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Review

The role of m6A in angiogenesis and vascular diseases

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SUMMARY

Angiogenesis, whether physiological or pathological, plays a pivotal role in various physiological and disease conditions. This intricate process relies on a complex and meticulously orchestrated signal transduction network that connects endothelial cells, their associated parietal cells (VSMCs and pericytes), and various other cell types, including immune cells. Given the significance of m6A and its connection to angiogenesis and vascular disease, researchers must adopt a comprehensive and ongoing approach to their investigations. This study aims to ascertain whether a common key mechanism of m6A exists in angiogenesis and vascular diseases and to elucidate the potential application of m6A in treating vascular diseases.

INTRODUCTION

There are three forms of epigenetic information: DNA and RNA modifications, posttranslational modification of chromatin, and the advanced structure of chromatin. RNA epigenetics, a cutting-edge domain of scientific inquiry that has flourished in recent years, represents an emerging avenue for posttranscriptional gene expression regulation. RNA epigenetic modification may cause changes in RNA pairing, thermodynamic, and folding properties, thus affecting variable splicing, translation, cell location, stability, and interactions with RNA. At the same time, it has universality and dynamic reversibility, which means that many cells can directly and instantaneously regulate gene expression by adding or removing these modifications to achieve a rapid response to microenvironment changes.

The preeminent methylation modification found within mRNA, N6-methyladenosine (m6A), pertains to the methylation of the 6th nitrogen atom situated within the adenosine acid nitrogen-containing base on the RNA molecule. This modification exists in almost all eukaryotic cells, mainly distributed in G(m6A)C (70%) or A(m6A)C (30%) conserved sequences. Within mammalian systems, the m6A RNA modification expedites the processing of primary mRNA as well as the transportation of mRNA. Although m6A was reported to exist in mRNA in mammalian cells as early as 1970,[1] its function has been rarely reported. It was not until 2011 that the obesity-related protein FTO was found to be an m6A demethylase on mRNA, revealing that m6A is a reversible modification, which reignited interest in its study.[2]

In 2012, two research groups independently reported the high level of the whole transcriptomic m6A.[3,4] To detect the content and location of RNA modifications, researchers have developed a variety of quantitative or site-specific RNA modification detection methods using liquid chromatography, mass spectrometry, and high-throughput sequencing. Currently, commonly used technologies for RNA quantitative detection mainly include two-dimensional cellulose thin-layer chromatography (2D-TLC), high-performance liquid chromatography (HPLC), and the coupling of liquid chromatography to mass spectrometry (LC-MS). RNA site-specific detection technology has evolved from primer extension technology and SCARLE technology, which had low throughput in the past, to high-throughput sequencing technology commonly used today. Presently, relatively mature high-throughput sequencing technologies include MeRIP-seq (methylated RNA immunoprecipitation sequencing), M6A-Seq, PA-m6A-seq (photo-crosslinking-assisted m6A sequencing), miCLIP (methylation individual nucleotide resolution crosslinking and immunoprecipitation), and other techniques.

The study of m6A involves the association of three crucial components: methyltransferase, demethylase, and binding protein. RNA m6A modification is performed by "writers," including methyltransferase (METTLs), Wilms tumor 1 associated protein (WTAP), zinc finger CCCH domain protein 13 (ZC3H13), and RNA-binding motif protein 15 (RBM15). The demodification of m6A is catalyzed by erasers, including human AlkB homologous H5 (ALKBH5) and alpha-ketoglutarate-dependent dioxygenase family fat mass and obesity (FTO); Thus, this m6A modification is reversible[5] (Figure 1). FTO catalyzes demethylation by the oxidation of m6A to N6-hydroxymethyladenosine and N6-formyladenosine, which are then hydrolyzed to adenine. In contrast, ALKBH5 directly removes the m6A modification. m6A "readers" are mainly divided into the following categories: Class I readers include those with YTH domains, including YTHDC1/2 and YTHDF1/2/3, which recognize and bind transcripts containing m6A through the YTH domain. Class II readers are heterogeneous ribonucleic acid proteins (hnRNPs), including hnRNP C and hnRNP A2B1, which regulate the alternative splicing or processing of transcription. IGF2BP family proteins IGF2BP1/2/3 are Class III readers that share six RNA-binding domains, including two RNA recognition motifs and four KH domains. Other readers include eukaryotic initiation factor 3 (EIF3), which promotes ncRNA translation, and human antigens that affect transcript stability.[6] After primary stimulation such as hypoxia, uncontrolled gene expression occurs, which can lead to tumor growth, angiogenesis and disease progression.

Essential for eliminating waste, preserving equilibrium, and blood circulation relies on the vascular system, comprising aortas, arteries, capillaries, and veins, which facilitate the transportation of blood throughout the entire body. Several mechanisms of angiogenesis have

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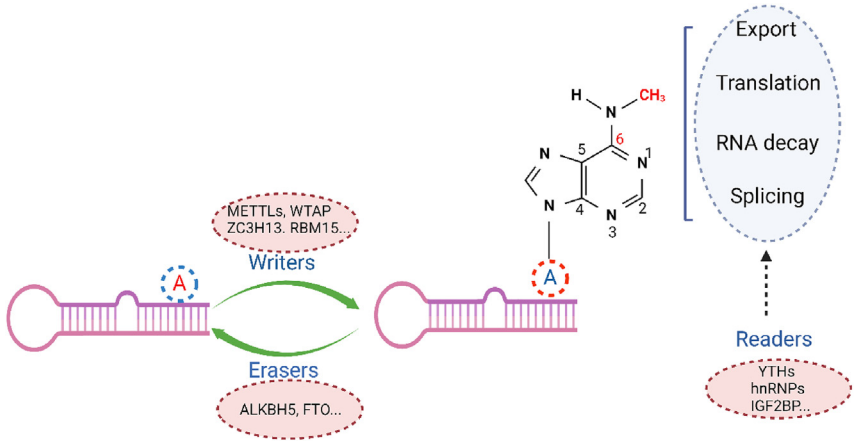

Figure 1. Three important components in m6A make m6A play a role as a complete and adjustable system

m6A modification occurs mainly on adenine in the RRACH sequence, whose function is determined by the "encoder," "Eraser," and "Reader." "Encoder (Writer)" is methyltransferase, and the components of this complex are known to be METTL3, METTL14, WTAP, and so forth; ALKBH5 and FTO, as demethylases, can reverse methylation. m6A is recognized by m6A binding proteins. Currently, it has been found that m6A binding proteins (readers) have YTH domain proteins (including YTHDF1, YTHDF2,YTHDF3, YTHDC1, and YTHDC2) and HNRNP family of nuclear heterogeneous proteins (HNRNPA2B1 and HNRNPC). YTHDF1 mainly affects the translation of m6A modified genes, YTHDF2 mainly affects the degradation of m6A modified genes, and YTHDC1 affects the splicing after binding to m6A modified genes. HNRNPC is a rich nuclear RNA binding protein involved in pre-mRNA processing and m6A mRNA modification performs its function mainly through two ways: fine-regulating the structure of methylated transcripts to prevent or induce protein-RNA interactions; Or is recognized directly by the m6A binding protein, inducing a subsequent response.

