Heliyon 10 (2024) e29817

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Bibliometric evaluation of global trends and characteristics of RNA methylation during angiogenesis

Bingyan Li [a,b,c,1], Zicong Wang [a,b,c,1], Haixiang Zhou [a,b,c], Wei Tan [a,b,c], Jingling Zou [a,b,c], Yun Li [a,b,c], Shigeo Yoshida [d], Yedi Zhou [a,b,c,*]

[a] Department of Ophthalmology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, 410011, China
[b] Hunan Clinical Research Center of Ophthalmic Disease, Changsha, Hunan, 410011, China
[c] National Clinical Research Center for Metabolic Diseases, The Second Xiangya Hospital of Central South University, Changsha, Hunan, 410011, China
[d] Department of Ophthalmology, Kurume University School of Medicine, Kurume, Fukuoka, 830-0011, Japan

ARTICLE INFO

Keywords:
RNA methylation
Angiogenesis
Bibliometric analysis
CiteSpace
VOSviewer

ABSTRACT

Background: RNA methylation is involved in major life processes. Angiogenesis is a normal phenomenon that occurs constantly in the bodies of all mammals, once it is aberrant or something goes wrong, it may lead to pathological changes. The bibliometric analysis could produce a comprehensive overview of RNA methylation during angiogenesis.
Methods: The Web of Science Core Collection (WoSCC) database was used to screen publications about RNA methylation during angiogenesis from Jan 1, 2000 to Nov 24, 2022. Bibliometric and visualization analyses were conducted to understand publication trends by CiteSpace and VOSviewer.
Results: In total, 382 publications from 2000 to 2022 were included in the bibliometric and visualization analyses. On the whole, the number of publications had exponential growth. China was the country and Sun Yat-Sen University was the university associated with the largest number of publications, although publications from the United Kingdom and Soochow University were currently having the strongest impact. Cancer was the most studied topic in this field, and N6-methyladenosine is the most studied RNA methylation type.
Conclusion: There is a continuously increasing trend in publications related to RNA methylation and angiogenesis, which has attracted much attention, particularly since 2011. RNA methylation might be a promising target in the investigation of pathological angiogenesis and related disorders, which deserves further investigation.

1. Introduction

RNA methylation is a dynamic and reversible modification that transfers methyl groups from S-adenosyl-*l*-methionine to nucleophilic acceptors of RNA such as O, As, N, S, or C via methyltransferases (MTases) [1,2]. It does not change the nucleotide sequence but may alter its expression in an epigenetic way [3]. Significantly, it may contribute to RNA stability, translation, degradation, the

* Corresponding author. Department of Ophthalmology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, 410011, China.
E-mail address: zhouyedi@csu.edu.cn (Y. Zhou).
[1] Bingyan Li and Zicong Wang are the co-first authors of the article.

https://doi.org/10.1016/j.heliyon.2024.e29817
Received 26 January 2023; Received in revised form 8 April 2024; Accepted 16 April 2024
Available online 16 April 2024

immune response, metabolic processes, and other cellular functions [4–6]. N6-methyladenosine (m^6A), N1-methyladenosine (m^1A), 5-methylcytosine (m^5C), 5-hydroxymethylcytosine (5hmC), pseudouridine (Ψ), ribose 2′-O-methylation (2′-O-Me) [7], N7-methylguanosine (m^7G), and adenosine-to-inosine editing (A-to-I editing) are the main components of RNA methylations [8,9], and they play important roles in mechanisms of embryonic development [10], initiation and progression of tumor growth [11,12], learning and memory [13], angiogenesis [14], and immunity [15,16].

Angiogenesis is involved in many pathological diseases, and it can be considered as an indicator of cancer, ischemic and inflammatory diseases [17] such as ocular neovascular diseases [18,19], malignant tumors [20,21], cardiovascular diseases [22], and rheumatoid arthritis [23]. Aberrant new blood vessels are dysfunctional compared to normal ones; they may have abnormal structures (incomplete tube walls without a smooth muscle component), show high vascular permeability and/or vascular malformations, and exhibit chaotic blood flow [17,24–26]. Therapy targeting angiogenesis diseases mainly focuses on inhibiting proangiogenic signals, immunotherapy, and surgical excision [27–29]. Herein, the formation of pathological neovascularization may lead to decreased vision, neurological disorders, tumor invasion and metastasis, and other symptoms which would may reduce the quality of life, survival rate, and lifetime [30,31].

Bibliometrics is a quantitative method of studying the literature, which can reveal active scholars, hot topics, developmental trends, and the outlook for a topic in the future [32–34]. In this study, we evaluated RNA methylation during angiogenesis utilizing bibliometrics to reveal the developmental trends in this research field. Our results clarified the current research trends, and provided a perspective on RNA methylation and angiogenesis.

2. Methods

2.1. Data source

The Web of Science is one of the largest and most comprehensive databases housing high-quality academic articles [35]. We used the Web of Science Core Collection (WoSCC) database for the analyses, and exported information of publication time, authors, keywords, countries, institutions, journals, and references.

2.2. Search strategy

As described in Fig. 1, the search phrases were TS= ((m^6A or N6-methyladenosine or m^5C or 5-methylcytosine or m^1A or N1-methyladenosine or m^7G or N7-methylguanine or 2′-O-methylation or Pseudouridine or 5hmC or 5-hydroxymethylcytosine or Adenosine-to-inosine editing or A-to-I editing or RNA methylation) AND (neovascularization or angiogenesis or neovascular disease or new blood vessel)), to identify as many relevant publications as possible about RNA methylation and neovascularization. The language was restricted to English, publication types were limited to articles and reviews, and the publication period was from Jan 1, 2000 to Nov 24, 2022, which were sufficient to illustrate the developmental trend and characteristics of the study topic.

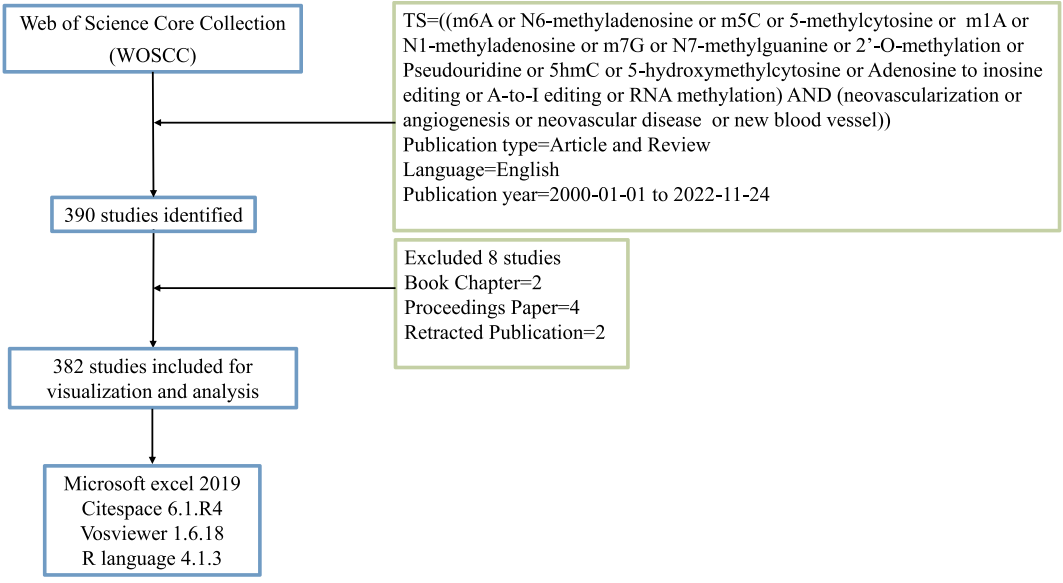


Fig. 1. Flow diagram of publication search and exclusion.

