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RNA Methylation and Tumor Occurrence

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ABSTRACT

RNA methylation is a post-transcriptional modification involving the addition of methyl groups to RNA molecules, playing a crucial role in gene expression regulation. Recent studies have highlighted the importance of RNA methylation, particularly N6-methyladenosine (m6A) modification, in cancer development and progression. RNA methylation affects mRNA stability, splicing, transport, and translation, thereby regulating various aspects of tumor cell biology, including proliferation, migration, and apoptosis. Abnormal RNA methylation patterns are closely linked to tumor aggressiveness and drug resistance, with dysregulation of methylation writers, erasers, and readers contributing to cancer onset and progression. Moreover, RNA methylation plays a significant role in cancer immunotherapy by influencing tumor cell immune evasion, offering new therapeutic targets. Future research should focus on elucidating the specific mechanisms of RNA methylation in different cancer types and its interactions with the tumor microenvironment. As technologies advance, RNA methylation modulators hold promising potential for cancer treatment, providing new strategies and therapeutic targets.

KEYWORDS

RNA methylation; N6 methyladenosine (m6A); Tumor; Gene expression regulation

1. INTRODUCTION

RNA methylation is a post-transcriptional modification of RNA that occurs in all living organisms and is associated with epigenetic regulation of key biological processes such as cell differentiation, embryonic development, gene expression, cell cycle, stress response, signal transduction, metabolic pathways, and cell death. This modification adds a methyl group to the RNA molecule through the action of methyltransferase enzymes, thereby affecting gene expression without altering the sequence. RNA methylation plays a role in not only the biophysical, biochemical, and metabolic stability but also in gene expression regulation, DNA repair, stress response, and the acetylation of histones and the function of exosomes.

2. COMMON TYPES OF RNA METHYLATION AND THE ROLE OF RNA METHYLATION IN THE RNA LIFECYCLE

There are various types of RNA methylation, the most common of which include N6-methyladenosine (m6A), 5-methylcytosine (m5C), N1-methyladenosine (m1A), and N7-methylguanosine (m7G). m6A was the first internal modification discovered in eukaryotic mRNA and is the most abundant. Added by a methyltransferase complex, the methylation or demethylation activity of m6A has been proven to affect the stability of transcriptional regulatory factors, providing a dynamic and rapid response to cellular signals, environmental stimuli, or programmed biological transitions (Jia et al., 2011) [1]. As one of the most studied modifications, m6A is the most prevalent

form of mRNA methylation in eukaryotic cells, affecting every process in the RNA life cycle. With the advancement of science and technology, more forms of RNA methylation have been discovered, such as m1A, m5C, m6Am, etc.

In recent years, the discovery of m6A demethylases (such as FTO, ALKBH5, etc.) and the development of high-throughput sequencing technologies, such as m6A-seq, MERIP-seq, etc., have promoted in-depth research on RNA methylation. m6A modification can promote phase separation through reader proteins such as YTHDF1/2/3, enhancing the multifunctionality of proteins. Moreover, m6A modification is also involved in regulating the immune response of cells to viruses by targeting Type I interferons. In cancer research, RNA methylation, especially m6A modification, has been proven to be closely related to the occurrence and development of various cancers. For example, METTL3 and METTL14 as "writers" of m6A play an important role in controlling myeloid differentiation in leukemia. FTO, as an "eraser" of m6A, is highly expressed in some subtypes of AML and can act as an oncogenes in leukemia. In terms of virus infection, m6A modification regulates the stability of viral RNA and the immune response of host cells, playing a regulatory role in virus replication and the antiviral response of host cells. For instance, HIV-1 infection can promote m6A methylation of host and viral RNA, and YTHDF proteins can recognize and bind to m6A modification sites in HIV-1 RNA, thereby inhibiting viral replication.

5-Methylcytosine (m5C) is a chemical modification on RNA molecules within the field of epigenetics. This modification involves the addition of a methyl group to the 5th carbon atom of cytosine. m5C has been found in various types of RNA, including ribosomal RNA (rRNA) and transfer RNA (tRNA), and significantly impacts the stability, structure, and function of RNA. In rRNA, the presence of m5C helps stabilize the secondary and tertiary structures of rRNA, which is crucial for the correct assembly and function of the ribosome. In tRNA, m5C modification contributes to the correct folding and stability of tRNA molecules, ensuring accurate recognition of codons and delivery of the corresponding amino acids during protein synthesis. With the advancement of high-throughput sequencing technologies, scientists have been able to map m5C sites at the genomic level across the human RNA transcriptome. Research by Squires et al. in 2012 using this approach revealed over 10,000 m5C sites in mRNA and other non-coding RNAs. This discovery indicates that m5C modification is more widely distributed in RNA than previously thought and plays a more complex role in gene expression regulation. The m5C modification on RNA molecules has multiple functions; it enhances the stability of RNA against intracellular degradation, thereby maintaining its functionality within the cell. During the maturation process of tRNA and rRNA, m5C is involved in the splicing and processing of RNA, ensuring the correct structure and function of these key RNA molecules. Moreover, m5C modification finely tunes gene expression by regulating the translation efficiency of RNA and the nuclear export process of mRNA. As an epigenetic mark, m5C can also be passed on to offspring during cell division, achieving gene expression regulation independent of DNA sequence changes. The dynamic changes of m5C, including its addition and removal, are regulated by specific methyltransferases and demethylases, whose abnormal activities are closely related to the occurrence and development of various diseases such as neurodegenerative diseases and cancer. Therefore, m5C is not only crucial for maintaining normal cell functions but also has become a new focus of research and treatment due to its potential role in diseases.