been confirmed (Figure 2). It is worth noting that unlike normal tissues that use germinated angiogenesis, angiogenesis, and intussusception, tumors can use all six angiogenic mechanisms.[7,8]

The biological process of angiogenesis plays a pivotal role in multiple life activities. Additionally, it gives rise to various pathological conditions, including neovascular diseases such as retinopathy, rheumatoid arthritis, AIDS/Kaposi's sarcoma, and cancer (tumorigenesis). Notably, both physiological and pathological angiogenesis share similar signal transduction activities and alterations in cellular function and behavior, rendering this process a potential target for novel disease treatments. However, a critical disparity lies in the uninterrupted progression of pathological angiogenesis even when tissue perfusion is inadequate, leading to uncontrolled, erratic growth that obstructs the advancement of new angiogenesis channels.

The process of angiogenesis is closely related to the formation and continuation of life (Figure 3). Angiogenesis can not only cause benign or malignant diseases but also be used as a treatment for diseases. Therefore, accurately regulating angiogenesis is crucial, although we are still far from the final goal. As an important RNA modification, m6A has been widely studied in the pathogenesis of many diseases, and the significance of m6A in angiogenesis has been underscored by numerous studies. This article focuses on the relationship between m6A, angiogenesis, and vascular diseases to determine whether there are common key mechanisms related to m6A involved in the occurrence and development of angiogenesis and vascular diseases and to introduce possible application prospects.

PHYSIOLOGICAL ANGIOGENESIS AND N6-METHYLADENOSINE

RNA m6A modification often occurs in many physiological processes especially in ontogenesis.[9] Parial et al. developed two METTL3 gene knockout (KO) zebrafish lines using CRISPR–Cas9 genome editing via PHLPP2/mTOR-Akt signaling.[10] In addition, METTL3-mediated methylation of m6A is crucial in the response to hypoxic stress, and the promotion of angiogenesis is confirmed. *In vitro* experiments showed that METTL3 mechanically methylated the scattered 1 (DVL1) of LRP6 and m6A to regulate Wnt signal transduction and further mediate angiogenesis.[11]

During osteogenesis, the overexpression of METTL3 activates the PI3K/Akt signaling pathway in EPCs, promoting their growth, migration, and tubular formation activity, ultimately stimulating EPC angiogenesis.[12] In osteogenic bone marrow mesenchymal stem cells (BMSCs), METTL3 demonstrates heightened expression and facilitates the secretion of VEGF, thereby fostering local angiogenesis. Depletion of METTL3 leads to a reduction in the expression of vascular endothelial growth factor A (VEGFA). Cai et al. noted a decline in the expression of ALKBH1 in BMSCs during the aging process. Knocking out ALKBH1 induces adipogenic differentiation in BMSCs while impeding their osteogenic differentiation.[13] Another study demonstrated that silencing FTO in EC could induce the hypermethylation of key angiogenic genes (such as FAK). The m6A reader YTHDF2 recognizes FAK and triggers RNA decay, thereby regulating ocular angiogenesis.[14] In contrast, METTL14 reduced the m6A methylation of TIE1, while miR-4729 was able to inhibit this process, and ultimately, the TIE1/VEGFA signaling pathway in EC was blocked.[15,16]

The immune microenvironment at the maternal-fetal interface is determined by the crosstalk between trophoblast and maternal-derived cells, which changes dynamically throughout the pregnancy. As innate immune cells, trophoblast cells talk to maternal cells according to the

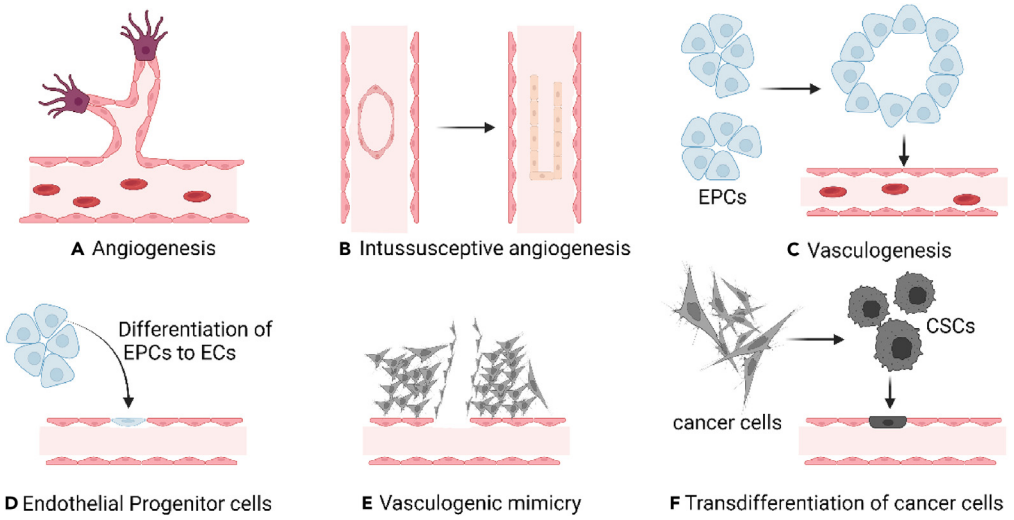

Figure 2. Several mechanisms of angiogenesis have been confirmed

Mechanisms of blood vessel formation. New blood vessel formation in normal tissues and tumors occurs through one or more of the following mechanisms: (A) Germinal angiogenesis: The process of formation and growth of buds (tip cells) that eventually fuse with existing blood vessels or newly formed buds.
(B) Enteroreceptive angiogenesis: The formation of a new vascular system when the original blood vessel splits in half.
(C) Angiogenesis: prenatal endothelial progenitor cell neovascularization. Endothelial progenitor cells proliferate and form lumens that eventually assemble into new blood vessels.
(D) Recruitment of endothelial progenitor cells: Formation of blood vessels in tumors by recruitment of circulating endothelial progenitor cells.
(E) Vascular simulation: fluid conduction network embedded by stroma formed by tumor cells.
(F) Trans differentiation of cancer stem cells (CSC): The formation of new blood vessels through the differentiation of CSC into endothelial cells in tumors.

local immune microenvironment to ensure early embryonic development. Therefore, the dysfunction of trophoblast cells and maternal deciduous cells is an important factor in pregnancy complications, especially repeated pregnancy loss in early pregnancy. Since many unknown regulatory factors still influence the complex immune state, it is necessary to explore new potential factors that may influence early pregnancy. RNA methylation plays an important role in transcriptional regulation in a variety of cells. Numerous studies have shown that N6-methyladenosine (m6A)- and m6A related - regulatory factors play a crucial role in embryo implantation.[17–19] They are also essential in regulating innate and adaptive immune cells and immune responses and in shaping local and systemic immune microenvironments. However, the function of m6A modification at the maternal-fetal interface is still lacking extensive research.