2.3. Data extraction and collection

In total, 390 publications were identified and exported in a plain text file, which was convenient for bibliometric analysis. Next, we excluded 8 publications including 2 book chapters, 4 proceedings papers, and 2 retracted publications by CiteSpace, and reserved 382 publications for visualization analysis.

2.4. Analysis

We utilized Microsoft Excel 2019, CiteSpace 6.2.R4, VOSviewer 1.6.18 and R language 4.1.3 for the bibliometric analysis [36,37]. We mainly focused on several specific characteristics, such as publications, countries or institutions, authors, journals, keywords and references.

3. Results

3.1. Annual publication trends

As shown in Fig. 2, we quantify the number of annual publications from Jan. 1, 2000, to Nov. 24, 2022. Publication numbers increase exponentially in this domain during this period. The increase is particularly obvious in 2011, when it more than doubled versus previous years, indicating that the topic suddenly attracts the attention of a large number of scholars. Between 2011 and 2016, the volume of annual publications remains stable. Beginning in 2017, however, the number increases again. Publications in 2022 decrease may because we only count to November 24. These results indicate that RNA methylation during angiogenesis is a research hotspot.

3.2. Distribution and cooperation of countries or institutions

Next, we present the different countries and institutions which publish these papers. As shown in Table 1, China is the most productive country (n = 195), followed by the United States (the USA, n = 90), India (n = 21), Germany (n = 19), the United Kingdom (UK), and the Netherlands (n = 17). Fig. 3A shows the publication numbers all over the world in the format of the map of the world, and the color depth of the country marked on the map is proportional to the number of publications, which also indicates China has the most publication numbers. CiteSpace identifies the cooperation and mutual exchanges among countries in Fig. 3B. A node represents a country, the size of a node signifies publications, the purple ring outside of a node stands for centrality and a greater influence on the network, and the line thickness stands for the degree of cooperation relationship. The top 5 core countries of centrality are the UK, Germany, Greece, the USA, and Australia. The UK establishes cooperation with other 8 countries, such as Germany, Finland, Japan, and Sweden. Australia links with

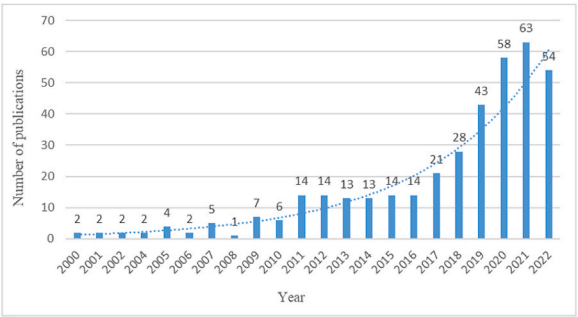


Fig. 2. Annual distribution trends of the study of RNA methylation during angiogenesis from 2000-01-01 to 2022-11-24.

Table 1
Top 10 countries in terms of publications and centrality.

Rank	Publications	Country	Rank	Centrality	Country
1	195	China	1	0.52	UK
2	90	USA	2	0.45	Germany
3	21	India	3	0.44	Greece
4	19	Germany	4	0.42	USA
5	17	UK	5	0.42	Australia
6	17	Netherlands	6	0.37	Sweden
7	15	Japan	7	0.22	Netherlands
8	14	Italy	8	0.22	Italy
9	11	Canada	9	0.20	Turkey
10	11	Australia	10	0.19	Japan

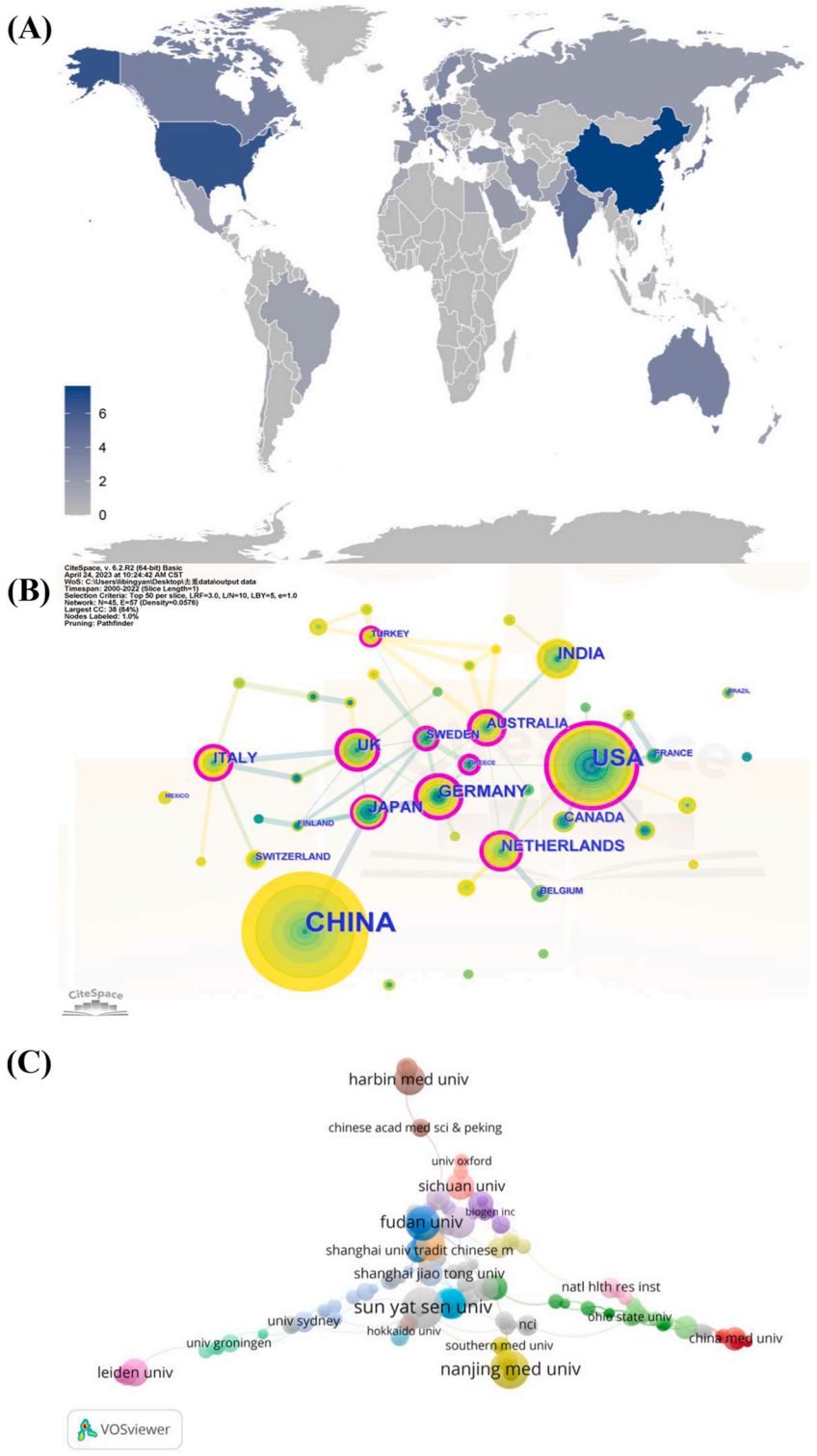


Fig. 3. Publication numbers and international cooperation analysis of studies of RNA methylation during angiogenesis among countries and institutions. (A) Visualization of publications around the world by using R language. (B) Network visualization for different countries by CiteSpace. A node represents a country, and the size of a node stands for publications, the purple ring at the periphery of a node signifies centrality, and the line represents cooperation between countries. (C) Institutional cooperation network by VOSviewer. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

India, Netherlands, and other regions. China has the largest publications in this field, the international collaborations are found with Japan. Some countries do not have academic exchange within the research topic, such as Mexico and Brazil.

