10, all from the United States (n=7) and the United Kingdom (n=3).

The dual-map overlay of journals stands for the topic distribution of academic journals (33), and that of WTAP papers is shown in *Figure 3*. The citing journals were located on the left, the cited journals were on the right, and the colored paths indicated the citation relationships. The diagram mainly includes an orange and green citation path. The orange course suggests that the articles published in Molecular/Biology/Genetics were cited primarily by the articles published in Molecular/Biology/Immunology. The green path indicates that articles published in Molecular/Biology/Genetics were mainly cited by papers published in Medicine/Medical/Clinical.

Authors in WTAP research

Haruo Sugiyama was the author with the most significant number of papers in the WTAP research field (n=17), followed by Yusuke Oji (n=12) and Yoshihiro Oka (n=11). Although the number of He Chuan publications was only five, the total citation times were as high as 2020. A total of 4,771 authors participated in the study. The author cooperation network diagram is constructed with the authors who have published at least three papers (*Figure 4*), the same color represents the same cluster, and the cooperation among authors in the same collection is relatively close; some authors also have cooperative relationships in different groups, such as He Jing and Wang Jia Xiang, Nakajima Hiroko and Kyodo Shigeo.

Keyword co-occurrence, clusters, and evolution

Keywords can not only express the most core and essential part of an academic paper clearly and intuitively, but also have the functions of indexing, quick reading, and

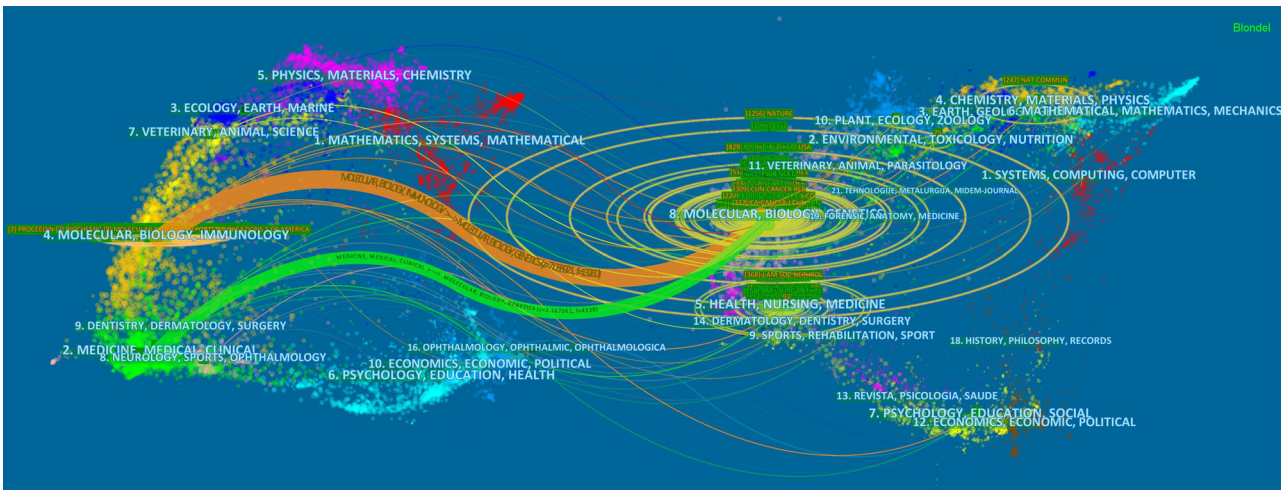


Figure 3 The dual-map overlay of journals related to WTAP research. The citing journals were on the left, the cited journals were on the right, and the colored path represents the citation relationship. WTAP, Wilms' tumor 1 associated protein.

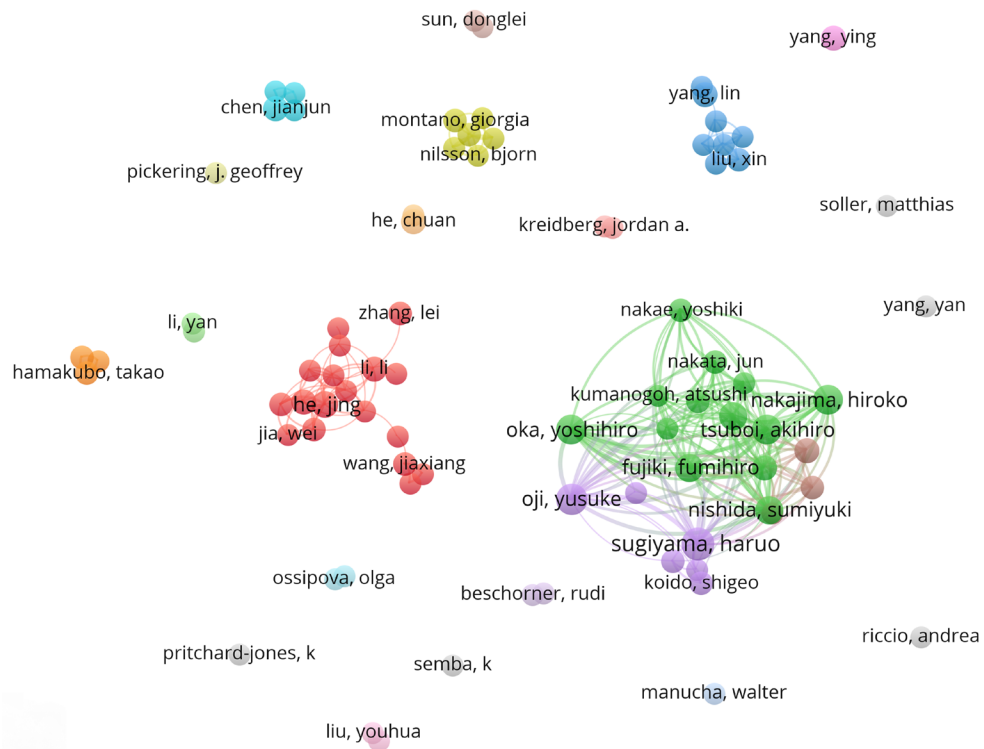


Figure 4 The co-occurrence map of authors in WTAP research (T≥3). The node size reflects the author's co-occurrence frequencies, the link indicates the co-occurrence relationship between authors, and the same node color represents the same cluster. WTAP, Wilms' tumor 1 associated protein.

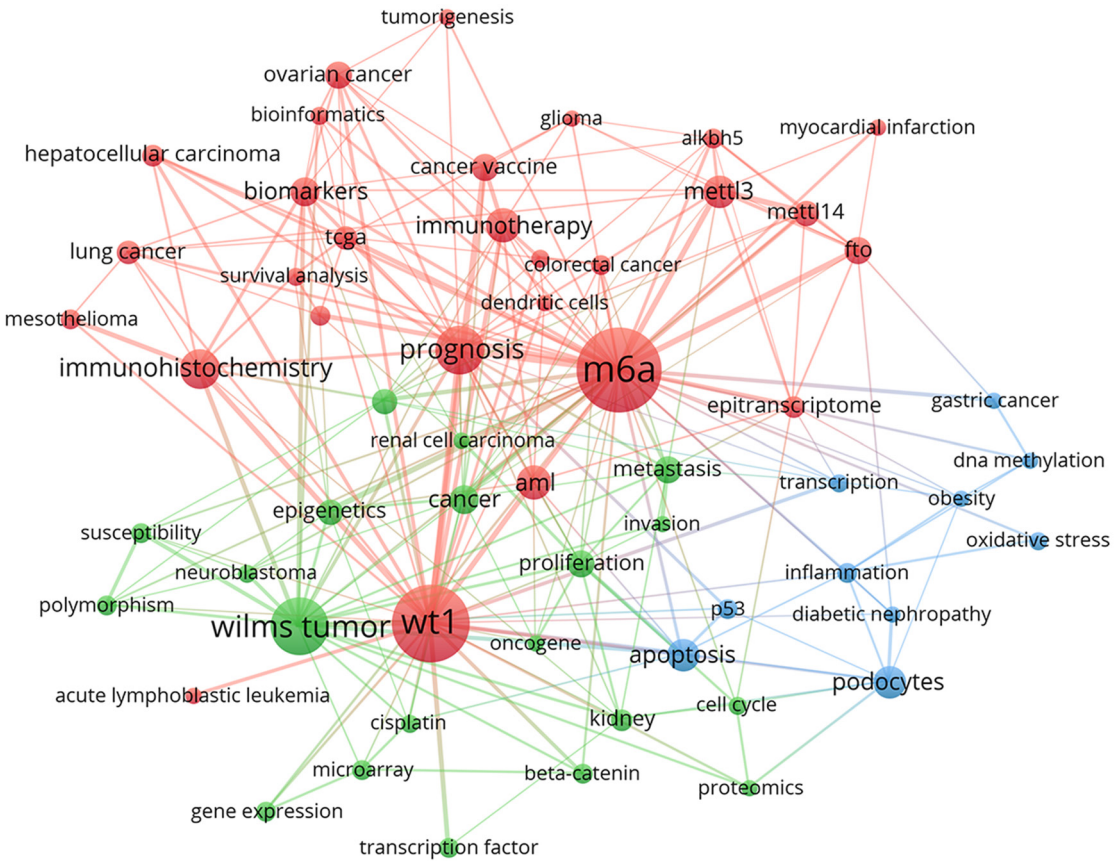


Figure 5 Terms co-occurrence network and clusters in WTAP research (T≥4). The size of the node and word reflects the co-occurrence frequencies, the link indicates the co-occurrence relationship, and the same color of the node represents the same cluster. WTAP, Wilms' tumor 1 associated protein.