N1-Methyladenosine (m1A) is an RNA modification found in transfer RNA (tRNA) that is essential for maintaining the structural stability and promoting correct folding of tRNA. m1A enhances the hydrogen bonding within the tRNA molecule or with other molecules by adding an additional methyl group, thereby increasing the overall structural stability. This modification aids tRNA in correctly folding into its functional three-dimensional structure during the synthesis process, ensuring its effective participation in protein synthesis. The presence of m1A also enhances the thermal stability of tRNA, allowing it to maintain structural integrity under high-temperature conditions and strengthening the cell's adaptability to various environmental conditions. Furthermore, m1A modification serves as a key recognition signal in the processing and maturation of tRNA, assisting

enzymatic and protein complexes within the cell in correctly processing tRNA precursors. The research by Motorin and Helm in 2010 highlighted the importance of m1A in tRNA structure and function, indicating that this modification is indispensable for the protein synthesis mechanism, and any disruption to m1A modification affects the accuracy of protein synthesis and normal cell function. The association of diseases such as obesity, neurodevelopmental disorders, and cancer with RNA methylation modifiers, demethylases, and other related factors has been confirmed (Chen et al., 2017) [2].

3. THE ASSOCIATION BETWEEN RNA METHYLATION AND TUMOR OCCURRENCE

RNA methylation is a process of adding methyl groups to RNA molecules, with N6-methyladenosine (m6A) being the most abundant internal modification form on eukaryotic mRNA. In recent years, the association between RNA methylation and tumor occurrence has gradually become a research focus, with its abnormal expression patterns discovered in various tumors and closely related to the biological behavior of tumor cells.

3.1. Abnormal Expression Patterns of RNA Methylation in Different Types of Tumors

Abnormal expression patterns of RNA methylation have been widely documented in different types of tumors. For instance, in multiple myeloma (MM), abnormal expression patterns of RNA methylation, especially m6A modification, are closely related to the occurrence and progression of tumors. Sha Song et al. (2021) [3] revealed the significant role of isocitrate dehydrogenase 2 (IDH2) in MM. IDH2 is a key enzyme that catalyzes the conversion of isocitrate to α-ketoglutarate (α-KG) in the tricarboxylic acid (TCA) cycle [4]. In the pathological process of MM, high expression of IDH2 is associated with disease progression and poor patient prognosis. IDH2 indirectly affects m6A RNA levels through its function in the TCA cycle. α-KG is a co-substrate for various dioxygenases, including RNA demethylase FTO. High expression of IDH2 leads to an increase in α-KG, thereby activating the activity of FTO. The activated FTO demethylase acts on m6A-modified RNA molecules, reducing m6A levels, especially for the mRNA of the WNT7B gene [5]. WNT7B is a key component of the Wnt signaling pathway, and increased expression levels can activate the Wnt signaling pathway, promoting the proliferation and survival of tumor cells. In MM, abnormal activation of the Wnt signaling pathway is closely related to the unrestricted proliferation of tumor cells and disease progression [6]. Therefore, IDH2 indirectly promotes the activation of the Wnt signaling pathway by regulating m6A RNA levels, especially by reducing the m6A modification of WNT7B mRNA, thereby driving the pathogenesis and progression of MM.

Additionally, research has found that the expression level of IDH2 is negatively correlated with the overall survival (OS) of MM patients. High levels of IDH2 expression predict poor patient prognosis due to its role in promoting tumor cell growth and survival. Thus, IDH2 is not only a key driver of tumor occurrence but also a potential target for MM therapy. By targeting IDH2 or its regulated m6A RNA demethylation pathway, new therapeutic strategies can be provided for MM patients. In diffuse large B-cell lymphoma (DLBCL), DLBCL is a highly heterogeneous hematological malignancy with diverse clinical manifestations, morphologies, and biological characteristics [7]. High expression of piRNA-30473 is closely related to the invasive phenotype of DLBCL, and its depletion can reduce the proliferation of DLBCL cells and induce cell cycle arrest.