Sun Yat-Sen University has published the most papers (n = 16), followed by Nanjing Medical University (n = 14), Funan University (n = 11), Huazhong University of Science and Technology (9), and Harbin Medical University (n = 9) (Table 2). As is listed in Table 2, the top 5 institutions of centrality are Soochow University, the Second Military Medical University, Ningxia Medical University, Tongji University, Huazhong University of Science and Technology, and Harbin Medical University. These results lack consistency with the rank of publications, which suggests that publication numbers are not proportional to influence and importance. Moreover, only 353 out of 642 institutions have established mutual connections. Fig. 3C presents 28 clusters from 353 institutions by different colors which contain 4 to 19 institutions each. For example, China Medical University, Dalian Municipal Central Hospital, Imperial College London, University of Turku, and other 15 institutions formed a cluster labeled by red color.

Table 2
Top 10 institutions in terms of publications and centrality.

Rank	Publications	Institution	Rank	Centrality	Institution
1	16	Sun Yat-Sen Univ	1	0.23	Soochow Univ
2	14	Nanjing Med Univ	2	0.20	Second Mil Med Univ
3	11	Fudan Univ	3	0.20	Ningxia Med Univ
4	9	Huazhong University Sci & Technol	4	0.18	Tongji Univ
5	9	Harbin Med Univ	5	0.17	Huazhong University Sci & Technol
6	8	Capital Med Univ	6	0.17	Shanghai Jiao Tong Univ
7	8	Zhejiang Univ	7	0.15	Helmholtz Zentrum Munchen
8	8	Zhengzhou Univ	8	0.14	University Munich
9	7	Leiden Univ	9	0.14	University Leicester
10	7	Sichuan Univ	10	0.14	University Nottingham

Table 3
Top 10 journals published and cited related to RNA methylation during angiogenesis.

Rank	Journal	Publications	JCR	IF (2021)	Rank	Journal	Citation	JCR	IF (2021)
1	Frontiers in Cell and Developmental Biology	11	Q1	6.081	1	Cancer Research	835	Q1	13.312
2	Frontiers in Oncology	10	Q2	5.738	2	Nature	789	Q1	69.504
3	Oncotarget	10	–	–	3	Proc Natl Acad Sci U S A	684	Q1	12.779
4	Frontiers in Genetics	8	Q1	4.772	4	Cell	648	Q1	66.850
5	Clinical Epigenetics	7	Q1	7.259	5	the Journal of Biological Chemistry	624	Q2	5.486
6	International Journal of Molecular Sciences	7	Q1	6.208	6	PLos One	489	Q2	3.752
7	Journal of Cellular Physiology	7	Q1	6.613	7	Oncogene	485	Q1	8.756
8	Molecular Cancer	7	Q1	41.444	8	Nucleic Acids Research	457	Q1	19.160
9	PLos One	7	Q2	3.752	9	Science	392	Q1	63.714
10	Cancer Cell International	5	Q2	6.429	10	Oncotarget	329	–	–

Proc Natl Acad Sci U S A: Proceedings of the National Academy of Sciences of the United States of America.

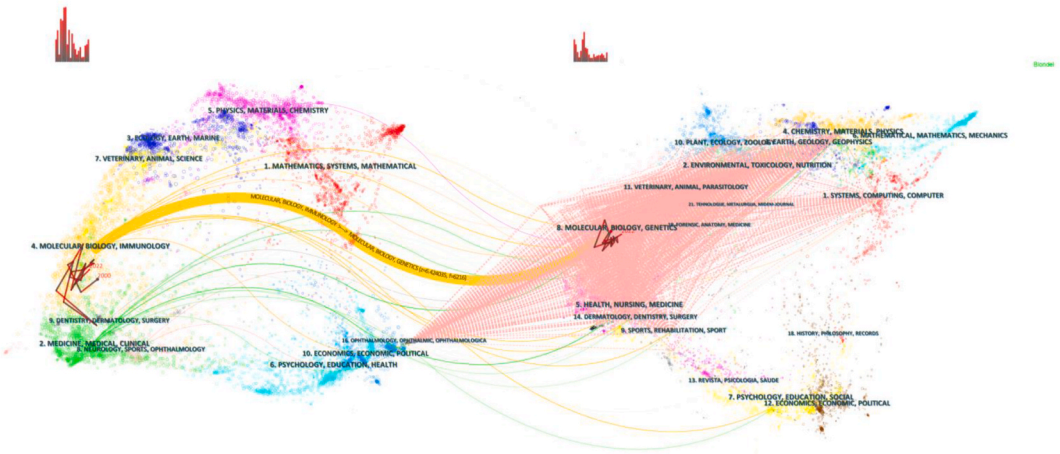


Fig. 4. Dual-map overlay of publishing and cited journals generated by CiteSpace. The publishing journals are shown on the left, and the citing journals are listed on the right.