highlighting the key points. VOSviewer was used to present the keyword co-occurrence and cluster analysis (*Figure 5*), replace and merge the synonyms before visualization, such as incorporating "N6-methyladenosine" and "m^{6}A" into "m^{6}A", and then deleting the keywords without obvious research significance, such as "disease" and "mouse". The top 20 high-frequency keyword tables were m^{6}A, WT1, Wilms tumor, prognosis, immunohistochemistry, AML, immunotherapy, METTL3, apoptosis, podocytes, biomarkers, cancer, proliferation, ovarian cancer, cancer vaccine, FTO, metastasis, breast cancer, METTL14, and epigenetics. High-frequency keywords show that WTAP research mainly focuses on m^{6}A modification and tumors. Cluster analysis can display the knowledge structure of the research field. The visualization map is clustered according to the co-occurrence link strength (*Figure 5*). The keywords of the red cluster are m^{6}A, METTL3, METTL14, ALKBH5, FTO, apoptosis, cell cycle, inflammatory reaction, oxidative stress, DNA methylation, transcription, epigenetic transcriptome, p53, oncogene, proliferation, invasion, and metastasis, and the research directions involved in these keywords are m^{6}A modification and its regulatory mechanism, and the biological characteristics of tumors. The keywords of the green cluster include WT1, nephroblastoma, cancer, tumor vaccine, immunotherapy, cisplatin, genechip technology, experimental embryology, dendritic cells, leukemia, breast cancer, renal cell carcinoma, which are closely related to tumor and its treatment. The blue cluster has minor keywords, including prognosis, biomarkers, bioinformatics, tumorigenesis, TCGA, immunohistochemistry, lung cancer, liver cancer, and ovarian cancer, which are related to tumor markers, and prognosis. It can be seen from the chart that m^{6}A is the most critical term, with a total of 109 occurrences (*Table 1*).

The timezone view can locate the time point when new keywords first appear and can quickly understand

Table 1 The top 20 keywords of WTAP research

Rank	Term	Count
1	m^6A	109
2	WT1	91
3	Wilms tumor	52
4	Prognosis	43
5	Immunohistochemistry	24
6	AML	18
6	Immunotherapy	18
8	METTL3	17
8	Apoptosis	17
10	Podocytes	16
11	Biomarkers	14
11	Cancer	14
13	Proliferation	12
13	Ovarian cancer	12
13	Cancer vaccine	12
13	FTO	12
17	Metastasis	12
17	Breast cancer	11
19	METTL14	11
20	Epigenetics	10

WTAP, Wilms' tumor 1 associated protein; AML, acute myeloid leukemia; FTO, fat mass and obesity-associated protein.

the development context of relevant fields, predict the development direction, and find research hotspots (26). In our analysis on WTAP research, the threshold value is set to 15, excluding keywords that only appear once or twice. Designed with CiteSpace software, the keyword's timezone view is shown in *Figure 6*. New high-frequency keywords in the last three years are displayed in different colors at the bottom right of the timezone view. In the last three years, the top five keywords were metabolism, m6a writer, myocardial infarction, phosphorylation, and Yes-associated protein (YAP), showing the new direction of WTAP research.

Co-cited reference and reference burst

In 1973, the American information scientist Small first proposed the concept of co-cited reference as a research method to measure the degree of relationship between documents. Through the co-cited network, we can explore the development and evolution of a specific field. The VOSviewer was used to detect the co-cited references (*Table 2*). The cited frequency of the top 10 co-cited references was at least 43 times, and the most mentioned was the article, "Mammalian WTAP is a regulatory subunit of the RNA N6-methyladenosine methyltransferase", published by Ping in 2014 (6). This study identified for the first time that WTAP and METTL14 are essential components of the mammalian m^6A methyltransferase complex.

References with citation bursts are defined as those that are cited frequently over a while (34). The burst duration is set to 2 years on the CiteSpaces, γ is set to 1, and a total of 64 documents meeting the requirements are detected; we select the top 40 papers with burst intensity and visualize them (*Figure 7*). According to this figure, there are four articles with a burst passion of more than 10, of which the highest burst intensity is 16.36, which is the article published by Ping on *Cell Research* in 2014, and also the paper cited the most times, indicating its milestone significance in the WTAP field. Up to now, there were still six references in a continuous burst, which can be used to analyze the frontier dynamics and development trends of this research field.

Pan-cancer analysis and immunoassay

We performed WTAP gene expression differential analysis and prognostic analysis of 23 tumors from the TCGA and GTEx databases using the Sangerbox3.0 online tool. The gene differential expression analysis results showed that WTAP was highly expressed in 16 tumors, including GBM, GBMLGG, LGG, ESCA, COAD, COADREAD, STAD, HNSC, KIRC, LIHC, WT, PAAD, TGCT, ALL, LAML, and CHOL (*Figure 8A*, the whole tumor names are listed in Table S1). The relationship between WTAP expression and overall survival of cancer patients was analyzed for 40 tumors (*Figure 8B*). Predictive analysis showed that the high expression of WTAP in GBMLGG, LGG, LAML, MESO, LIHC, KIPAN and CESC was an essential factor affecting the poor prognosis of patients (*Figure 9*). Clinical staging and gene expression analysis suggested that WTAP expression in KIPAN and BLCA tumors affected tumor invasion and metastasis (KIPAN: P=0.006; BLCA: P=0.04).

A standardized pan-cancer dataset, TCGA TARGET GTEx (PANCAN, N=19,131, G=60,499), was downloaded from the UCSC database for immune correlation analysis.

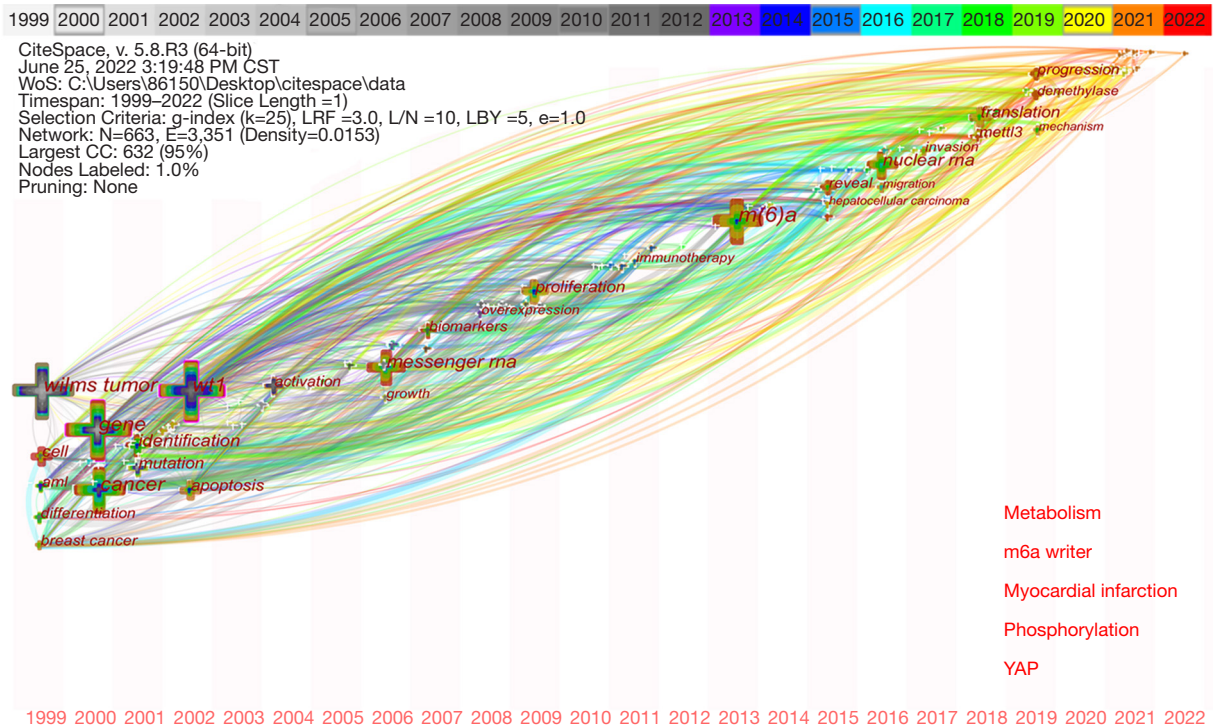


Figure 6 Keywords timezone view of WTAP research. Keywords with co-occurrence ≥15 were shown. The size of the cross and word reflects the co-occurrence frequencies, and the link indicates the co-occurrence relationship. The colors of node and line represent different years; colors vary from gray to red as time goes from 1999 to 2022. WTAP, Wilms' tumor 1 associated protein.