In the investigation by Lin et al., the differentiation of ADSCs into VSMCs under hypoxic conditions appeared to be linked to METTL3. Upon the silencing of METTL3 in ADSCs, the expression levels of characteristic VSMC markers, including VEGF and TGF-β, exhibited a decline during ADSC differentiation. Moreover, the expression levels of paracrine factors also decreased, highlighting the pivotal role of METTL3 as a key regulatory element in promoting ADSC differentiation into VSMCs.[20]

PATHOLOGICAL ANGIOGENESIS AND N6-METHYLADENOSINE

N6-methyladenosine and tumor angiogenesis

The vasculature is an important channel for tumor metastasis. Uncontrolled angiogenesis is a sign of tumor invasion. There is compelling evidence indicating the extensive involvement of m6A in angiogenesis across various tumors.[21,22] Furthermore, METTL3 facilitates the maturation of miR-143-3p by splicing its precursors, while miR-143-3p can also serve as a target of angiostatin-1, resulting in a reduction in VEGFA ubiquitination, inhibition of VEGFA degradation, and the promotion of cancer angiogenesis.[23]

Studies have shown that miR-320b can cause tumor cell apoptosis and inhibit its proliferation.[24]Within cancerous tissues, the heightened expression of miR-320b hampers the expression of IGF2BP2, subsequently diminishing the stability of thymidine kinase 1 (TK1) mRNA. Given the pivotal role of TK1 as a significant kinase in angiogenesis, the involvement of miR-320b in suppressing cancer progression through the inhibition of IGF2BP2/TK1 becomes evident.[25]

Gastrointestinal tumors

The acceleration of angiogenesis in malignant tumors by vascular mimicry (VM) has been substantiated, yet the precise mechanism underlying VM remains incompletely elucidated. Recent research has revealed that METTL3 targets EphA2 and VEGFA via an IGF2BP3-dependent mechanism in colorectal cancer. These findings have also been corroborated in the domain of gastric cancer.[26] Wang et al. showed that in gastric cancer, the overexpression of METTL3 promoted liver metastasis and angiogenesis, This is linked to the methylation status of

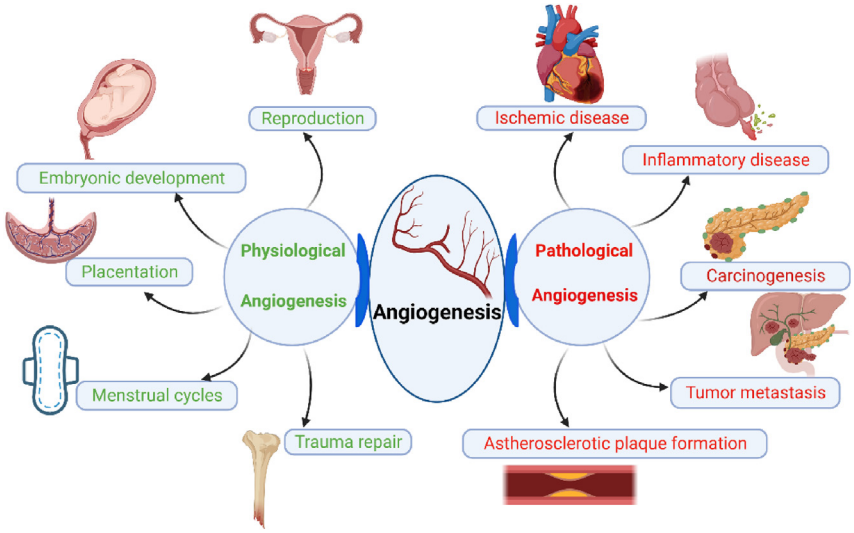

Figure 3. The role of angiogenesis in participating in different life processes, both physiologically and pathologically

Nutrients, oxygen, metabolites, chemical mediators, and metabolic waste can be transported through blood vessels between cells to maintain the dynamic balance of the immune system, body temperature, and PH. Blood vessels play an important role in embryonic development, body growth, and wound healing. Although blood vessels are good for tissue growth and regeneration, they fuel inflammation and malignant disease and are used by tumor cells to metastasize and kill patients with cancer. Because blood vessels nourish nearly every organ in the body, deviations from normal blood vessel growth can lead to many diseases. To name just a few, inadequate blood vessel growth or maintenance can lead to stroke, myocardial infarction, ulcerative disease, and neurodegeneration, as well as abnormal blood vessel growth or remodeling leading to cancer, inflammatory diseases, pulmonary hypertension and blind eye disease.

secreted heparin-binding growth factor (HDGF).[27] Furthermore, HDGF acts as the substrate of IGF2BP3, which enhances the stability of HDGF mRNA, consequently fostering tumor angiogenesis. Chen combined m6A with circular RNA, confirming the methylation of m6A on circular RNA (circRNA), which contributes to angiogenesis in colorectal cancer (CRC).[28,29] By suppressing the expression of miR-30c-5p, Circ3823 augments the translation of TCF7. In addition, TCF7 induces the expression of Myc and CCND1 to promote growth, metastasis, and angiogenesis in CRC.[29]

Significantly reducing the recognition of the m6A modification by CCND1 and VEGF, the downregulation of IGF2BP3 expression consequently diminishes mRNA expression and stability. Acting as an m6A reader, IGF2BP3 inhibits colon cancer angiogenesis by controlling VEGF, effectively suppressing cancer-related angiogenesis.[29] Zhang et al. showed that VEGFA, METTL3 and linc00662 RNA were highly expressed in 64 pairs of CRC and adjacent normal tissues.[30]

Liver cancer

In the context of human hepatocellular carcinoma (HCC), gene ontology research has revealed that FTO is involved in the regulation of angiogenesis. Furthermore, a connection has been established between decreased FTO expression and microvessel density (MVD) in intrahepatic cholangiocarcinoma (ICC), hinting at a potentially unfavorable prognosis.[31] Additionally, research has demonstrated that the overexpression of YTHDF2 can impair the growth of HCC. Regarding the proliferation of hepatocellular carcinoma, an investigation into the association between YTHDF2 and tumor blood vessels proposed that the escalation of serine endopeptidase inhibitor 2 (SERPINE2) in YTHDF2-silenced cells might contribute to the stimulation of angiogenesis and the advancement of HCC growth.[32]