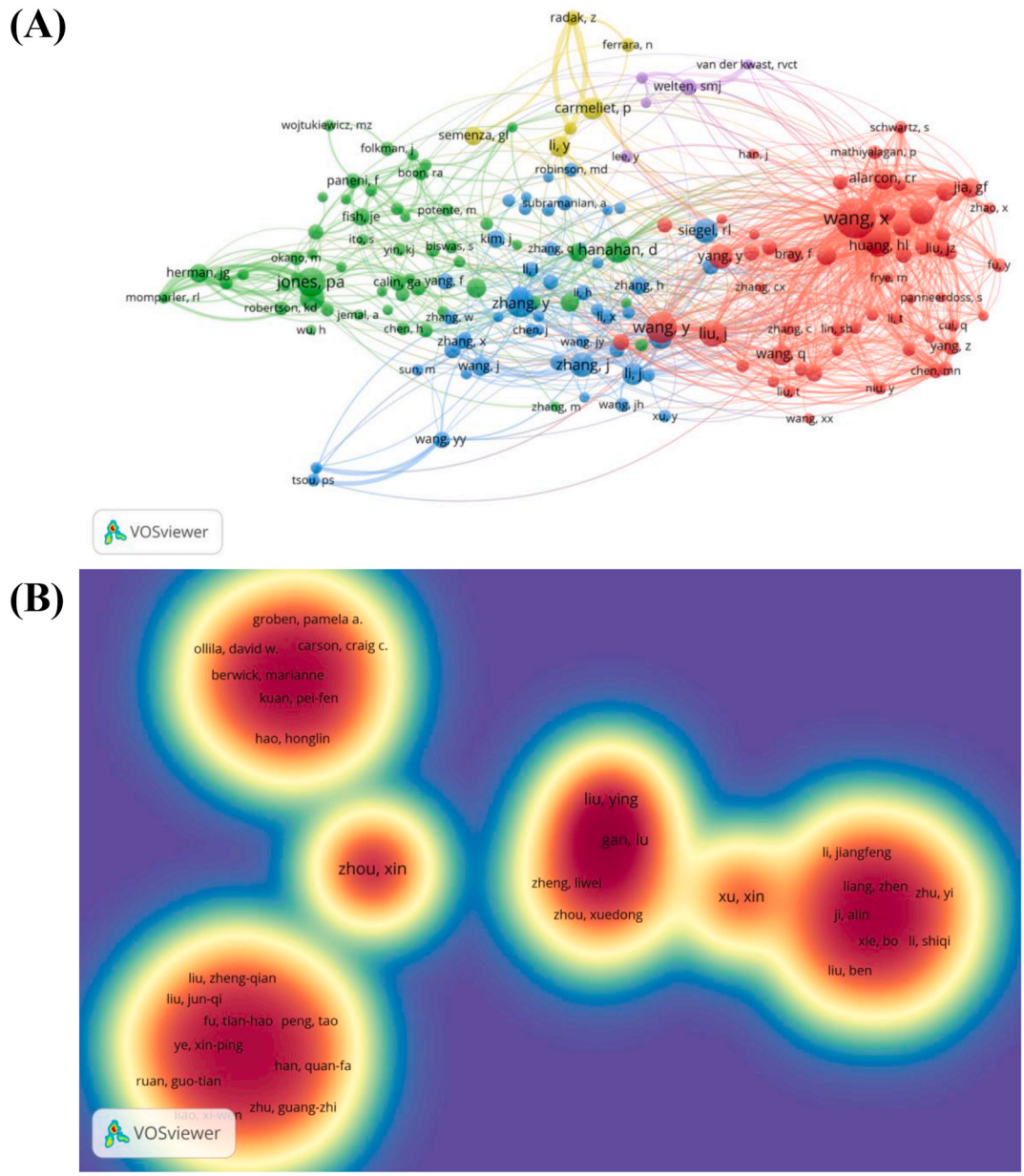


Fig. 5. Author co-citation (A) and co-authorship (B) visualization map by VOSviewer.

Table 4
Top 5 co-cited references related to RNA methylation during angiogenesis.

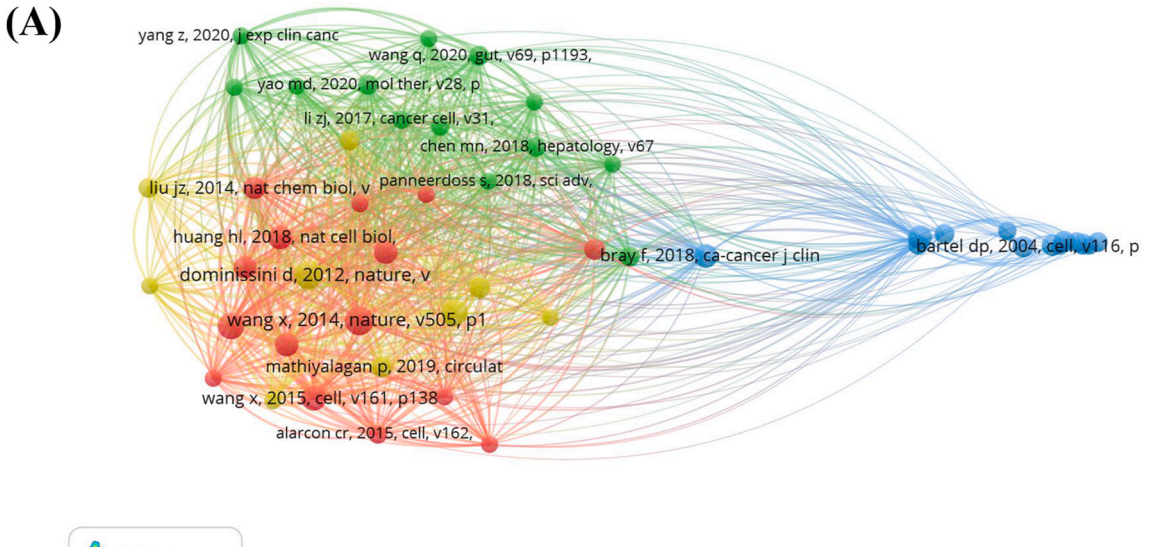
Rank	Title	First Author	Co-citation	Journal	JCR	IF (2021)	Reference
1	N6-methyladenosine-dependent regulation of messenger RNA stability	Xiao Wang	28	Nature	Q1	69.504	[43]
2	Topology of the human and mouse m6A RNA methylomes revealed by m6A-seq	Dan Dominissini	28	Nature	Q1	69.504	[44]
3	Comprehensive analysis of mRNA methylation reveals enrichment in 3′ UTRs and near stop codons	Kate D Meyer	24	Cell	Q1	66.850	[45]
4	N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO	Guifang Jia	23	Nature Chemical Biology	Q1	16.174	[46]
5	N (6)-methyladenosine Modulates Messenger RNA Translation Efficiency	Xiao Wang	21	Cell	Q1	66.850	[47]

3.3. Analysis of published and cited journals

The top 10 publications and cited journals are enumerated in Table 3. *Frontiers in Cell and Development Biology* has the largest number of publications (n = 11), 6 of the top 10 publications are in Journal Citation Reports Quarter 1 (JCR Q1). *Cancer Research* is the most quoted journal, which is cited 835 times in total. At the same time, 8 of the top 10 cited journals are in JCR Q1; *Cell*, *Nature*, and *Science* are also cited many times. These results suggest that scholars are more inclined to publish and quote literature in high-quality journals. Next, we use a dual-map overlay of journals to explore the citation relationships among journals (Fig. 4). The left is the cited journal, and the right is the citing journal, and the discipline source of the journal is distinguished by different colors. Journals between Molecular/Biology/Immunology and Molecular/Biology/Genetics (the yellow link) show the strongest conjunction relationship. Scholars can focus on such journals to quickly find appropriate articles related to this topic.

3.4. Author analysis

A co-citation relationship exists when publications by two authors are cited by a third author. The higher the co-citation frequency,