Table 2 Top ten co-cited references for WTAP research

Rank	Reference	Journal	Citation
1	Mammalian WTAP is a regulatory subunit of the RNA N6-methyladenosine methyltransferase	*Cell Research*	125
2	Topology of the human and mouse m^6A RNA methylomes revealed by m^6A-seq	*Nature*	98
3	A METTL3-METTL14 complex mediates mammalian nuclear RNA N^6-adenosine methylation	*Nature Chemical biology*	98
4	ALKBH5 is a mammalian RNA demethylase that impacts RNA metabolism and mouse fertility	*Molecular Cell*	87
5	N^6-Methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO	*Nature Chemical Biology*	86
6	Perturbation of m^6A writers reveals two distinct classes of mRNA methylation at internal and 50 sites	*Cell Reports*	63
7	Identification of WTAP, a novel Wilms' tumour 1-associating protein	*Human Molecular Genetics*	62
8	m(6)A RNA methylation promotes XIST-mediated transcriptional repression	*Nature*	47
9	Identification of Wilms' tumor 1-associating protein complex and its role in alternative splicing and the cell cycle	*The Journal of Biology Chemistry*	44
10	WTAP is a novel oncogenic protein in acute myeloid leukemia	*Leukemia*	43

WTAP, Wilms' tumor 1 associated protein.

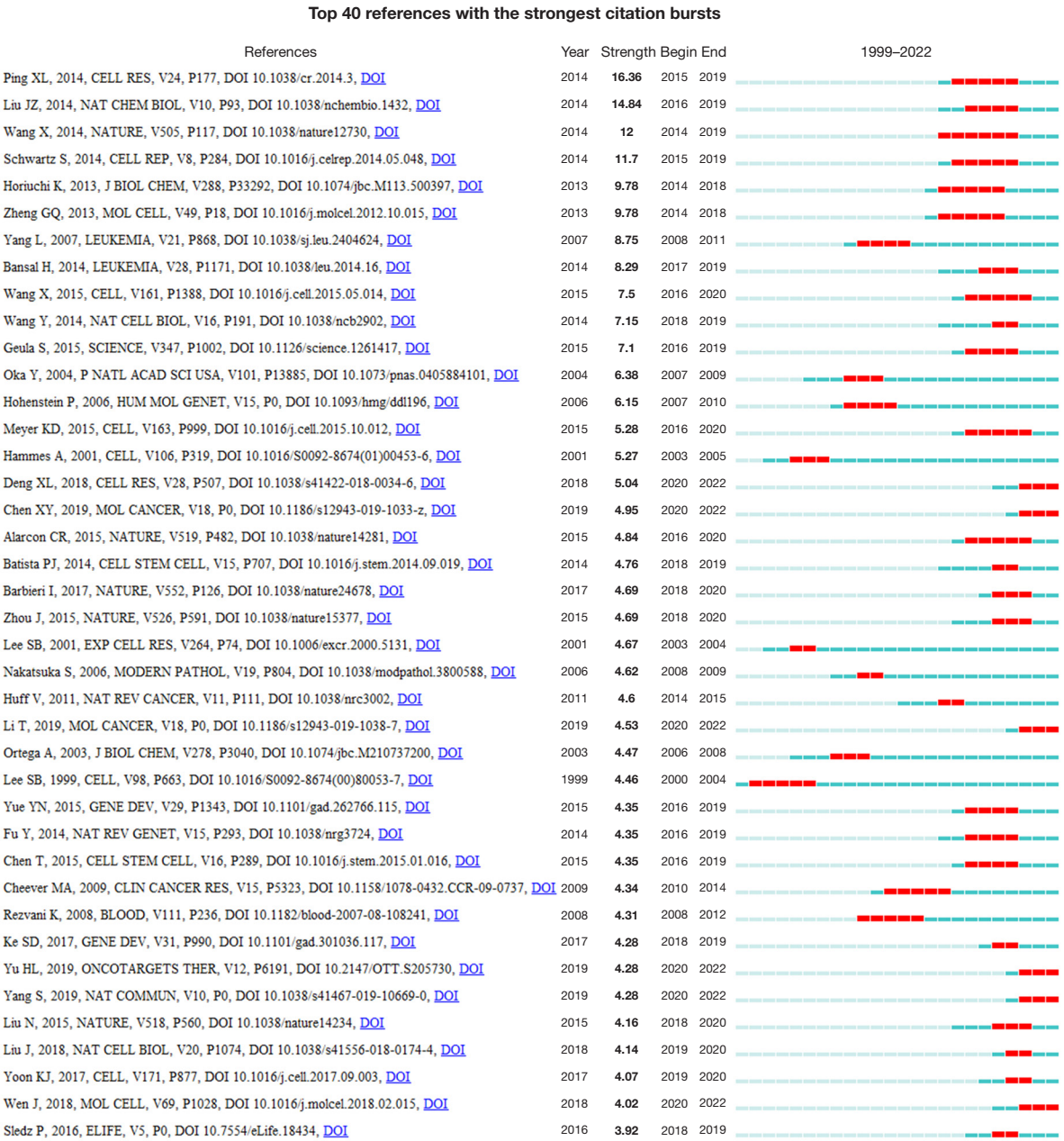
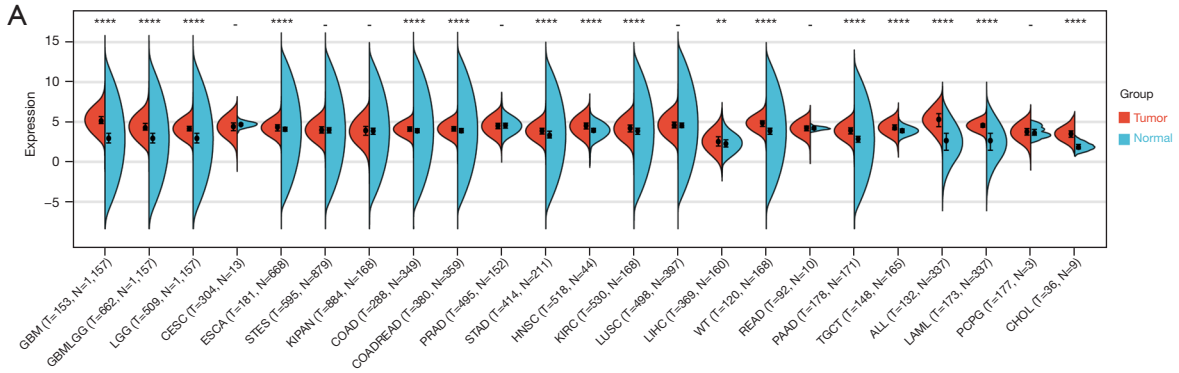


Figure 7 The top 40 references with the most potent citation bursts (sorted by the beginning year of the outbreak). The blue bars mean the reference had been published and the red bars represent citation burst.

The Timer method of R software package IOBR was used to evaluate the infiltration scores of B cell, T cell CD4, T cell CD8, neutrophil, macrophage, and DC of each patient tumor. The results showed that the expression of WTAP was correlated with six types of immune cells in most tumors (*Figure 10A*). The stromal cells, immune cells, and ESTIMATE scores of WTAP in each cancer were calculated using the R software package ESTIMATE and visualized using scatter plots. The results showed that WTAP had the strongest positive correlation with the stromal cell scores of GBMLGG, KIPAN, and PAAD, with the immune cell scores of GBMLGG, KIPAN, and DLBC, and with the ESTIMATE scores of GBMLGG, KIPAN, and DLBC (*Figure 10B*).