The prognostication of patients is progressively incorporating the utilization of angiogenesis-related genes (ARGs). Qu generated 13 prognostic genes through univariate Cox regression analysis of m6A-related ARGs (mARGs), analyzed their enriched functions and pathways, constructed a prognostic feature score and verified its reliability. In the construction of prognostic features and risk group identification, four parameters are employed. Among these, EGF, itga5, and itgav were identified as prognostic risk factors, whereas PLG was classified as a prognostic protective factor. In comparison to patients deemed low-risk, those in the high-risk group displayed poorer prognoses among patients with HCC, demonstrating notable distinctions in clinical characteristics and the tumor microenvironment. This study underscores variances in the tumor immune microenvironment among patients with HCC, potentially furnishing novel targets for forthcoming treatments.[33]

It is well known that the combination of immune checkpoint inhibitors and antiangiogenic therapy has been approved as a new first-line treatment for advanced HCC, and m6A regulator-mediated modification plays a key role in regulating tumor immunity and the angiogenesis microenvironment. Wang et al. identified three m6A clusters with different microenvironments of immunity and angiogenesis through bioinformatics methods and further constructed a 5-gene prognostic marker (called the m6Asig score), which can predict immune and antiangiogenic responses. The results showed that a high m6Asig score was related to poor prognosis, late TNM stage and a high frequency of TP53 mutation, which may guide strategies for the combined treatment of HCC with immunotherapy and antiangiogenic therapy.[34]

Tumors of the urinary system

In bladder cancer tissue, METTL3 has been shown to enhance the Tek/PI3K/VEGF cascade and is involved in tumor cell angiogenesis.[21] Liu et al. focused on the relationship between PM2.5 and bladder cancer and discovered that PM2.5 heightened the expression of METTL3 through the induction of hypomethylation in the METTL3 promoter and the augmentation of binding affinity for the transcription factor HIF1α. BIRC5 was identified as the target of METTL3, and BIRC5 is involved in the proliferation and metastasis of bladder cancer, as well as angiogenesis regulated by VEGFA.[35] Furthermore, recent studies have confirmed the m6A modification of circPOLR1A in renal cell carcinoma, and the m6A reader YTHDF2 can regulate the expression of circPOLR1A in renal cell carcinoma.[36] Sunitin is mainly used to treat patients with metastatic renal cell carcinoma. Chen et al. identified a tumor necrosis factor receptor-related factor (TRAF1) and showed that silencing TRAF1 increased apoptosis and the anti-angiogenic effect of Sunitinib. Mechanistically, this effect is caused by an increase in m6A levels in a METTL14-dependent manner.[37]Lymphatic metastasis is considered the primary mode of metastasis for bladder cancer (BLCa), but blood metastasis accounts for the majority of cancer-related deaths. In the past two decades, lncRNAs have received a great deal of attention as a new hope for the development of targeted drug therapies for metastatic cancer; However, the underlying mechanism of lncRNA's involvement in BLCa hematometastasis remains to be elucidated. Here, we found BLCA-associated transcript 3 (BLACAT3), a lncRNA that is abnormally upregulated in BLCa and associated with poor prognosis in patients with muscle-invasive bladder cancer. Methods: m6A table transcriptome chip, RNA sequencing and mass spectrometry were used to screen the key molecules of the regulatory axis. Function analysis, animal models and clinical samples were used to investigate the role of BLACAT3 *in vitro* and *in vivo* BLCa. Mechanistically, m6A modification promotes BLACAT3 upregulation by stabilizing RNA structure. BLACAT3 recruits YBX3 into the nucleus, synergically enhances NCF2 transcription and promotes BLCa angiogenesis and blood metastasis by activating the downstream NF-κB signaling pathway. The findings will provide prognostic tools for patients with BLCa and identify new therapeutic biological targets for metastatic BLCa.[38]

Lung cancer

m6A modification is essential in every biological behavior of lung cancer cells, such as proliferation or metastasis. In addition to revealing the role of the m6A enzyme in each stage of lung cancer progression, a holistic exploration of the role of the m6A enzyme in the continuum of lung cancer cell proliferation, invasion, and metastasis will allow us to better understand how the vast m6A regulatory network is orchestrated to regulate lung cancer progression. First, m6A modification plays its major role in lung cancer progression by modifying various cancer-associated mRNAs.

Zhang et al. found that m6A triggers lung cancer angiogenesis by upregulating VEGFA, a central regulator of new blood vessels and blood vessel growth.[39] m6A sequencing and functional studies confirmed that m6A modifies the 5′UTR (untranslated region) of VEGFA to regulate its translation. Specifically, methylation of ribosome entry sites (IRES) within the 5′UTR recruits the YTHDC2/eIF4GI complex to trigger cap-independent translation initiation. Interestingly, the m6A methylation site A856 of the 5′UTR is located within the conserved upstream open reading frame (uORF) of VEGFA IRES-A, which overcomes UORF-mediated translation inhibition while promoting G-tetrad induced VEGFA translation. Targeting specific demethylation of VEGFA m6A significantly reduces VEGFA expression and reduces lung cancer cell-driven angiogenesis. *In vivo* and clinical data confirm the positive effects of m6A modified VEGFA on lung cancer angiogenesis and tumor growth.

The researchers collected lung cancer tissue and adjacent non-cancerous tissue from 66 patients with lung cancer. The low level of miR-320b expression in cancer tissues was determined by experiments.[40] The results showed that overexpression of mir-320b inhibited cancer cell invasion, tubule formation, tumor volume, and angiogenesis in xenografted nude mice. Based on chip analysis, hepatic nuclear factor 4γ (HNF4G) was identified as the target of miR-320b. Dual luciferase reporter gene assay further confirmed the binding relationship between HNF4G and miR-320b. The expressions of HNF4G and insulin-like growth factor 2 mrna binding protein 2 (IGF2BP2) were increased in lung cancer. At the same time, hnf4g knockdown inhibited the expression of igf2bp2, thereby inhibiting the invasion of cancer cells and the formation of tubules. In addition, IGF2BP2 modifies m6A and increases the expression of thymidine kinase 1 (TK1), thereby promoting angiogenesis. In nude mice, the restoration of TK1 reversed the inhibitory effects of miR-320b overexpression on tumor growth rate and CD31 expression. In summary, miR-320b inhibits the growth and angiogenesis of lung cancer by inhibiting HNF4G, IGF2BP2 and TK1.