(B) **Top 25 References with the Strongest Citation Bursts**

References	Year	Strength	Begin	End	2000 - 2022
Kouzarides T, 2007, CELL, V128, P693, DOI 10.1016/j.cell.2007.02.005, DOI	2007	3.04	2009	2011	
Jemal A, 2011, CA-CANCER J CLIN, V61, P69, DOI 10.3322/caac.20107, DOI	2011	2.69	2015	2015	
Michalik KM, 2014, CIRC RES, V114, P1389, DOI 10.1161/CIRCRESAHA.114.303265, DOI	2014	4.55	2018	2019	
Love MI, 2014, GENOME BIOL, V15, P0, DOI 10.1186/s13059-014-0550-8, DOI	2014	3.41	2018	2019	
Boon RA, 2016, J AM COLL CARDIOL, V68, P2589, DOI 10.1016/j.jacc.2016.09.949, DOI	2016	2.84	2018	2019	
He C, 2017, DNA CELL BIOL, V36, P475, DOI 10.1089/dna.2017.3682, DOI	2017	2.27	2018	2019	
Ha M, 2014, NAT REV MOL CELL BIO, V15, P509, DOI 10.1038/nrm3838, DOI	2014	2.27	2018	2019	
Siegel RL, 2016, CA-CANCER J CLIN, V66, P7, DOI 10.3322/caac.21332, DOI	2016	3.34	2019	2020	
Louis DN, 2016, ACTA NEUROPATHOL, V131, P803, DOI 10.1007/s00401-016-1545-1, DOI	2016	2.45	2019	2019	
Wang X, 2015, CELL, V161, P1388, DOI 10.1016/j.cell.2015.05.014, DOI	2015	4.48	2020	2020	
Huang HL, 2018, NAT CELL BIOL, V20, P285, DOI 10.1038/s41556-018-0045-z, DOI	2018	3.51	2020	2022	
Bray F, 2018, CA-CANCER J CLIN, V68, P394, DOI 10.3322/caac.21492, DOI	2018	3.29	2020	2022	
Roundtree IA, 2017, CELL, V169, P1187, DOI 10.1016/j.cell.2017.05.045, DOI	2017	3.28	2020	2022	
Cai XL, 2018, CANCER LETT, V415, P11, DOI 10.1016/j.canlet.2017.11.018, DOI	2018	3.23	2020	2022	
Zhao BXS, 2017, NAT REV MOL CELL BIO, V18, P31, DOI 10.1038/nrm.2016.132, DOI	2017	2.99	2020	2022	
Mathiyalagan P, 2019, CIRCULATION, V139, P518, DOI 10.1161/CIRCULATIONAHA.118.033794, DOI	2019	2.87	2020	2022	
Lin SB, 2016, MOL CELL, V62, P335, DOI 10.1016/j.molcel.2016.03.021, DOI	2016	2.82	2020	2022	
Chen MN, 2018, HEPATOLOGY, V67, P2254, DOI 10.1002/hep.29683, DOI	2018	2.55	2020	2022	
Han DL, 2019, NATURE, V566, P270, DOI 10.1038/s41586-019-0916-x, DOI	2019	2.42	2020	2022	
Yao MD, 2020, MOL THER, V28, P2191, DOI 10.1016/j.ymthe.2020.07.022, DOI	2020	4.17	2021	2022	
Yang Z, 2020, J EXP CLIN CANC RES, V39, P0, DOI 10.1186/s13046-020-01714-8, DOI	2020	3.52	2021	2022	
Huang HL, 2020, CANCER CELL, V37, P270, DOI 10.1016/j.ccell.2020.02.004, DOI	2020	3.33	2021	2022	
Panneerdoss S, 2018, SCI ADV, V4, P0, DOI 10.1126/sciadv.aar8263, DOI	2018	3.24	2021	2022	
Yang Y, 2018, CELL RES, V28, P616, DOI 10.1038/s41422-018-0040-8, DOI	2018	3.2	2021	2022	
Wang HS, 2019, MOL CANCER, V18, P0, DOI 10.1186/s12943-019-1108-x, DOI	2019	2.88	2021	2022	

Fig. 6. Reference analysis of studies of RNA methylation during angiogenesis. (A) Network map of co-cited references by VOSviewer. (B) Top 25 references with the strongest citation bursts by CiteSpace.

the closer their academic relationship and the shorter their "distance" in the figure. Fig. 5A shows the results of co-citation analysis, a total of 173 authors with at least 10 citations are included. The top 5 authors with the largest total link strength are Wang X, Meyer KD, Wang Y, Dominissini D, and Liu J. The link strength of the top 2 is particularly high, above 1000, which indicates that their research has a profound impact on studies in RNA methylation and angiogenesis. Moreover, the top 5 authors account for 4/5 of the top 5 co-cited references, which once again confirms the importance and influence of their articles to others (Table 4). We only identify 58 co-authors, which suggests that individual research is the norm in this field; and a wide range of academic communities of authors has not yet been formed (Fig. 5B).

3.5. References analysis

Co-cited reference analysis is similar to author co-citation analysis, which represents the closeness of a partnership. The resulting networks of co-cited references are shown in Fig. 6A. The time of the citation bursts is only 1 or 2 years (Fig. 6B), which illustrates that the hotspot of study direction changes fast, enabling scholars to have a forward-looking perspective. We list the top 5 co-cited references in the field (Table 4), find that "N6-methyladnosine-dependent regulation of messenger RNA stability" reported by Wang X in *Nature* is the most frequently co-cited, and all of them are associated with the characteristics of m^6A modification, such as functions of methylation modification-related enzymes, findings of recognition sites and technical analysis. As for the top 10 cited references shown in Table 5, there are 4 papers summarize the biological functions of RNA methylation, such as the stability of target RNA and the process of translation, 5 papers that are closely associated with cancers, and 1 paper on the cardiac system.

3.6. Trending topics

Keywords are crucial for a paper, which represent the core content and central idea of a paper. Table 6 lists the top 20 keywords of frequency, and Fig. 7A shows the results of co-occurrence analysis of keywords. Angiogenesis is the major keyword of our research topic. m^6A is included in RNA methylation, METTL3 and IGF2BP3 are the two enzymes in m^6A modification. VEGF is a growth factor, while inflammation and proliferation are crucial pathological processes which are involved in neovascularization. miRNA, lncRNA,

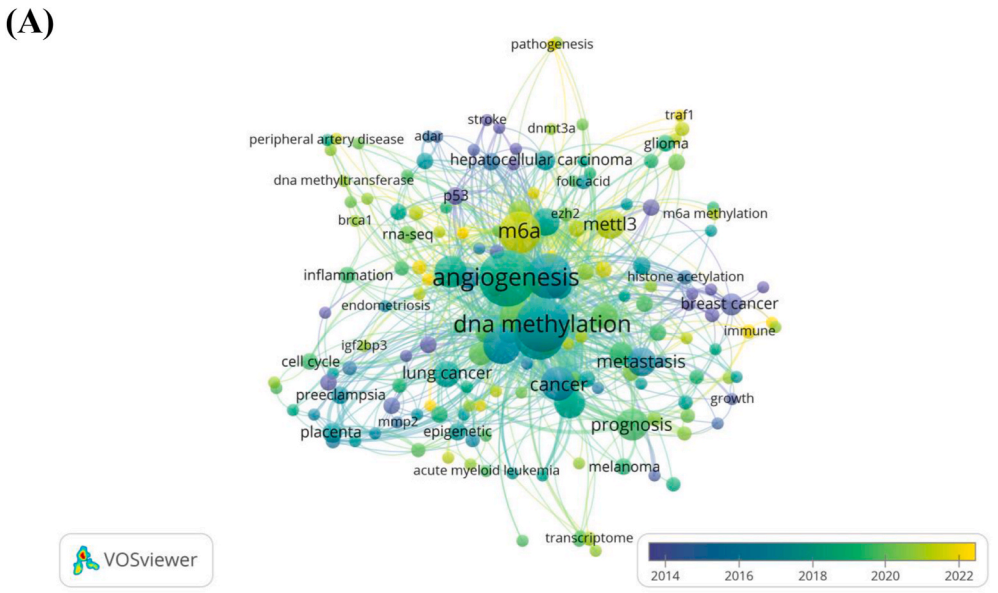
Table 5
Top 10 cited references related to RNA methylation during angiogenesis.

Rank	Reference	citation	Journal	JCR	IF (2021)	Reference
1	Recognition of RNA N^6-methyladenosine by IGF2BP proteins enhances mRNA stability and translation	19	Nature Cell Biology	Q1	28.213	[48]
2	Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries	18	CA: A Cancer Journal for Clinicians	Q1	286.130	[49]
3	Post-transcriptional gene regulation by mRNA modifications	16	Nature Reviews Molecular Cell Biology	Q1	113.915	[50]
4	Dynamic RNA Modifications in Gene Expression Regulation	15	Cell	Q1	66.850	[51]
5	RNA N6-methyladenosine methyltransferase-like 3 promotes liver cancer progression through YTHDF2-dependent posttranscriptional silencing of SOCS2	14	Hepatology	Q1	17.298	[52]
6	FTO-Dependent N^6-Methyladenosine Regulates Cardiac Function During Remodeling and Repair	14	Circulation	Q1	39.918	[53]
7	Role of METTL3-Dependent N^6-Methyladenosine mRNA Modification in the Promotion of Angiogenesis	13	Molecular Therapy	Q1	12.910	[54]
8	FTO Plays an Oncogenic Role in Acute Myeloid Leukemia as a N^6-Methyladenosine RNA Demethylase	11	Cancer Cell	Q1	38.585	[55]
9	RNA N6-methyladenosine reader IGF2BP3 regulates cell cycle and angiogenesis in colon cancer	11	Journal of Experimental & Clinical Cancer Research	Q1	12.658	[56]
10	m^6A RNA Methylation Regulates the Self-Renewal and Tumorigenesis of Glioblastoma Stem Cells	10	Cell Reports	Q1	9.995	[57]

Table 6
Top 20 keywords related to RNA methylation during angiogenesis.