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Cancer code	P value	Hazard ratio (95% CI)
TCGA-GBMLGG (N=619)	2.8e−33	2.91 (2.44, 3.47)
TCGA-LGG (N=474)	1.4e−4	2.09 (1.44, 3.02)
TARGET-LAML (N=142)	1.1e−3	1.53 (1.19, 1.97)
TCGA-LIHC (N=341)	8.4e−3	1.40 (1.09, 1.81)
TCGA-KIPAN (N=855)	0.01	1.25 (1.05, 1.49)
TCGA-CESC (N=273)	0.04	1.58 (1.03, 2.42)
TCGA-MESO (N=84)	0.04	1.50 (1.03, 2.20)
TCGA-BRCA (N=1,044)	0.10	1.25 (0.96, 1.62)
TCGA-ACC (N=77)	0.10	1.51 (0.93, 2.48)
TCGA-KIRP (N=276)	0.14	1.43 (0.89, 2.30)
TARGET-WT (N=80)	0.17	1.45 (0.85, 2.48)
TCGA-KICH (N=64)	0.28	1.74 (0.64, 4.73)
TCGA-UVM (N=74)	0.33	1.25 (0.80, 1.97)
TCGA-OV (N=407)	0.46	1.07 (0.90, 1.26)
TCGA-LUAD (N=490)	0.47	1.09 (0.86, 1.39)
TCGA-GBM (N=144)	0.47	1.11 (0.83, 1.49)
TCGA-THCA (N=501)	0.57	1.34 (0.48, 3.71)
TCGA-TGCT (N=128)	0.64	1.75 (0.17, 18.37)
TCGA-UCS (N=55)	0.64	1.20 (0.55, 2.61)
TCGA-HNSC (N=509)	0.67	1.05 (0.84, 1.32)
TCGA-CHOL (N=33)	0.75	1.15 (0.49, 2.68)
TCGA-PRAD (N=492)	0.76	1.18 (0.40, 3.54)
TCGA-PAAD (N=172)	0.84	1.04 (0.71, 1.53)
TCGA-PCPG (N=170)	0.85	1.14 (0.30, 4.39)
TCGA-LUSC (N=468)	0.92	1.01 (0.77, 1.33)
TCGA-ESCA (N=175)	0.99	1.00 (0.63, 1.60)
TCGA-SKCM-P (N=97)	1.00	1.00 (0.72, 1.39)
TCGA-KIRC (N=515)	0.09	0.82 (0.65, 1.03)
TCGA-READ (N-90)	0.11	0.46 (0.18, 1.17)
TCGA-THYM (N=117)	0.21	0.59 (0.25, 1.35)
TCGA-COADREAD (N=368)	0.34	0.78 (0.46, 1.31)
TCGA-STAD (N=372)	0.40	0.87 (0.62, 1.21)
TCGA-UCEC (N=166)	0.41	0.84 (0.56, 1.27)
TCGA-LAML (N=209)	0.46	0.91 (0.70, 1.17)
TCGA-DLBC (N=44)	0.47	0.64 (0.19, 2.16)
TCGA-STES (N=547)	0.74	0.96 (0.74, 1.24)
TCGA-SARC (N=254)	0.78	0.96 (0.70, 1.31)
TARGET-ALL (N=86)	0.87	0.97 (0.68, 1.38)
TCGA-COAD (N=278)	0.90	0.96 (0.52, 1.77)
TCGA-BLCA (N=398)	0.91	0.99 (0.78, 1.25)

Figure 8 Expressions of WTAP in different tumors and their relationship with overall survival of patients. (A) Expressions of WTAP in different tumor tissues and adjacent normal tissues; **, P<0.01; ****, P<0.0001; "-" indicates no significant difference. (B) Relationship between WTAP expression and overall survival of cancer patients. WTAP, Wilms' tumor 1 associated protein. The whole tumor names are listed in Table S1.

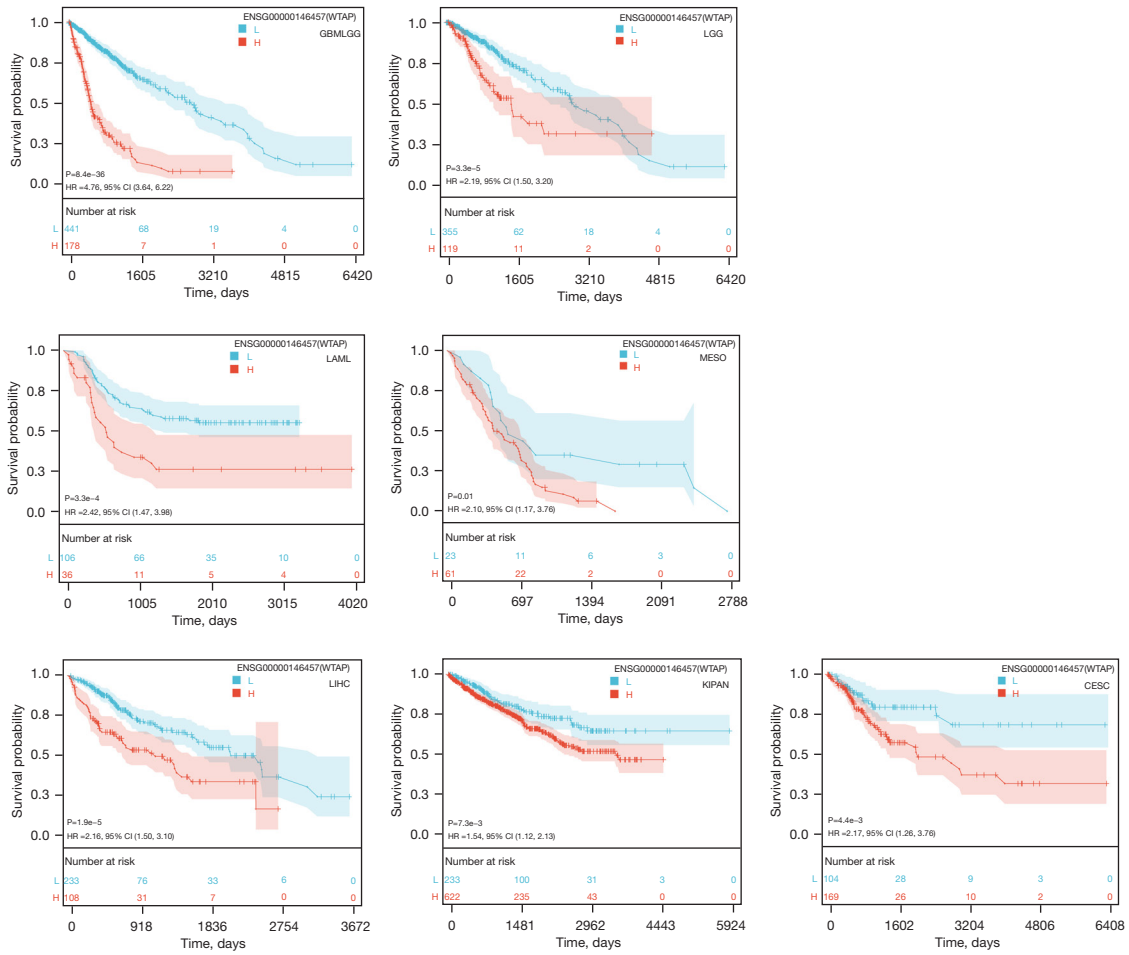

Figure 9 Survival curve evaluating the prognostic value of WTAP in patients with GBMLGG, LGG, LAML, MESO, LIHC, KIPAN, and CESC tumors. WTAP, Wilms' tumor 1 associated protein. The whole tumor names are listed in Table S1.

Immune checkpoint gene analysis showed that WTAP expression levels significantly correlated with these 40 checkpoint genes in numerous tumors (*Figure 11A*). Tumor mutation burden (TMB) and microsatellite instability (MSI) are emerging predictive markers for tumor immunotherapy. This study found that in GBMLGG, LGG, STES, KIPAN, STAD, OV, and ACC, the expression of WTAP was positively correlated with TMB, while in PRAD, LIHC, THCA, and UVM, the expression of WTAP was negatively correlated with TMB. It strongly correlates with GBMLGG (R=0.41) (*Figure 11B*). The expression of WTAP was positively correlated with MSI in COAD, STES, STAD, and TGCT. In GBM, GBMLGG, LUAD, KIPAN, PRAD, LUSC, THCA, and DLBC, the expression of WTAP was negatively correlated with MSI, and the strongest correlation was found with DLBC (R=0.54) (*Figure 11C*).