Fang et al. performed single-cell transcriptomic analyses of 11 distal normal lung tissues, 11 primary LUAD tissues, and 4 metastatic LUAD tissues from the GSE131907 dataset.[41] The lung multicellular ecosystem was characterized at single-cell resolution and the potential mechanisms of LUAD angiogenesis and metastasis were explored. A global single-cell landscape of 93,610 cells from both primary and metastatic LUAD was constructed and IGF2BP2 was found to be specifically expressed in both LUAD cell subsets (called LUAD_IGF2BP2) and endothelial cell subsets (called En_IGF2BP2). The LUAD_IGF2BP2 subgroup gradually formed and dominated the ecology of metastatic LUAD during the process of metastatic evolution. IGF2BP2 is preferentially secreted by exosomes in the LUAD_IGF2BP2 subgroup and absorbed by the En_IGF2BP2 subgroup in the tumor microenvironment. Subsequently, IGF2BP2 improves the RNA stability of FLT4 through m6A modification, thereby activating the PI3K-Akt signaling pathway and ultimately promoting angiogenesis and metastasis. These findings provide new insights into the multicellular ecosystem of primary and metastatic LUAD and demonstrate that specific LUAD_IGF2BP2 subpopulations are key coordinators of the promotion of angiogenesis and metastasis, with gene regulatory mechanisms for the evolution of LUAD metastasis, representing them as potential anti-angiogenic targets.

Shen et al. showed through bioinformatics analysis that the expression level of m6a related genes in lung cancer tissues changed significantly compared with normal lung tissues.[42] Through analysis of public databases, it was found that ALKBH5 expression was up-regulated in lung cancer tissues and was associated with poor prognosis in patients with lung cancer. Knockdown of ALKBH5 inhibited the proliferation and migration of cultured lung cancer cell lines. The results showed that ALKBH5 silencing also inhibited the growth and metastasis of

zebrafish lung cancer grafts. Furthermore, knockdown ALKBH5 inhibits lung cancer angiogenesis *in vitro* and *in vivo*. Mechanism studies have shown that the knockdown of ALKBH5 can reduce the expression and stability of PVT1 in lung cancer cells. Next, PVT1 was observed to promote the progression of lung cancer cells and regulate VEGFA expression and lung cancer angiogenesis. These results confirm that ALKBH5 promotes the progression and angiogenesis of lung cancer by regulating the expression and stability of PVT1, providing a potential target for the prognosis and treatment of patients with lung cancer.

Others

Metastasis is the leading cause of death in patients with breast cancer (BC). Cancer-associated fibroblasts (CAFs) are the main stromal components in the tumor microenvironment and the main factor in tumor metastasis. However, the function and mechanism of primary CAFs in the pre-organ metastasis niche of BC secondary remain unclear. Zeng et al. found that LncSNHG5 is highly expressed in mammary CAFs and plays an important role in pre-metastatic niche formation by promoting angiogenesis and vascular leakage in CAFs through the regulation of ZNF281. lncSNHG5 enhances the stability of ZNF281 mRNA by binding to the m6A reader IGF2BP2.[43] Inhibitors RS102895, marasviroc, and cenicriviroc inhibit PMN angiogenesis and vascular permeability by blocking CCL2/CCR2 and CCL5/CCR5 binding. Their study suggests that lncSNHG5 and its downstream signaling pathway, ZNF281-CCL2/CCL5, play a critical role in the formation of pre-metastatic breast cancer niche and may be potential targets for the diagnosis and treatment of BC metastasis.

Angiogenesis and metastasis are the main causes of poor prognosis in patients with ovarian cancer. Liu et al. found that long-chain noncoding RNA NEAT1 is highly expressed in tissues and cell lines of patients with ovarian cancer.[44] MiR-214-3p was identified as the target of NEAT1, and they antagonize each other in a reciprocal manner. SKOV-3 and A2780 cells overexpressed with neat1 showed significantly increased proliferation, decreased apoptosis, and enhanced migration and invasion, while cells with low neat1 knockdown showed significantly reduced malignant tumor characteristics. In addition, the expression level of NEAT1 was positively correlated with the expression levels of angiogenesis related molecules, including Sema4D (Sema4D), Sema4D receptor plexin B1, T-lymphoma invasion and metastasis induction protein 1 (Tiam1), and RHO-like GTPases Rac1/2. In xenografted mouse models, the higher the NEAT1 expression, the faster the tumor growth *in vivo*, the more angiogenesis in tumor tissue, and the higher the expression levels of angiogenesis related molecules and CD31. This result confirms that NEAT1 promotes angiogenesis and metastasis in human ovarian cancer. NEAT1 and miR-214-3p are promising targets for the development of treatments for human ovarian cancer.

The aim of Wen et al.'s pharyngitis was to explore the potential mechanism of alkaline leucine zips ATF-like transcription factor 2 (BATF2) in tongue squamous cell carcinoma (TSCC).[45] They examined the expression of BATF2 in TSCC tissues and adjacent normal TSCC tissues, human TSCC cell lines (SCC-15 and CAL-27), and NTEC in normal human tongue epithelial cells. Then, stable SCC-15 cells with low BATF2 knock and CAL-27 cells with BATF2 overexpression were established to study the effect of BATF2 on TSCC function. Not only that, they also examined the effects of BATF2 on TSCC angiogenesis and BATF2 m6A methylation. BATF2 is significantly down-regulated in TSCC tissues and cell lines, and overexpression of BATF2 inhibits the growth, metastasis and angiogenesis of TSCC. Mechanically, vascular endothelial growth factor A (VEGFA) was identified as a downstream gene of BATF2 and confirmed that BATF2 inhibits TSCC growth, metastasis, and angiogenesis by inhibiting VEGFA. This suggests that the METTL14/BATF2 axis is promising as a new candidate therapeutic target for anti-angiogenesis of TSCC.

Diabetic retinopathy

Diabetic retinopathy (DR) affects most patients with diabetes and has become the main cause of vision decline. In addition, various limitations related to current diagnosis and treatment strategies, such as the lack of early diagnosis and treatment methods, differences in treatment responses among patients and cost-effectiveness, urge people to find alternative solutions. Angiogenesis is not only the most critical factor in controlling the progression and pathogenesis of DR but is also the main target of current treatments. METTL14 and ALKBH5 regulate the transformed m6A-modified growth factor by reciprocally controlling their expression and inhibiting YTHDF3 (RNA demethylase activity blocker) β^6. Altering the conversion efficiency and stability of TGF-β, the primary factor in DR microvascular disease, could significantly influence DR management. Additionally, METTL3-mediated m6A modification during hypoxia fosters angiogenesis through its interaction with YTHDF1, thereby regulating the translation of genes associated with Wnt signal transduction.[11] The Wnt signaling pathway is significantly altered in DR, regulates a variety of biological phenomena, and contributes to angiogenesis. In contrast, WTAP inhibits angiogenesis in endothelial cells.[46] In addition, FTO regulates endothelial cell function and ocular angiogenesis in an m6A- and YTHDF2-dependent manner.[14] FTO overexpression regulates angiogenesis and fibrosis pathways,[16] both of which have key impacts on the pathogenesis and progression of DR. Consequently, m6A and its intermediaries engage in the regulation of angiogenesis, thereby reinforcing their significance as a target in DR management.