Rank	Keywords	Counts	Rank	Keywords	Counts
1	angiogenesis	60	11	histone modification	16
2	DNA methylation	56	12	Mettl3	15
3	epigenetics	47	13	metastasis	14
4	miRNA	38	14	hypoxia	13
5	m^6A	32	15	lung cancer	12
6	methylation	25	16	biomarker	11
7	cancer	20	17	ncRNA	11
8	lncRNA	18	18	colorectal cancer	10
9	prognosis	18	19	proliferation	9
10	VEGF	17	20	renal cell carcinoma	9

and ncRNA are the target molecules of RNA methylation. Also, Fig. 7A indicates other targets of RNA methylations, such as p53, EZH2, BRCA1, MMP2, and TRAF1, and they have been intensively studied in the cancer field. Moreover, acute myeloid leukemia, hepatocellular carcinoma, glioma, metastasis, lung cancer, melanoma, breast cancer, colorectal cancer, and renal cell carcinoma are the keywords that are closely associated with tumor or cancer, which demonstrate that they are the research hotspots and trends of RNA methylation during angiogenesis. Also, some keywords are describing the technique analysis, such as RNA-seq and transcriptome which can be linked with some top co-cited references. Fig. 7B lists the top 25 keywords with the strongest citation bursts in time sequence, cancer or tumor occupy the majority of keywords since 2000; diabetic retinopathy and inflammation are new and developing topics that start trending in 2021.



(B) Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2000 - 2022
tumor suppressor	2000	4.07	2000	2011	
carcinoma	2000	2.52	2006	2011	
endothelial growth factor	2001	3.45	2011	2013	
histone deacetylase inhibitor	2011	2.38	2011	2013	
squamous cell carcinoma	2012	2.41	2012	2013	
biomarker	2013	2.35	2013	2019	
invasion	2000	2.24	2014	2017	
prostate cancer	2004	2.37	2015	2016	
metastasis	2016	2.49	2016	2018	
down regulation	2009	2.4	2016	2019	
promoter methylation	2017	3.41	2017	2019	
prognosis	2017	2.81	2017	2019	
protein	2005	3.12	2018	2019	
stem cell	2015	2.64	2018	2020	
epithelial mesenchymal transition	2009	2.38	2018	2020	
gene	2014	4.52	2019	2020	
nuclear rna	2020	3.62	2020	2022	
microrna	2020	2.99	2020	2022	
receptor	2020	2.67	2020	2020	
translation	2020	2.32	2020	2022	
n6 methyladenosine	2019	7.4	2021	2022	
pathway	2006	2.84	2021	2022	
diabetic retinopathy	2021	2.52	2021	2022	
inflammation	2021	2.52	2021	2022	
gastric cancer	2020	2.39	2021	2022	

Fig. 7. Keywords analysis of studies on RNA methylation during angiogenesis. (A) Keyword co-occurrence map by VOSviewer. (B) Top 25 keywords with the strongest citation bursts by CiteSpace.

4. Discussion

As a common epigenetic modification, RNA methylation is widely included in research fields, such as angiogenesis, immunity and metabolic process [38,39]. Abnormal angiogenesis is a pathological process in many diseases, which has attracted the attention of a large number of scholars [40]. In this study, regarding RNA methylation during angiogenesis, bibliometric analysis has been conducted to summarize the developmental trends and other characteristics of publications and research in this field.

In all, 382 publications were included in our analysis. Original articles and reviews made up 290 and 92 of these papers, respectively, which indicated that most studies were original research. The annual publication trends (Fig. 2) demonstrated the appearance of a sudden increase in pertinent publications in 2011, with a continuous increase starting from 2017. We only included publications since 2000, because only one paper was published before 2000, which may not influence the results. These data showed that the study of RNA methylation during angiogenesis had expanded rapidly in recent years, and would likely maintain this trend in the future. We found that 7 of 10 countries with the top number of publications were in the list of the top 10 centrality ranking (Table 1). Moreover, there was only one overlap in the top 10 institutions in terms of publication and centrality ranking (Table 2). These results suggested that publication numbers did not equate to publication influence and quality. Fig. 3B and C illustrated that academic circles have been initially formed among countries or institutions. We believe that cooperation between different countries or institutions could promote academic exchanges and communications, stimulate novel research ideas, accelerate the progress of research, and even promote the transformation of achievements. High-influenced countries or institutions in this field may also drive academic progress in other countries.

The top cited and co-cited references in the field of RNA methylation during angiogenesis were closely linked with biological functions of RNA methylation and cancer-related diseases, especially for m^6A modification. The reason for high citation frequency of these articles summarizing functions of RNA methylation is that they are the basic and an integral part of the studies and could help to deeply investigate the roles and mechanisms in the diseases.

Angiogenesis can be involved in multiple domains of research, such as immune rejection and wound healing [41,42]. Fig. 7A and Table 6 showed research highlights and focus by analysis of the keywords. m^6A, METTL3, and IGF2BP3 were keywords for describing m^6A modification, and the top cited or co-cited references were all under the theme of m^6A evidencing m^6A modification was the most widely studied direction in RNA methylation during angiogenesis. Moreover, cancer was the most widely and deeply explored in this field by the presentation of keywords, such as hepatocellular carcinoma, glioma, and metastasis, which may still be the promising research direction in the future.

In the present study, the results identified the developmental trends of RNA methylation and angiogenesis, the associated countries, institutions, authors, journals, references, and the involved keywords. Investigators may use the results as a guide for a quick and comprehensive understanding of the research field and to generate research ideas; the major research hotspots in the field have also been identified. However, some limitations still exist in our study. For example, we limited the search criteria to a specific period, specific article types, the English language, and only one database (WoSCC), which may result in possible bias in literature research. In addition, the citation frequency of a paper is related to the journal's influence and reputation, self-citation, and time of publication to some extent, thus, the citation number may not be exactly consistent with its real scientific worth and influence.

5. Conclusion

To sum up, the study presents the past patterns and prospects in RNA methylation during angiogenesis, which has been developing vigorously since 2011. Most included studies focused on this topic in the context of tumors, while there has been a recent increase in the number of studies focused on other aspects such as ocular diseases. Our results demonstrate that RNA methylation is a promising target in research of angiogenesis and related disorders, which deserves further investigations in the future.

Funding statement

This work was supported by grants from the National Natural Science Foundation of China (No. 82271110), and the Fundamental Research Funds for the Central Universities of Central South University (No. 2021zzts1068).

Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Bingyan Li: Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition. **Zicong Wang:** Writing – review & editing, Data curation, Formal analysis, Visualization, Writing – original draft. **Haixiang Zhou:** Data curation, Formal analysis. **Wei Tan:** Data curation, Formal analysis. **Jingling Zou:** Data curation, Formal analysis. **Yun Li:** Supervision, Writing – review & editing. **Shigeo Yoshida:** Supervision, Writing – review & editing. **Yedi Zhou:** Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: we declare that Yedi Zhou serves as an Associate Editor for Heliyon Clinical Research.

References

[1] Y. Motorin, M. Helm, RNA nucleotide methylation: 2021 update, Wiley Interdiscip Rev RNA 13 (1) (2022) e1691, https://doi.org/10.1002/wrna.1691.
[2] J. Li, C. Sun, W. Cai, et al., Insights into S-adenosyl-l-methionine (SAM)-dependent methyltransferase related diseases and genetic polymorphisms, Mutat. Res. Rev. Mutat. Res. 788 (2021) 108396, https://doi.org/10.1016/j.mrrev.2021.108396.
[3] C. He, Grand challenge commentary: RNA epigenetics? Nat. Chem. Biol. 6 (12) (2010) 863–865, https://doi.org/10.1038/nchembio.482.
[4] W. Huang, T.Q. Chen, K. Fang, et al., N6-methyladenosine methyltransferases: functions, regulation, and clinical potential, J. Hematol. Oncol. 14 (1) (2021) 117, https://doi.org/10.1186/s13045-021-01129-8.
[5] V. Khoddami, B.R. Cairns, Identification of direct targets and modified bases of RNA cytosine methyltransferases, Nat. Biotechnol. 31 (5) (2013) 458–464, https://doi.org/10.1038/nbt.2566.
[6] N.M. Mannion, S.M. Greenwood, R. Young, et al., The RNA-editing enzyme ADAR1 controls innate immune responses to RNA, Cell Rep. 9 (4) (2014) 1482–1494, https://doi.org/10.1016/j.celrep.2014.10.041.
[7] H. Shi, P. Chai, R. Jia, et al., Novel insight into the regulatory roles of diverse RNA modifications: Re-defining the bridge between transcription and translation, Mol. Cancer 19 (1) (2020) 78, https://doi.org/10.1186/s12943-020-01194-6.
[8] X. Chen, Y.Z. Sun, H. Liu, et al., RNA methylation and diseases: experimental results, databases, Web servers and computational models, Briefings Bioinf. 20 (3) (2019) 896–917, https://doi.org/10.1093/bib/bbx142.
[9] J. Liu, G. Jia, Methylation modifications in eukaryotic messenger RNA, J Genet Genomics 41 (1) (2014) 21–33, https://doi.org/10.1016/j.jgg.2013.10.002.
[10] W. Xu, J. Li, C. He, et al., METTL3 regulates heterochromatin in mouse embryonic stem cells, Nature 591 (7849) (2021) 317–321, https://doi.org/10.1038/s41586-021-03210-1.
[11] P. Nombela, B. Miguel-Lopez, S. Blanco, The role of m(6)A, m(5)C and Psi RNA modifications in cancer: novel therapeutic opportunities, Mol. Cancer 20 (1) (2021) 18, https://doi.org/10.1186/s12943-020-01263-w.
[12] P. Song, S. Tayier, Z. Cai, et al., RNA methylation in mammalian development and cancer, Cell Biol. Toxicol. 37 (6) (2021) 811–831, https://doi.org/10.1007/s10565-021-09627-8.
[13] S.U. Madugalle, K. Meyer, D.O. Wang, et al., RNA N(6)-methyladenosine and the regulation of RNA localization and function in the brain, Trends Neurosci. 43 (12) (2020) 1011–1023, https://doi.org/10.1016/j.tins.2020.09.005.
[14] K. Qiao, Y. Liu, Z. Xu, et al., Correction: RNA m6A methylation promotes the formation of vasculogenic mimicry in hepatocellular carcinoma via Hippo pathway, Angiogenesis (2022), https://doi.org/10.1007/s10456-022-09857-2.
[15] R. Su, L. Dong, Y. Li, et al., Targeting FTO suppresses cancer stem cell maintenance and immune evasion, Cancer Cell 38 (1) (2020) 79–96 e11, https://doi.org/10.1016/j.ccell.2020.04.017.
[16] D. Han, J. Liu, C. Chen, et al., Anti-tumour immunity controlled through mRNA m(6)A methylation and YTHDF1 in dendritic cells, Nature 566 (7743) (2019) 270–274, https://doi.org/10.1038/s41586-019-0916-x.
[17] P. Carmeliet, R.K. Jain, Angiogenesis in cancer and other diseases, Nature 407 (6801) (2000) 249–257, https://doi.org/10.1038/35025220.
[18] R. Jia, P. Chai, S. Wang, et al., m(6)A modification suppresses ocular melanoma through modulating HINT2 mRNA translation, Mol. Cancer 18 (1) (2019) 161, https://doi.org/10.1186/s12943-019-1088-x.
[19] K. Shan, R.M. Zhou, J. Xiang, et al., FTO regulates ocular angiogenesis via m(6)A-YTHDF2-dependent mechanism, Exp. Eye Res. 197 (2020) 108107, https://doi.org/10.1016/j.exer.2020.108107.
[20] C. Viallard, B. Larrivee, Tumor angiogenesis and vascular normalization: alternative therapeutic targets, Angiogenesis 20 (4) (2017) 409–426, https://doi.org/10.1007/s10456-017-9562-9.
[21] R. Lugano, M. Ramachandran, A. Dimberg, Tumor angiogenesis: causes, consequences, challenges and opportunities, Cell. Mol. Life Sci. 77 (9) (2020) 1745–1770, https://doi.org/10.1007/s00018-019-03351-7.
[22] D. Kir, E. Schnettler, S. Modi, et al., Regulation of angiogenesis by microRNAs in cardiovascular diseases, Angiogenesis 21 (4) (2018) 699–710, https://doi.org/10.1007/s10456-018-9632-7.
[23] H.A. Elshabrawy, Z. Chen, M.V. Volin, et al., The pathogenic role of angiogenesis in rheumatoid arthritis, Angiogenesis 18 (4) (2015) 433–448, https://doi.org/10.1007/s10456-015-9477-2.
[24] D. Ribatti, B. Nico, E. Crivellato, et al., The structure of the vascular network of tumors, Cancer Lett. 248 (1) (2007) 18–23, https://doi.org/10.1016/j.canlet.2006.06.007.
[25] G. Gupta, S. Kulasekaran, K. Ram, et al., Local characterization of neovascularization and identification of proliferative diabetic retinopathy in retinal fundus images, Comput. Med. Imag. Graph. 55 (2017) 124–132, https://doi.org/10.1016/j.compmedimag.2016.08.005.
[26] A.L. Magnussen, I.G. Mills, Vascular normalisation as the stepping stone into tumour microenvironment transformation, Br. J. Cancer 125 (3) (2021) 324–336, https://doi.org/10.1038/s41416-021-01330-z.
[27] R.R. Ramjiawan, A.W. Griffioen, D.G. Duda, Anti-angiogenesis for cancer revisited: is there a role for combinations with immunotherapy? Angiogenesis 20 (2) (2017) 185–204, https://doi.org/10.1007/s10456-017-9552-y.
[28] P. Carmeliet, R.K. Jain, Molecular mechanisms and clinical applications of angiogenesis, Nature 473 (7347) (2011) 298–307, https://doi.org/10.1038/nature10144.
[29] S. Vimalraj, A concise review of VEGF, PDGF, FGF, Notch, angiopoietin, and HGF signalling in tumor angiogenesis with a focus on alternative approaches and future directions, Int. J. Biol. Macromol. 221 (2022) 1428–1438, https://doi.org/10.1016/j.ijbiomac.2022.09.129.
[30] M. Dorrell, H. Uusitalo-Jarvinen, E. Aguilar, et al., Ocular neovascularization: basic mechanisms and therapeutic advances, Surv. Ophthalmol. 52 (Suppl 1) (2007) S3–S19, https://doi.org/10.1016/j.survophthal.2006.10.017.
[31] Y. Lin, J. Xu, H. Lan, Tumor-associated macrophages in tumor metastasis: biological roles and clinical therapeutic applications, J. Hematol. Oncol. 12 (1) (2019) 76, https://doi.org/10.1186/s13045-019-0760-3.
[32] Z. Mao, C. Liu, S. Chen, et al., A bibliometric analysis of exertional heat stroke research in Web of Science, Mil Med Res 3 (2016) 31, https://doi.org/10.1186/s40779-016-0101-6.
[33] X. Liu, S. Zhao, L. Tan, et al., Frontier and hot topics in electrochemiluminescence sensing technology based on CiteSpace bibliometric analysis, Biosens. Bioelectron. 201 (2022) 113932, https://doi.org/10.1016/j.bios.2021.113932.
[34] A. Ninkov, J.R. Frank, L.A. Maggio, Bibliometrics: methods for studying academic publishing, Perspect Med Educ 11 (3) (2022) 173–176, https://doi.org/10.1007/s40037-021-00695-4.
[35] M.E. Falagas, E.I. Pitsouni, G.A. Malietzis, et al., Comparison of PubMed, scopus, Web of science, and google scholar: strengths and weaknesses, Faseb. J. 22 (2) (2008) 338–342, https://doi.org/10.1096/fj.07-9492LSF.
[36] N.J. van Eck, L. Waltman, Software survey: VOSviewer, a computer program for bibliometric mapping, Scientometrics 84 (2) (2010) 523–538, https://doi.org/10.1007/s11192-009-0146-3.
[37] Z. Jiang, C. Wu, S. Hu, et al., Research on neck dissection for oral squamous-cell carcinoma: a bibliometric analysis, Int. J. Oral Sci. 13 (1) (2021) 13, https://doi.org/10.1038/s41368-021-00117-5.