Summary of the mechanism of WTAP in cancer progression

The mechanism of WTAP in cancer progression is summarized in *Figure 12* and will be elaborated in the Discussion. Previous studies have shown that m^6A methylation in tumor cells will affect the infiltration, activation, and efficacy of immune cells in TME, and promote the formation of TME (19). WTAP regulates N^6A methylation modification and participates in the occurrence and development of tumor via the effects of m^6A. Our analysis revealed that the expression of WTAP was significantly correlated with immune infiltration in most tumors, and WTAP was most strongly associated with

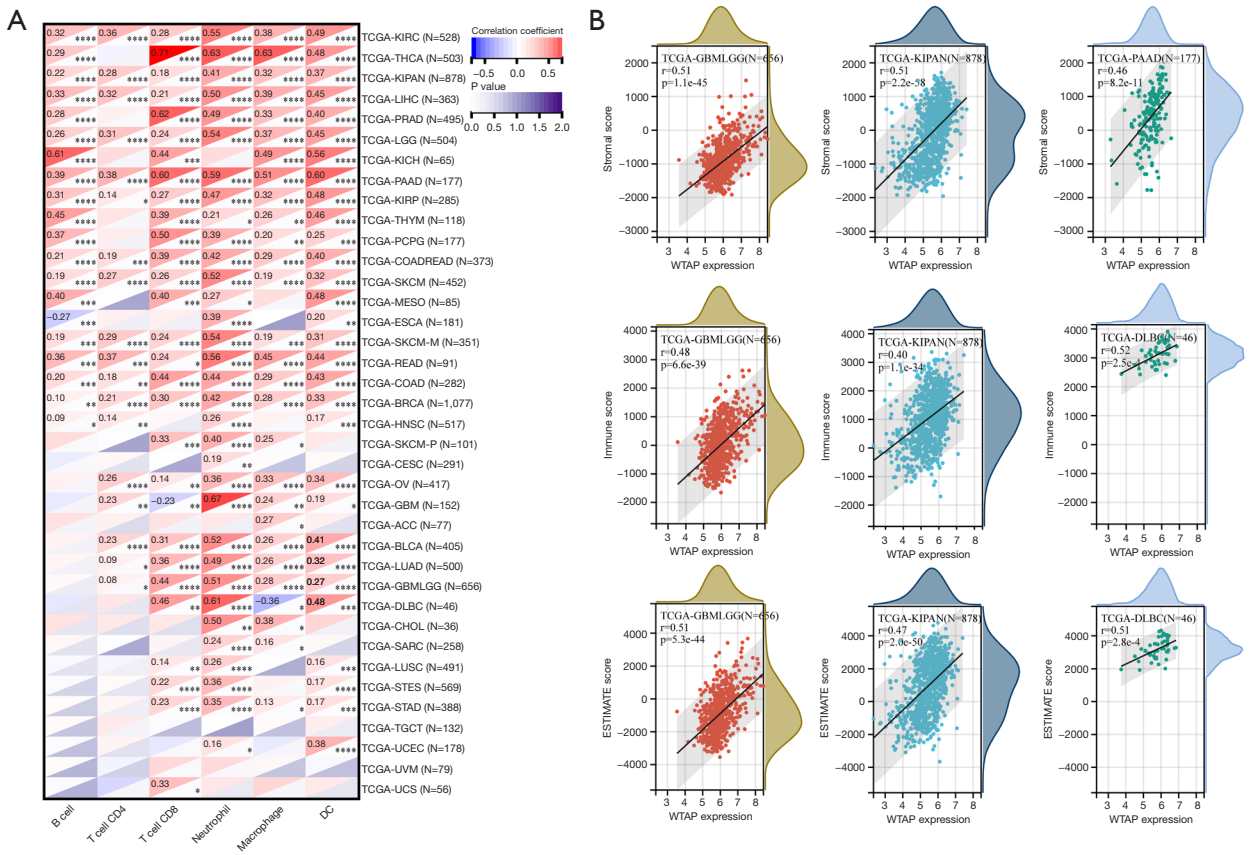

Figure 10 Correlation of WTAP with immune cells. (A) Relationship between WTAP expression and B cell, T cell CD4, T cell CD8, neutrophil, macrophage, and DC in each tumor; *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001. (B) Relationship between WTAP expression in GBMLGG, KIPAN, PAAD, DLBC, and stromal score, immune score, and ESTIMATE score. WTAP, Wilms' tumor 1 associated protein. TCGA, The Cancer Genome Atlas; The whole tumor names are listed in Table S1.

stromal cell scores and immune cell scores. These results suggest that WTAP is highly involved in tumor immune microenvironment remodeling.

Discussion

General information

In this study, CiteSpace and VOSviewer were used to conduct bibliometric analysis on the documents collected in the WOSCC database and to manually mine and sort out the node information of the visual atlas. Through the atlas, the cooperative network relationships among the countries, institutions, authors, journals, keywords, and references included in the literature are intuitively displayed, the research status in the field of WTAP is summarized and analyzed, and research hotspots and emerging topics are explored, looking forward to the future development trend. We collected and collated the relevant literature on WTAP research in the core collection database of Web of Science from January 1999 to June 2022. A total of 691 papers were included; these papers came from 49 countries, 1,071 institutions, and 4,771 authors and were published in 371 academic journals. The annual publication volume is an important indicator showing the development trend of the research field (35). Since 1999, the number of publications on WTAP-related research has gradually increased, attracting more and more attention from researchers.

There are significant differences in WTAP research among different countries and institutions. The top three countries with the most important number of papers were China, the United States, and Japan. The United States is not only the main cooperation center in this field but also

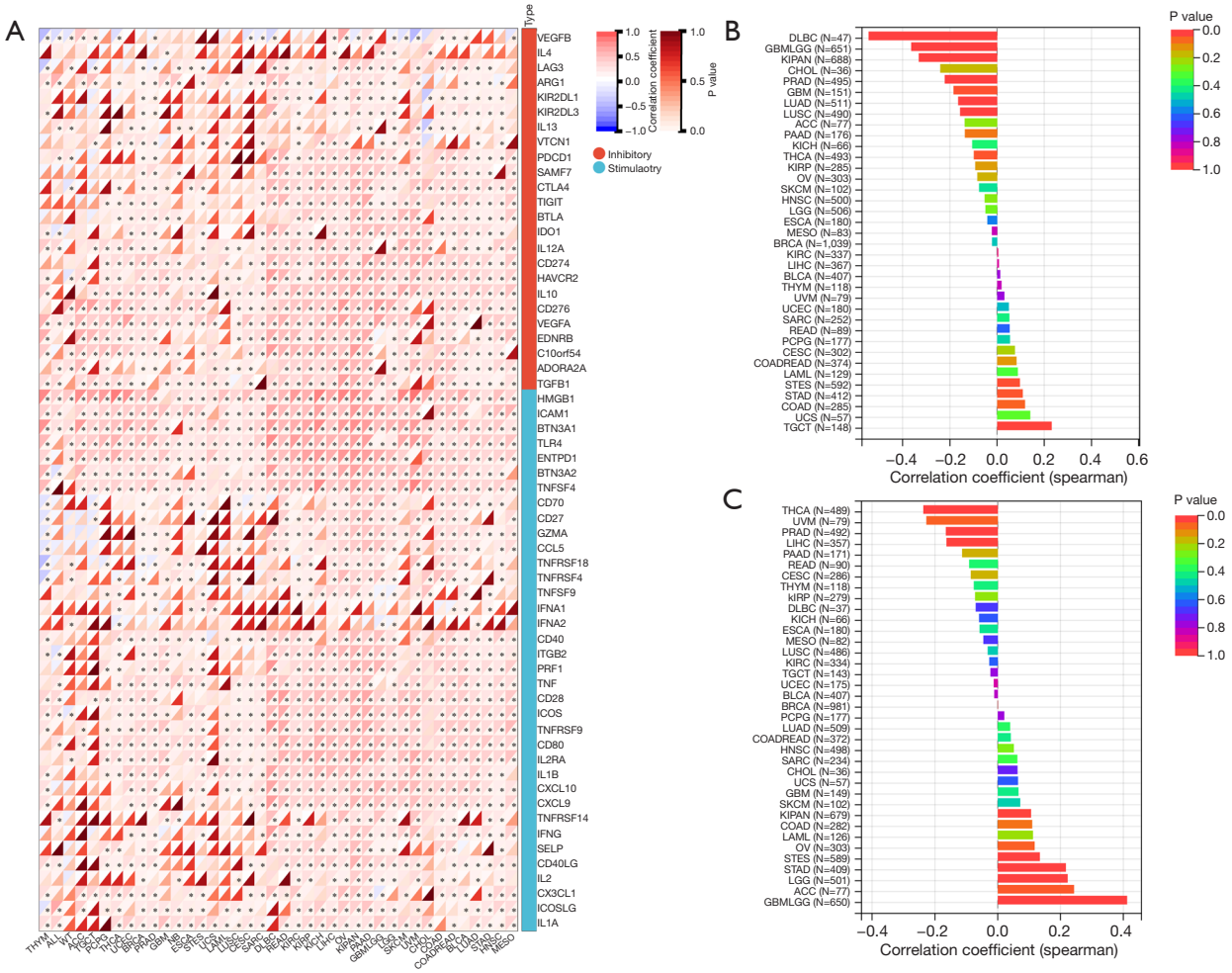

Figure 11 Relationship between WTAP expression and immune checkpoint gene expression, TMB, MSI. (A) Correlations between WTAP expression levels and gene expression levels of immune checkpoints; *, P<0.05. (B) Relationship between WTAP expression and TMB. (C) Relationship between WTAP expression and MSI. WTAP, Wilms' tumor 1 associated protein; TMB, tumor mutation burden; MSI, microsatellite instability. The whole tumor names are listed in Table S1.

has made milestone contributions to research progress and breakthroughs. Germany, Britain, and France are also significant to the development of WTAP. Most of the top ten institutions with the most important number of articles were from China. China Medical University was the largest institution with the most significant number of pieces, followed by Zhejiang University and the University of the Chinese Academy of Sciences. Osaka University in Japan also ranks fifth in the number of articles, but the cooperation between Osaka University and other institutions is not close. Among the top 100 highly cited papers, China is still the country with the most significant number of articles and has frequent academic exchanges with the United States, Britain, and other countries. Through the visual knowledge map, we find that there are active cooperation and exchange relations between different countries and different institutions. The research in the field of WTAP has attracted extensive attention worldwide.