Huang found that circFAT1 promoted autophagy and inhibited pyroptosis in retinal pigment epithelial (RPE) cells induced by high glucose and could bind with YTHDF2.[47] This study provides new ideas for DR prevention and treatment. Some studies have confirmed that METTL3-mediated m6A methylation regulates diabetes-induced pericyte dysfunction, while the METTL3-YTHDF2-PKC-η/FAT4/PDGFRA signaling axis can be a target for the treatment of microvascular complications.[48] Some studies have confirmed that the low expression of A20 leads to increased M1 polarization of retinal microglia in diabetic retinopathy, which is caused by the m6A modification mediated by ALKBH5.[49] The upregulation of KAT1 inhibited inflammation, neovascularization and vascular leakage in mouse retinal tissue. KAT1 activated the transcriptional activity of YTHDF2 through the histone acetylation of the promoter. YTHDF2 triggers the instability of ITGB1 mRNA and induces mRNA degradation in the form of m6A.[50]

PARP1 knockout not only significantly increased the activity of hRMECs (human retinal microvascular endothelial cells) but also prevented glucose-induced inflammation, fibrosis and angiogenesis *in vivo* even under high glucose conditions. This process is closely related to YTHDF2.[51]

Breakdown of the blood–retinal barrier (BRB) is the main cause of many eye diseases, including diabetic retinopathy, age-related macular degeneration, and retinal vascular occlusive diseases, augmented vascular permeability may culminate in angiogenic edema and tissue impairment, significantly impacting vision. Overexpression of CYP2J2 in ECs maintained the integrity of the BRB after ischemia–reperfusion injury, thus protecting against the loss of retinal ganglion cells. CYP2J2 upregulates the expression of METTL3, promoting the translation of ANXA1 through the m6A modification of ANXA1 in endothelial cells under oxidative stress. Ultimately, the CYP2J2-METTL3-ANXA1 pathway emerged as a plausible therapeutic target for mitigating BRB injury.[52]

The role of N6-methyladenosine in atherosclerosis (AS)

Cardiovascular and cerebrovascular diseases are among the diseases with the highest disability and mortality rates in the world. As the main cause and basis of most cardiovascular and cerebrovascular diseases, AS is a chronic inflammatory disease characterized by endothelial cell dysfunction, lipid influx and accumulation, immune cell activation and infiltration, and the formation of vascular wall foam cells. Recent studies have shown that the m6A methylation modification may affect the occurrence and development of AS,[53] but the specific mechanism of its role in AS remains to be clarified. Vascular endothelial cells, smooth muscle cells, and macrophages are thought to be important players in the progression of atherosclerotic plaques, and m6A methylation may affect the function of these three cell types. Endothelial cell damage and dysfunction of cell structure caused by inflammation is one of the important mechanisms for the occurrence and development of AS, and so protecting endothelial cells is of great importance in AS.

The N6-methyladenosine methylation modification and ECs

Recently, it was reported that METTL14 expression is significantly elevated during the inflammatory response of vascular endothelial cells. Identification of m6A methylation-modified mRNAs by methylated RNA immunoprecipitation sequencing showed that FoxO1 was a potential target. RNA coimmunoprecipitation experiments demonstrated that METTL14 could bind to FoxO1 mRNA directly and recognize the methylation site by YTHDF1, which promoted FoxO1 mRNA translation. Knockdown of METTL14 significantly attenuated inflammation-induced FoxO1 expression, alleviated EC inflammation and delayed the development of AS, suggesting that the m6A methylation modification is involved in vascular EC inflammation and plays an important role in AS.[54] In addition, atorvastatin reduced FTO expression in vascular endothelial cells. Knockdown of FTO enhanced Kruppel-like factor 2 (KLF2) and endothelial nitric oxide synthase (eNOS) expression and decreased inflammation-induced vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) expression in endothelial cells. Methylated RNA coimmunoprecipitation and dual luciferase reporter assays showed that FTO could bind to KLF2 and eNOS and regulate their expression in an m6A-dependent manner, suggesting a role for the m6A methylation modification in regulating endothelial cell function.[55] Zhang et al.[56] found that the expression of ALKBH5 was significantly decreased during endothelial cell apoptosis. However, ALKBH5 overexpression significantly decreased endothelial cell apoptosis, and the expression of BCL2 increased significantly. However, silencing BCL2 reversed ALKBH5-mediated inhibition of TNF-α-induced apoptosis, indicating that ALKBH5 suppresses vascular endothelial cell apoptosis by increasing BCL2 expression. In addition, studies have shown that the m6A methylation modification plays a role in regulating angiogenesis in endothelial cells. RNA transcriptome sequencing analysis showed that the expression of METTL3, a core enzyme in the m6A methyltransferase complex, was decreased and differentially localized in arteriovenous malformations with different lesion sizes. Knockdown of METTL3 can persistently activate the Notch signaling pathway, which affects endothelial cell angiogenesis.[57] Additionally, a study reported that ALKBH5 plays a role in maintaining angiogenesis in endothelial cells after acute ischaemic stress by reducing SphK1 m6A methylation and downstream eNOS Akt signaling.[58] Overall, the m6A methylation modification can affect the biological functions of vascular endothelial cells and play a role in the corresponding diseases.

The N6-methyladenosine methylation modification and vascular smooth muscle cells

Vascular smooth muscle cells have phenotypic and functional plasticity in response to vascular injury. In the presence of damaged blood vessels, VSMCs are able to switch from a quiescent contractile phenotype to a secretory phenotype with proliferation, migration, and synthesis abilities. The postoperative occurrence of AS and vascularization are related to stenosis. Intimal hyperplasia caused by vascular smooth muscle cell proliferation and migration is one of the important causes of arterial restenosis.

Recently, Zhu et al. examined the m6A methylation modification in balloon-injured rat carotid arteries and showed that the m6A methylation modification was reduced.[59] After treatment with Panax notoginseng saponins, WTAP expression increased, VSMC proliferation and migration decreased, suggesting that WTAP via the m6A methylation modification, which in turn affects VSMC viability, proliferation and migration. These findings reveal that the m6A methylation modification plays a critical role in intimal hyperplasia and provide a potential biomarker and novel target for the prevention and treatment of AS after angioplasty. Similarly, a recent study by Zhang et al. reported the involvement of the m6A methylation modification in insulin resistance-induced abnormal proliferation of vascular smooth muscle cells.[60] In that study, FTO levels were increased in insulin-treated vascular smooth muscle cells and mice with type 2 diabetes combined with vascular intimal injury, and knockout of FTO inhibited the insulin-induced abnormal proliferation and migration of vascular smooth muscle cells. Mechanistically, the m6A binding protein IGF2BP2 regulated cardiac hypertrophy by recognizing and binding to smooth muscle 22 α (SM22 α) m6A methylation sites on mRNA, enhancing the stability of SM22 α mRNA. However, in insulin-treated VSMCs, the increase in FTO could