[38] G. Chang, L. Shi, Y. Ye, et al., YTHDF3 induces the translation of m(6)a-enriched gene transcripts to promote breast cancer brain metastasis, Cancer Cell 38 (6) (2020) 857–871 e7, https://doi.org/10.1016/j.ccell.2020.10.004.
[39] Q. Wang, C. Chen, Q. Ding, et al., METTL3-mediated m(6)A modification of HDGF mRNA promotes gastric cancer progression and has prognostic significance, Gut 69 (7) (2020) 1193–1205, https://doi.org/10.1136/gutjnl-2019-319639.
[40] Y.C. Yi, X.Y. Chen, J. Zhang, et al., Novel insights into the interplay between m(6)A modification and noncoding RNAs in cancer, Mol. Cancer 19 (1) (2020) 121, https://doi.org/10.1186/s12943-020-01233-2.
[41] P. Libby, D.X. Zhao, Allograft arteriosclerosis and immune-driven angiogenesis, Circulation 107 (9) (2003) 1237–1239, https://doi.org/10.1161/01.cir.0000059744.64373.08.
[42] A.P. Veith, K. Henderson, A. Spencer, et al., Therapeutic strategies for enhancing angiogenesis in wound healing, Adv. Drug Deliv. Rev. 146 (2019) 97–125, https://doi.org/10.1016/j.addr.2018.09.010.
[43] X. Wang, Z. Lu, A. Gomez, et al., N6-methyladenosine-dependent regulation of messenger RNA stability, Nature 505 (7481) (2014) 117–120, https://doi.org/10.1038/nature12730.
[44] D. Dominissini, S. Moshitch-Moshkovitz, S. Schwartz, et al., Topology of the human and mouse m6A RNA methylomes revealed by m6A-seq, Nature 485 (7397) (2012) 201–206, https://doi.org/10.1038/nature11112.
[45] K.D. Meyer, Y. Saletore, P. Zumbo, et al., Comprehensive analysis of mRNA methylation reveals enrichment in 3' UTRs and near stop codons, Cell 149 (7) (2012) 1635–1646, https://doi.org/10.1016/j.cell.2012.05.003.
[46] G. Jia, Y. Fu, X. Zhao, et al., N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO, Nat. Chem. Biol. 7 (12) (2011) 885–887, https://doi.org/10.1038/nchembio.687.
[47] X. Wang, B.S. Zhao, I.A. Roundtree, et al., N(6)-methyladenosine modulates messenger RNA translation efficiency, Cell 161 (6) (2015) 1388–1399, https://doi.org/10.1016/j.cell.2015.05.014.
[48] H. Huang, H. Weng, W. Sun, et al., Recognition of RNA N(6)-methyladenosine by IGF2BP proteins enhances mRNA stability and translation, Nat. Cell Biol. 20 (3) (2018) 285–295, https://doi.org/10.1038/s41556-018-0045-z.
[49] F. Bray, J. Ferlay, I. Soerjomataram, et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J Clin 68 (6) (2018) 394–424, https://doi.org/10.3322/caac.21492.
[50] B.S. Zhao, I.A. Roundtree, C. He, Post-transcriptional gene regulation by mRNA modifications, Nat. Rev. Mol. Cell Biol. 18 (1) (2017) 31–42, https://doi.org/10.1038/nrm.2016.132.
[51] I.A. Roundtree, M.E. Evans, T. Pan, et al., Dynamic RNA modifications in gene expression regulation, Cell 169 (7) (2017) 1187–1200, https://doi.org/10.1016/j.cell.2017.05.045.
[52] M. Chen, L. Wei, C.T. Law, et al., RNA N6-methyladenosine methyltransferase-like 3 promotes liver cancer progression through YTHDF2-dependent posttranscriptional silencing of SOCS2, Hepatology 67 (6) (2018) 2254–2270, https://doi.org/10.1002/hep.29683.
[53] P. Mathiyalagan, M. Adamiak, J. Mayourian, et al., FTO-dependent N(6)-methyladenosine regulates cardiac function during remodeling and repair, Circulation 139 (4) (2019) 518–532, https://doi.org/10.1161/CIRCULATIONAHA.118.033794.
[54] M.D. Yao, Q. Jiang, Y. Ma, et al., Role of METTL3-dependent N(6)-methyladenosine mRNA modification in the promotion of angiogenesis, Mol. Ther. 28 (10) (2020) 2191–2202, https://doi.org/10.1016/j.ymthe.2020.07.022.
[55] Z. Li, H. Weng, R. Su, et al., FTO plays an oncogenic role in acute myeloid leukemia as a N(6)-methyladenosine RNA demethylase, Cancer Cell 31 (1) (2017) 127–141, https://doi.org/10.1016/j.ccell.2016.11.017.
[56] Z. Yang, T. Wang, D. Wu, et al., RNA N6-methyladenosine reader IGF2BP3 regulates cell cycle and angiogenesis in colon cancer, J. Exp. Clin. Cancer Res. 39 (1) (2020) 203, https://doi.org/10.1186/s13046-020-01714-8.
[57] Q. Cui, H. Shi, P. Ye, et al., m(6)A RNA methylation regulates the self-renewal and tumorigenesis of glioblastoma stem cells, Cell Rep. 18 (11) (2017) 2622–2634, https://doi.org/10.1016/j.celrep.2017.02.059.