The analysis of journals and co-cited journals showed that *Frontiers in Cell and Developmental Biology* was the journal with the most significant number of articles, and *Nature* was the co-cited journal with the most important number of citations. Among the top 100 highly cited papers, *Frontiers in Oncology* was the journal with the most significant number of articles, and *Nature* was still the journal with the most important number of citations.

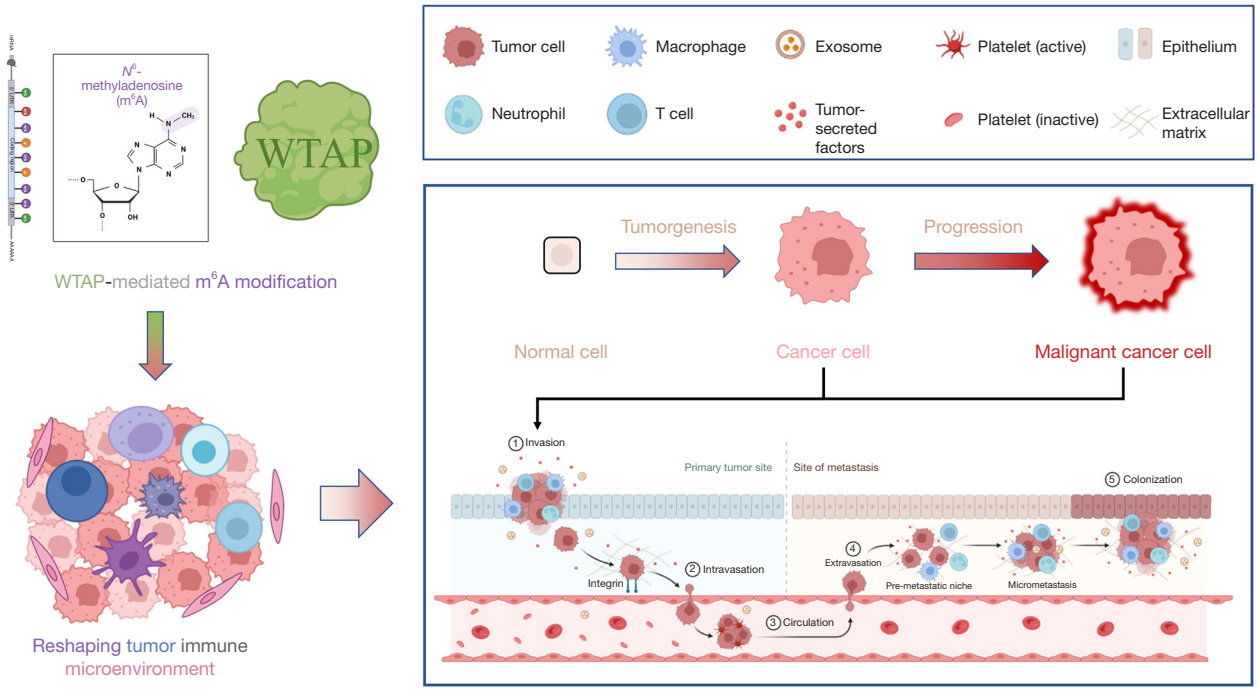

Figure 12 WTAP-mediated aberrant m^{6}A modification promotes cancer progression by remodeling the tumor microenvironment. WTAP, Wilms' tumor 1 associated protein.

WTAP research was mainly concentrated in molecular biology, consistent with the results shown in the journal overlay view. The journal double view overlay represents the theme distribution of academic journals. The overlay map drawn by CiteSpace mainly has two connecting paths. The orange path indicates that the articles published in the journal Molecular/Biology/Genetics were particularly cited by those published in the journal Molecular/Biology/Immunology. The green path represents that the literature published in Molecular/Biology/Genetics were mainly cited by the articles published in Medicine/Medical/Clinical. Currently, WTAP-related research focuses on basic medical research, but it is still exploring and developing in clinical medicine and pharmaceutical research. In the future, WTAP is expected to become a piece of good news for cancer patients.

The number of published articles can analyze the core authors who greatly influence this research field. Haruo Sugiyama was the author with the most published reports, followed by Yusuke Oji and Yoshihiro, all leading figures related to WTAP research. Researchers in this field have active collaborative relationships within or between institutions, especially among high-impact authors. Through bibliometric analysis, we can get relevant information about potential collaborators and influential research groups, which can provide direction and guidance for the subsequent research of scholars.

Knowledge base

The knowledge base is a collection of commonly cited references cited by corresponding research groups (30,36), which is not entirely equivalent to highly cited references. The knowledge base of the WTAP research field was evaluated by analyzing the top 10 co-cited references. In this bibliometric analysis, the ten co-cited references were as follows: (I) in 2014, *Cell Research* published the most co-cited study authored by Ping and other scholars outstanding in WTAP research. In this paper, it was first confirmed that WTAP and METTL14 are essential components of the mammalian m^{6}A methyltransferase complex; WTAP is a regulatory subunit necessary for m^{6}A methyltransferase activity and plays a crucial role in the transcriptional regulation of RNA metabolism. (II) The second co-cited publication in *Nature* in 2012 by Dominissini *et al.* The research results showed that the RNA modification of m^{6}A plays a vital role in regulating gene expression. Silencing methyltransferase will significantly affect gene

expression and alternative splicing, thus affecting the TP53 signaling pathway and cell apoptosis (37). (III) Liu *et al.* published the third co-cited study in *Nature Chemical Biology* in 2014, which proposed that WTAP interacts with METTL3 and METTL14 and co-localizes with METTL3-METTL14 heterodimers in the nucleus to participate in m^6A methylation modification. This paper demonstrated that WTAP alone had no methyltransferase activity *in vitro*. However, knockdown of WTAP could significantly reduce m^6A levels (38). (IV) Zheng's work published in *Molecular Cell* in 2013 showed that ALKBH5, as another mammalian RNA demethylase, can remove m^6A modification from mRNA both *in vivo* and *in vitro*, thus affecting RNA metabolism and gene expression (39). (V) In 2011, Jia *et al.* published the fifth co-cited paper in *Nature Chemical Biology*, which shows that FTO exhibits efficient oxidative demethylation activity *in vitro*. It was also proved that m^6A, as the physiological substrate of FTO, may affect the processing of pre-mRNA or nuclear RNAs (40). The fourth and fifth articles are all about the study of m^6A demethylase (ALKBH5, FTO), which acts as the "eraser" of m^6A RNA and the "writer" of m^6A RNA (METTL3, METTL14, WTAP) to demethylate and methylate RNA respectively, and maintain the dynamic balance between deposition and clearance of m^6A modification, which is essential for normal biological processes and development. (VI) In 2014, Schwartz *et al.* published the sixth co-cited paper on *Cell Reports*, the novel components of methylated transferase complex (WTAP, METTL14, and KIAA1429) were identified by proteomic screening and experimentally verified to be essential for m^6A methylation. This study also showed that WTAP-dependent methylation is closely related to mRNA stability (41). (VII) The seventh reference, published in 2000 in *Human Molecular Genetics* by Little *et al.*, was the first to identify a nuclear protein that interacts with the WT1 gene, in a yeast two-hybrid screen, known as WTAP (1). (VIII) The eighth co-cited publication was published in *Nature* in 2016 by Patil *et al.*, these studies have shown that m^6A methylation can promote an extended non-coding RNA XIST mediated gene silencing function, and WTAP can also regulate this function by promoting m^6A methylation (42). (IX) Horiuchi *et al.* published the ninth paper in *The Journal of Biology Chemistry* in 2013. This study found that the WTAP complex regulates the alternative splicing of pre-mRNA by promoting the production of truncated isomers, which leads to a change in WTAP protein expression. The experiment verified that the consumption of WTAP complex components would lead to the arrest of the cell cycle, indicating that WTAP plays an essential role in the regulation of the cell cycle (43). (X) The last co-cited reference was published by Bansal *et al.* in 2014, which verified that WTAP, as a novel oncogenic protein in AML, plays an oncogenic role in AML by promoting the abnormal proliferation of bone marrow cells and blocking the terminal differentiation of bone marrow cells (44). The top 10 co-cited references focused on m^6A modification, mainly including the mechanism of methyltransferase (WTAP, METTL3, METTL14) and demethylase (ALKBH5, FTO), and the correlation of WTAP regulating gene expression through m^6A methylation modification, and the influence of abnormal expression of WTAP on the occurrence, development, and treatment of some diseases.