specifically remove SM22 α m6A methylation sites on mRNA, downregulating SM22 α expression, which in turn promoted the proliferation and migration of vascular smooth muscle cells. The m6A methylation modification can upregulate SM22α expression and plays an important role in regulating the proliferation and migration of vascular smooth muscle cells. Qin et al. found that the expression levels of METTL3 and YTHDF2 were significantly increased in pulmonary artery smooth muscle cells under hypoxic conditions and in a rat model of hypoxia, and silencing METTL3 attenuated the proliferation and migration of pulmonary artery smooth muscle cells.[61] Further studies proved that YTHDF2 could recognize METTL3 to mediate the m6A methylation modification of PTEN mRNA and promote PTEN degradation, and the decrease in PTEN led to the hyperproliferation of pulmonary artery smooth muscle cells by activating the PI3K Akt signaling pathway. In addition, it was found that METTL3 and related paracrine factors such as VEGF and TGF were involved in the differentiation of adipose stem cells into vascular smooth muscle stem cells induced by hypoxia-β. The expression was upregulated. The results showed that hypoxic stress promoted the differentiation of adipose stem cells into vascular smooth muscle cells and regulated the expression of paracrine factors by regulating the expression of METTL3, thus affecting the migration, proliferation and differentiation of cells.[20] In summary, our study demonstrated that the m6A methylation modification could regulate the activities, migration and proliferation of VSMCs and, to a certain extent, affect the stability of VSMCs under pathological conditions, providing potential therapeutic targets and biomarkers for the prevention and treatment of vascular stenosis.

The N6-methyladenosine methylation modification and macrophages

AS is a chronic inflammatory disease. Monocytes and macrophages are important effector cells in the immune system. In AS, monocytes and macrophages play a central role in the initiation, progression, and eventual rupture of arterial plaques. Therefore, exploring new biological functions and mechanisms of monocytes and macrophages in regulating inflammation is critical for the treatment of AS. Mitochondria play a crucial role in regulating the inflammatory state of monocytes. Zhang et al. found that METTL3 cooperates with YTHDF2 to decrease cellular adenosine triphosphate (ATP) production, consequently increasing cellular and mitochondrial ROS accumulation and promoting proinflammatory cytokine release by inflammatory monocytes.[62] In addition, Zheng et al. demonstrated that in macrophages with METTL14 knockdown, the anti-inflammatory M2 macrophage phenotype was increased, and foam cell formation was decreased. Mechanistically, METTL14 can increase the expression level of MyD88 and affect the nuclear distribution of p65 through the m6A methylation modification, which in turn promotes the secretion of the inflammatory factor IL-6. These results suggest that METTL14 can regulate macrophage inflammation and thereby plays an important role in AS.[63] Cai et al. recently reported that the expression of METTL3 was reduced in endotoxin-stimulated macrophages and that TNF-α and proinflammatory cytokines such as IL-6 were significantly upregulated following METTL3 knockout. Further experiments revealed that the loss of METTL3 inhibited YTHDF2-mediated degradation of nucleotide binding oligomerization domain-like receptor 1 (Nod1) and serine threonine kinase 2 (ripk2) mRNA, upregulated the Nod1 pathway, and promoted endotoxin-induced macrophage inflammatory responses.[64] The level of the m6A methylation modification and the expression of METTL3 are increased in macrophages stimulated with oxidized LDL,were showed in another study, and silencing METTL3 can inhibit LDL-induced macrophage inflammation and the m6A methylation modification. Further experiments demonstrated that m6A methylation modification of METTL3-mediated transcriptional activator 1 (STAT1) mRNA upregulated its expression levels, which promoted LDL-induced IL-6 and TNF-α and the transcription of other inflammatory factors.[65] Liu et al. examined the effect of METTL3-mediated methylation modification of STAT1 mRNA on macrophage polarization. Consistent with previous findings, STAT1 is a target of METTL3.[66] In conclusion, METTL3-mediated m6A methylation modification could affect monocyte/macrophage state and polarization by modulating mitochondrial function and transcriptional activator expression and influencing the transcription and expression of inflammatory factors, thus participating in the inflammatory response. METTL3 is a potential anti-inflammatory target during vascular inflammation.

The role of N6-methyladenosine in aneurysm

Research on the relationship between m6A and aneurysms has primarily focused on aortic aneurysms, especially abdominal aortic aneurysms (AAAs). AAA is a common disease and has high mortality. AAA is characterized by the chronic inflammation of the medial and outer membranes, many proteolytic enzymes were activated and ultimately leading to rupture.

The exact mechanism leading to AAA remains unclear. He et al. found that m6A modification was significantly increased in AAA. METTL14 may cause inflammatory infiltration and neovascularization, and the increase of FTO is associated with the abnormal modification of m6A. Higher m6A levels were also associated with higher rupture risk. There was a significant correlation between m6A modification levels and the mRNA expression levels of m6A components, suggesting tight crosstalk between these regulators. It is worth noting that higher m6A levels were positively correlated with AAA diameter and haematological parameters.[67] Aberrant m6A modification is therefore essential for AAA initiation and progression. Zhong et al. revealed that the KD of METTL3 inhibited AAA formation in angiotensin II-treated ApoE−/− mice and in a calcium chloride-induced mouse model. Mechanistically, METTL3 mediates m6A modification and promotes miR-34a maturation from pre-mir-34a, which then negatively regulates SIRT1 expression.[68] A bioinformatics study showed that METTL14 and HNRNPC were downregulated m6A regulators and the methyltransferase RBM15B was upregulated in abdominal aortic aneurysm tissue.[69] The functions of m6A are mainly associated with RNA catabolism, translation regulation, local adhesion, transcriptional coregulator activity, ribosomes, RNA transport, and the cell cycle. Moreover, m6A regulators play a nonnegligible role in the occurrence of rAAA.[70]

The role of N6-methyladenosine in vascular calcification

Chronic kidney disease (CKD) is a major issue worldwide that affects many individuals. Patients with CKD have a significantly higher risk of cardiovascular disease (CVD) and mortality than those who are healthy.[71] Vascular calcification, which is a major cause of increased CVD mortality, is more common in patients with CKD than in those without CKD.[72]

Indoxyl sulfate (IS), a uraemic toxin that is bound to proteins, has been shown to be associated with renal and vascular progression.[73] Chen and colleagues studied the epigenetic translation of induced vascular calcification and found strong evidence suggesting an important role for METTL14 in vascular calcification induction *in vitro* and *in vivo*.[74] The authors discovered significantly elevated the changes in total RNAm6A levels in the arteries of patients with end-stage renal disease as well as calcified mice and METTL14 plays a significant role. These findings suggest that IS-induced elevated levels of METTL14 mediate an increase in m6A modifications, which may be a marker of vascular calcification. Furthermore, overexpression of METTL14 *in vitro* leads to loss of repair function. This study provides evidence for the functional significance of METTL14 in IS-induced vascular calcification, suggesting that modulating METTL14 may be a potential anti-vascular calcification therapy.