Research hotspots and emerging topics

In bibliometrics, keywords can reflect the research frontiers and hotspots in an academic field (45). The timezone view can show the evolution process of research hotspots more intuitively and even predict the research trend in the future (46). The most frequent keyword was m^6A, followed by WT1, Wilms tumor, prognosis, etc. WTAP research is in the stage of rapid development, and the emerging keywords mainly include m^6A modification, methyltransferase, P53, RNA translation, ovarian cancer, demethylation, phosphorylation, etc., representing the hot spot in recent years. References with high burst intensity can also characterize an emerging topic in an academic field (35,47). Half of the connections with top 10 intensive burst references coincide with the top 10 co-cited references, which indicates that concerns with higher burst intensity are more likely to become co-cited references with higher cited frequency. This consistency also reflects the influence of papers with high burst intensity in this research field. Six articles of top 40 authorities with the most vigorous citation burst are still in business, and they are following. (I) Review by Deng *et al.* published in *Cell Research* in 2018, which summarized the m^6A "writers" (METTL3, METTL14, WTAP), "Eraser" (FTO, ALKBH5); "reader" (IGF2BP) in different tumors, and the intervention measures against cancer caused by dysregulation of m^6A modification (48). (II) An article in *Nature Communications* by Yang *et al.* showed that FTO, as an m^6A demethylase, plays a crucial role in promoting melanoma development and resistance to anti-PD-1 immunotherapy, the combination of FTO inhibition and anti-PD-1 blockade may reduce the resistance of melanoma to immunotherapy (49). (III)

The article summarizes recent advances in the biological functions of m^{6}A methylation modifications in cancer and discusses potential therapeutic strategies (50). (IV) An article published by Li *et al.* on *Molecular Cancer* in 2019 demonstrated that METTL3 promotes the development of colorectal cancer through an m^{6}A-IGF2BP2-dependent regulatory mechanism (51). Relevant references also pointed out that WTAP, as an oncogene, promotes the progression of colorectal cancer through the WTAP/WT1/TBL1 axis in the Wnt signaling pathway (52). (V) The study published on *Molecular Cell* in 2019 by Wen *et al.* found that Zc3h13, an essential regulatory protein of m^{6}A, can interact with WTAP, Virilizer and Hakai proteins to form a regulatory complex and anchor it in the nucleus to promote m^{6}A methylation repair and regulate the self-renewal of mESCs (mouse embryonic stem cells) (53). (VI) The study showed that WTAP is highly expressed in high-grade serous ovarian cancer (HGSOC) and plays its function by promoting the proliferation and migration of ovarian cancer cell lines and inhibiting cell apoptosis. After preliminary experiments, it was speculated that the mechanism of WTAP may be related to MAPK and AKT pathways (54); the WTAP gene is localized on human chromosome 6q25-27 (1), which is also a chromosomal region of ovarian cancer (55), demonstrating the potential correlation between WTAP and HGSOC. In this study, the reference burst and keyword co-occurrence analysis show that the research topics and hotspots in the field of WTAP are concentrated in the following three directions.

The first is that WTAP regulates m^{6}A methylation modification and relies on m6A to participate in the occurrence and development of diseases. WTAP is a methyltransferase without a catalytic domain and has no catalytic capacity for RNA alone, but it can stabilize the core complex and promote the localization of the METTL3-METTL14 complex in nucleophiles rich in mRNA splice genes and enucleation transporters (6). At the same time, the down-regulation of WTAP can lead to the degradation of METTL14 and METTL3, thereby reducing the level of m^{6}A and affecting the regulation of gene expression (38), since WTAP was first found to be highly expressed in glioblastoma and an essential indicator of poor prognosis (56), more and more studies have found that it is abnormally said in a variety of malignant tumors and affects the survival and prognosis of patients. For example, the overexpression of WTAP in cholangiocarcinoma, especially in lymph nodes or vascular metastatic cholangiocarcinoma cells, can significantly increase tumor cells' migration and invasion ability. However, its involvement as an m^{6}A modifying enzyme in carcinogenesis has not been elucidated (57). Li *et al.* found that WTAP is highly expressed in gastric cancer, and its carcinogenic effect may be related to the high methylation of RNA of T-cell immune response-related genes (58). WTAP can down-regulate the expression of CAV-1 by regulating the m^{6}A modification of CAV-1 mRNA, thereby activating the NF-κB signaling pathway to promote the progression of endometrial cancer (59). In addition to solid tumors, WTAP promotes diffuse large B-cell lymphoma (DLBCL). Kuai *et al.* found that WTAP was highly expressed in DLBCL and demonstrated that WTAP formed stable complexes with heat shock protein 90 (Hsp90) and B-cell lymphoma six protein (Bcl-6). Thus, the proliferation and anti-apoptosis ability of DLBCL cells were promoted (60). WTAP can also regulate the expression of HMBOX1 in an m^{6}A-dependent manner and promote the progression and metastasis of osteosarcoma through PI3K/AKT signaling pathway (61). WTAP depends not only on m^{6}A to participate in the occurrence and development of tumors but is also closely related to other diseases. For example, WTAP can increase endoplasmic reticulum stress and apoptosis by regulating m^{6}A modification of ATF4 mRNA, promoting myocardial ischemia and reperfusion injury (62), WTAP-mediated m^{6}A modification of lncRNA NORAD promotes nucleus pulposus cell senescence and intervertebral disc degeneration (63). As an essential component of the m^{6}A methyltransferase complex, WTAP not only participates in the occurrence, development, and metastasis of various malignant tumors by regulating m^{6}A methylation modification but also plays an essential role in the development of non-neoplasia diseases such as renal injury (64), myocardial injury and intervertebral disc degeneration.

Secondly, the abnormal modification of m^{6}A mediated by WTAP can affect cancer occurrence, development, and metastasis by reshaping TME. WTAP is significantly associated with the event and product of cancer and the poor prognosis of patients, but the specific mechanism of action is still unclear. As a virtual environment for tumor survival, TME plays an essential role in the tumor progression process and affects immunotherapy (65). Increasing evidence indicates that m^{6}A modification in tumor cells is closely related to immune microenvironment. On the one hand, m^{6}A can not only regulate the differentiation and function of immune cells in the immune microenvironment, such as macrophage polarization and T-cell activation, but also regulate the expression of immune cytokines, such as the production of interferon

and tumor necrosis factor affecting the interaction between immune cells and the immune regulatory process (19). On the other hand, m^{6}A can also directly regulate the transcription and translation of immune-related genes and affect the immune response. In head and neck squamous cell carcinoma (HNSCC), PD-L1 expression and immune cell infiltration in TME significantly correlate with m^{6}A regulators (66). Bioinformatics analysis of nasopharyngeal carcinoma (NPC) showed that m^{6}A methylation was associated with immune infiltration and escape in TME (67). Tang *et al.* investigated the relationship between the mutation status of m^{6}A-related genes and the tumor immune microenvironment of pancreatic cancer (PAAD), showing that m^{6}A modification may be involved in immune cell infiltration, and the composition of infiltrating immune cells may affect m^{6}A modification (68). It was found that m^{6}A modification is also involved in forming TME and immune-related pathways in lung adenocarcinoma (LUAD) (69). WTAP, as a methyltransferase, has been confirmed to regulate m^{6}A methylation, and m^{6}A modification is closely related to the infiltration of immune cells in TME; m^{6}A modification can affect the abundance of immune cell infiltration in TME through a variety of signaling pathways, thus affecting the biological behavior of tumors (70). This paper also preliminarily verified that as an essential regulator of m^{6}A methylation, WTAP is highly expressed in many tumors and closely related to TME remodeling. Therefore, we speculate that WTAP may reshape the TME through abnormal modification of m^{6}A, thus affecting cancer's occurrence, development, and survival prognosis, but its specific mechanism needs further experimental studies.