The role of N6-methyladenosine in pulmonary hypertension

Pulmonary hypertension (PH) is a pathophysiological state of abnormally high pulmonary artery pressure caused by a variety of known or unknown reasons. At the end of the disease, patients often die of right heart failure. Whether m6A RNA modification and m6A effector proteins play a role in PH and pulmonary vascular remodeling has not been demonstrated. Hypoxic pulmonary hypertension (HPH) is caused by hypoxia, which causes vascular endothelial cell damage, and the imbalance in various vasodilation factors synthesized and secreted by the vascular endothelium leads to early pulmonary vasoconstriction and later pulmonary vascular reconstruction. Hu et al. found that the level of m6A was increased and the expression of YTHDF1 protein was increased in human and rodent PH samples and hypoxic pulmonary artery smooth muscle cells (HPASMCs). The study confirmed that m6A RNA modification was a new mediator of pathological changes in HPASMCs and PH.[75] Hu et al. revealed a novel mechanism linking m6A RNA modification with changes in macrophage phenotype, inflammation and oxidative stress in PH and identified Hmox1 as a downstream target of YTHDF2, suggesting that YTHDF2 may be a therapeutic target in PH.[76] GRAP (Grb-2-related adaptor protein) couples signaling molecules from membrane receptors and cytoplasmic tyrosine kinases to Ras/ERK signal transduction. Liu et al. designed a study to determine whether m6A modification and its effector protein play a role in pulmonary vascular resistance. GRAP overexpression significantly reduced the proliferation and invasion of HPASMCs by inhibiting the Ras/ERK signaling pathway *in vitro* and *in vivo*. In addition, METTL14 and the m6A binding protein YTHDF2 in PH were increased significantly. Moreover, m6A-modified GRAP mRNA was recognized by YTHDF2 to mediate degradation, and the expression of GRAP was negatively correlated with METTL14 and YTHDF2 *in vivo* and *in vitro*. This study describes the function and therapeutic target value of GRAP and expands the understanding of the importance of RNA epigenetics in PH.[77] Kang et al. also focused on the role of YTDF family members in HPHYTHDF1 silencing-mediated inhibition of hypoxic PASMC proliferation by regulating Foxm1 translation in an m6A-dependent manner.[78]

Certain researchers observed an increase in the expression of SETD2 and METTL14 in the PASMCs of PH mice induced by hypoxia. Upon establishing a mouse model with a specific knockout of SETD2 in smooth muscle cells, it was discovered that the absence of SETD2 in SMCs shielded mice from the consequences of hypoxia-induced PAH, leading to a significant reduction in right ventricular systolic pressure (RVSP). Furthermore, the elimination of SETD2 diminished the expression level of METTL14 and the m6A RNA methylation level. These findings suggest that the targeted inhibition of SETD2/METTL14 activity could serve as a viable therapeutic strategy for HPH in clinical settings.[79] Hypoxic pulmonary vascular remodeling is an important pathological basis of hypoxic pulmonary hypertension. It has been reported that hypoxia may cause m6A methylation disorder and the promotion of tumorigenesis. The effect of hypoxia on m6A modification is cell type dependent.[80–82]

Recently, the roles of circRNAs, lncRNAs and m6A in HPH have been repeatedly confirmed. Wang et al. first identified the circRNA expression profile in the lung tissue of an HPH mouse model.[83] LncFENDRR was significantly downregulated in the nucleus of hypoxic pulmonary artery endothelial cells (HPAECs), and the overexpression of LncFENDRR inhibited hypoxia-induced HPAEC pyroptosis. Notably, the m6A reader YTHDC1 plays an important role in m6A-modified lncFENDRR degradation. The overall m6A levels of circRNAs of HPH rats were lower than healthy individuals.[79] *In vitro*, the m6A abundance in circRNAs was also decreased under hypoxic conditions. CircRNAs mainly sponge miRNAs and are involved in the regulation of target miRNAs.[84]

The role of N6-methyladenosine in nervous system diseases

Chang et al. reported YTHDF3 overexpression in patients with clinical brain metastasis. Overexpression of YTHDF3 can promote cancer cells to cross the blood–brain barrier because it enhances the translation of several m6A-rich transcripts related to brain metastasis.[85] The expression of WTAP was downregulated in cerebral arteriovenous malformation (AVM) and pontin kinase (DSP) mRNA. Due to the reduction in m6A methylation, the expression of WTAP decreased rapidly. In conclusion, under both physiological and pathological circumstances, m6A is implicated in the regulation of angiogenesis. Many studies have confirmed the key role of m6A modification in VM. Zhang et al. confirmed the function and mechanism of hotairm1 modified by m6A and further established a glioma xenotransplantation mouse model for VM evaluation *in vivo*.[86] The findings indicated an upregulation of hotairm1, METTL3, and IGFBP2 levels in both glioma tissues and cell lines. While hotairm1 serves as an oncogene in glioma advancement, its knockout led to a substantial decrease in cell viability, migration, invasion, and VM formation. Particularly, the METTL3-dependent m6A modification bolstered the stability of hotairm1 mRNA, with the deletion of METTL3 significantly curbing VM in glioma. In addition, it was found that Hotairm1 combined with IGFBP2 and that the lack of Hotairm1 prevented the progression of glioma and the formation of VM *in vivo*.

CONCLUSION AND PERSPECTIVE

Currently, most studies have focused on the mechanism of m6A methylation but the application of m6A mentioned rarely, especially targeted drug therapy of m6A in VD. Further exploration is needed. The fact that tumor blood vessels are different from normal one can be used to formulate treatment strategies specifically for malignant cells and tumor blood vessels. The inhibition of angiogenesis and reduction in the growth of human tumor xenografts, as well as the enhancement of the effectiveness of anticancer medications, can be achieved by obstructing the tumor endothelial marker TEM8/anthrax toxin receptor 1 using antibodies directed against its extracellular domain, which may bring new ideas to m6A researchers.[87] Disorders of methyltransferases, demethylases and m6A-binding proteins play a role in the occurrence and development of cardiovascular diseases. Some studies have shown that the regulation of these m6A components may reduce the progression of heart disease.[88] Therefore, can these regulators possibly provide prospective biomarkers for diagnosis or therapeutic approaches for vascular conditions?

With a few exceptions, most of the studies discussed above have been published in the past three years, which means that the research of m6A in angiogenesis and vascular diseases is exciting and worthy of further research. But it is undeniable that these mechanisms can only partially reflect the real situation, and the role of m6A in angiogenesis should be a complex map, which is far from being fully understood. In this article, we reviewed the concept of m6A and angiogenesis, analyzed the latest progress in various fields, and looked forward to the treatment of vascular related diseases. M6A may be a new research direction as a disease diagnosis marker and treatment target.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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