The third is the application prospect of m^{6}A and WTAP as potential therapeutic targets in cancer. As the most extensive modification of eukaryotic mRNA, m^{6}A links epitranscriptomics to the occurrence and development of tumors, affecting self-renewal and differentiation of tumor stem cells, proliferation and apoptosis (37), drug resistance (71), immunosuppression (72) and other processes. m^{6}A methylation and demethylation modification is a reversible process. The level of m^{6}A in cells can be changed by promoting or inhibiting some critical enzymes in the process of m^{6}A modification to achieve the purpose of intervening in tumor progression. Huang *et al.* found that meclofenamic acid (MA) could inhibit the m^{6}A demethylase activity of FTO, performing a selective chemical intervention in RNA demethylation (73). Subsequently, the ethyl ester derivative MA2 of MA has been approved for clinical treatment in the United States and has shown promising efficacy in glioma models (74). In 2019, Huang *et al.* reported two potent small-molecule FTO inhibitors (FB23 and FB23-2), which directly bind to FTO and selectively inhibit the m^{6}A demethylase activity of FTO, promote apoptosis and inhibit the proliferation of AML cells (75). Visvanathan *et al.* found that silencing METTL3 could inhibit glioblastoma growth by enhancing tumor sensitivity to radiotherapy (76). In addition, baicalin hydrate can promote splicing of histone methylase SUV39H1 by enhancing m^{6}A methylation, induce cell cycle arrest and apoptosis, and play a role in inhibiting the proliferation of nasopharyngeal carcinoma cells (77). Since understanding m^{6}A modification and the regulatory mechanism of key enzymes needs to be further studied, the current achievements mainly focus on the selective inhibitors of FTO, and the therapeutic effect requires more clinical verification. Many studies have shown that WTAP plays an essential role in tumorigenesis and development and may also promote tumor cell apoptosis, immunosuppression, and drug resistance as potential therapeutic targets. For pediatric tumors, such as leukemia and osteosarcoma, WTAP-related studies have contributed to a better understanding of their molecular mechanisms and developmental processes. By studying the expression level and function of WTAP in pediatric tumors and its relationship with prognosis, we can explore its potential as a prognostic assessment for pediatric tumors. These findings may help clinicians to develop better individualized treatment plans to improve the therapeutic efficacy and survival rate of pediatric tumors. For the aspect of adult tumors, the related studies of WTAP are also of great significance. Understanding the expression pattern, function, and relationship with prognosis of WTAP in different types of adult tumors can help us better understand the different subtypes and molecular features of adult tumors. This has important clinical implications for the development of precise treatment strategies and the prediction of patient response to immunotherapy. Currently, targeted drug therapy and immunotherapy for WTAP are still developing. However, with the deepening of RNA methylation research, the application of WTAP-related targeted drugs, as well as the development of small-molecule inhibitors targeting m^{6}A regulatory proteins and their novel drugs in combination with immune checkpoint blockers are bound to play an important value in the future.

TME and immune infiltration analysis

TME is closely related to the occurrence and development

of tumors. Understanding the microenvironment of tumors, including the infiltration of immune cells, will help to explore the mechanism of tumor development further and provide ideas for novel cancer treatment. WTAP is associated with the occurrence and development of various tumors and may affect the survival and prognosis of patients. To further analyze the expression difference of WTAP in tumor tissues and explore its predictive value for tumor prognosis. We performed gene expression differential analysis and prognosis analysis. The results showed that WTAP was significantly differentially expressed between most tumors and adjacent normal tissues, and the expression of WTAP had an essential impact on the survival rate of cancer patients. High expression of WTAP was negatively correlated with the overall survival rate in various tumors. To investigate whether WTAP is involved in regulating tumor-related immune responses, we performed immune cell analysis, immune infiltration analysis, and immune checkpoint analysis. The results showed that the expression of WTAP was significantly correlated with immune infiltration in most tumors, and WTAP was correlated considerably with TME in many cancers and was most strongly associated with stromal cell scores in GBMLGG, KIPAN, and PAAD, and with immune cell scores in GBMLGG, KIPAN and DLBC. The strongest correlation was found with the ESTIMATE scores of GBMLGG, KIPAN, and DLBC. These results suggest that WTAP is highly involved in TME remodeling in these tumors. At the same time, in the ESTIMATE score, we observed that WTAP expression was significantly correlated with immune infiltration in 25 cancer species, of which nineteen were significantly positively correlated, and six were significantly negatively correlated. The relationship between WTAP and immune checkpoint gene expression showed that the expression level of WTAP in each tumor was associated with more than 40 checkpoints, most of which were positively correlated. It has also been shown that inhibition of m^6A modification can increase tumor sensitivity to immunotherapy by altering TME and $CD8^+$ T cell recruitment, revealing the function of RNA methylation in adaptive immunity (78).

All these immune correlation analyses suggest that WTAP may be essential as a potential biomarker in tumor immunity. Tumor mutation burden (TMB) and microsatellite instability (MSI) are new tumors immunotherapy prediction markers. Studies have shown that they can guide the clinical treatment of patients with non-small cell lung cancer (79) and colon adenocarcinoma (80). This study found that the expression of WTAP was significantly correlated with TMB of 11 cancers, and the strongest correlation was found with GBMLGG (R=0.41). WTAP was connected considerably with MSI of 12 cancers, and DLBC (R=0.54) had the strongest correlation. Therefore, WTAP is considered an important indicator to evaluate the efficacy of immunotherapy, and it can further regulate tumor immunity by affecting TMB and MSI and becoming a new target in immunotherapy. In conclusion, this study found that WTAP is associated with various cancers' TMEs and immune infiltration, especially GBMLGG, KIPAN, and DLBC. It is expected to become a breakthrough for new cancer immunotherapy and targeted therapy.

Limitations of this study

This is the first bibliometric analysis of WTAP-related research areas, and there are inherent limitations in using CiteSpace and VOSviewer for visual analysis. Firstly, to meet the reference format requirements of the two software, data retrieval was conducted only from the Web of Science core collection database, leaving out the literature not included in the database (26). Secondly, some keywords extracted based on software have no prominent discussion and research significance, so it is necessary to combine the researcher's comprehensive understanding of keywords in the research field to select, so there may be deviation (27). As for the first limitation, WoSCC, the most commonly used scientometric analysis database, is one of the most authoritative scientific reference retrieval tools, representing most of the information (26). However, only a few reference data are not included, which will not significantly impact bibliometric analysis. As for the second limitation, for the possible deviation caused by the choice of keywords, researchers must read a large number of relevant references, and cultivate rigorous scientific research logical thinking ability, to minimize the subjective deviation.

Conclusions

As an essential component of the m^6A methyltransferase complex, WTAP participates in the occurrence and development of many diseases, especially tumors, by regulating m^6A methylation modification. Currently, the research on WTAP is in the stage of rapid growth, and the cooperation between the countries, institutions, and authors is close. Although the research on WTAP has been

preliminarily recognized, there are still many problems to be solved, so it is imperative to carry out further research in this field. The bibliometric analysis results show that current WTAP research's main aspects include m^{6}A modification, tumor, cancer treatment, and regulatory mechanisms.

The research frontiers and hotspots are m^{6}A modification, methyltransferase, demethylation, TME, and immunotherapy. The results of bioinformatics analysis showed that the expression of WTAP was up-regulated in various tumors and affected patients' survival prognoses. WTAP was associated with remodeling tumor immune microenvironment in multiple cancers, which is expected to become a potential molecular target for cancer treatment and drug development. Based on these results, the emerging topics will be closely related to the basic mechanism research and clinical application research of m^{6}A and WTAP-related diseases and explore the in-depth mechanism research of WTAP through abnormal m^{6}A modification and remodeling of TME to promote the occurrence, development, and metastasis of cancer. This paper can provide relevant researchers with research hotspots and frontier trends in this field and reference ideas for finding new topics and directions.

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Footnote

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1243/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1243/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 The whole tumor names

ACC: adrenocortical carcinoma
BLCA: bladder urothelial carcinoma
BRCA: breast invasive carcinoma
CESC: cervical squamous cell carcinoma and endocervical adenocarcinoma
CHOL: cholangiocarcinoma
COAD: colon adenocarcinoma
COADREAD: colon adenocarcinoma/rectum adenocarcinoma esophageal carcinoma
DLBC: lymphoid neoplasm diffuse large B-cell lymphoma
ESCA: esophageal carcinoma
GBM: glioblastoma multiforme
GBMLGG: glioma
HNSC: head and neck squamous cell carcinoma
KICH: kidney chromophobe
KIPAN: pan-kidney cohort (KICH + KIRC + KIRP)
KIRC: kidney renal clear cell carcinoma
KIRP: kidney renal papillary cell carcinoma
LAML: acute myeloid leukemia
LGG: brain lower grade glioma
LIHC: liver hepatocellular carcinoma
LUAD: lung adenocarcinoma
LUSC: lung squamous cell carcinoma
MESO: mesothelioma
OV: ovarian serous cystadenocarcinoma
PAAD: pancreatic adenocarcinoma
PCPG: pheochromocytoma and paraganglioma
PRAD: prostate adenocarcinoma
READ: rectum adenocarcinoma
SARC: sarcoma
SKCM: skin cutaneous melanoma
STAD: stomach adenocarcinoma
STES: stomach and esophageal carcinoma
TGCT: testicular germ cell tumors
THCA: thyroid carcinoma
THYM: thymoma
UCEC: uterine corpus endometrial carcinoma
UCS: uterine carcinosarcoma
UVM: uveal melanoma

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