3.2. How RNA Methylation Affects the Biology of Tumor Cells

How RNA methylation affects the biological behavior of tumor cells is also a focus of research. m6A modification can regulate the expression of tumor-related genes by altering the stability, splicing patterns, and translation efficiency of mRNA [8]. For example, m6A modification can promote the

proliferation and migration of tumor cells while inhibiting apoptosis. m6A modification can promote the proliferation of tumor cells through various mechanisms. For instance, m6A modification can enhance the stability of certain oncogenes mRNA, extending their half-life within the cell, thereby increasing the expression levels of these genes, promoting the progression of the cell cycle, and the proliferation of cells. Moreover, m6A modification can also produce protein variants that are more conducive to the proliferation of tumor cells by altering the splicing patterns of mRNA.

3.3. The Interaction Between RNA Methylation and the Tumor Microenvironment

In terms of tumor cell migration, m6A modification also plays a significant role. The increased level of m6A modification of mRNAs related to cell migration, such as cell adhesion molecules and extracellular matrix remodeling enzymes, can promote their translation efficiency, enhancing the invasiveness and metastatic ability of tumor cells. At the same time, m6A modification is also related to the inhibition of apoptosis. The increased level of m6A modification of mRNAs of some anti-apoptotic genes, such as members of the Bcl-2 family, can reduce the degradation of these mRNAs, increasing the expression levels of anti-apoptotic proteins, thus helping tumor cells evade apoptosis [9]. In the tumor microenvironment, RNA methylation is also involved in interactions with immune escape and the maintenance of tumor stem cell characteristics. For example, m6A modification can affect the interaction between tumor cells and immune cells, thereby promoting the immune escape of tumors.

4. THE SPECIFIC MECHANISM OF RNA METHYLATION IN TUMOR DEVELOPMENT

RNA methylation is a widespread and dynamically reversible internal modification of RNA found in higher eukaryotes, and its mechanism of action in tumor development is gradually becoming a focus of research. RNA methylation finely regulates the expression of tumor-related genes through the coordinated action of modifying enzymes (Writers), demethylases (Erasers), and recognition proteins (Readers), thereby affecting the biological behavior of tumor cells [10].

Modifying enzymes such as METTL3 and METTL14 are responsible for catalyzing the generation of m6A, while demethylases such as FTO and ALKBH5 remove this modification, thereby regulating the stability and translation efficiency of mRNA (Chi et al., 2018) [11]. Recognition proteins such as YTHDF1-3 and YTHDC1-2 affect the splicing, nuclear export, stability, and translation of mRNA by recognizing m6A sites (Wang et al., 2015) [12]. For example, YTHDF2 can promote the degradation of m6A-modified mRNA, while YTHDF1 enhances the translation efficiency of specific mRNAs by interacting with the translation initiation factor eIF3 [13].

He Y et al. (2021) [14] conducted an in-depth study on the role of the m6A demethylase ALKBH5 in pancreatic cancer, revealing its significant role in tumor occurrence and chemosensitivity. The study found that in patient-derived xenograft (PDX) models of pancreatic cancer, the expression level of ALKBH5 decreased after gemcitabine treatment, while overexpression of ALKBH5 could make pancreatic ductal adenocarcinoma (PDAC) cells more sensitive to chemotherapeutic drugs. The downregulation of ALKBH5 is associated with adverse clinical outcomes in pancreatic cancer and various other types of cancer. The study further found that the loss of ALKBH5 significantly increased the proliferation, migration, and invasion capabilities of PDAC cells, with the opposite effects observed upon its overexpression. Among the global methylation profile affected by ALKBH5, the change in m6A modification level of Wnt signaling pathway inhibitor 1 (WIF-1) was associated with the transcriptional activation of WIF-1 and the regulation of the Wnt signaling pathway [15]. These findings indicate that ALKBH5 exerts tumor-suppressing and chemosensitizing effects in PDAC by regulating m6A modification levels, particularly by reducing m6A modification of WIF-1 mRNA, promoting WIF-1 expression, and thereby inhibiting the activity of the Wnt signaling

pathway. These results not only provide new strategies for the treatment of pancreatic cancer but also offer a new perspective for understanding the role of m6A modification in tumor development.

Different scholars have varying research focuses on the association between RNA methylation and tumor occurrence. Some studies emphasize the role of specific m6A modifying enzymes or demethylases in tumor development, while others focus on the impact of m6A modification on the entire transcriptome. For instance, Bo Tang et al. (2020) [16] revealed the tumor-suppressing role of ALKBH5 in pancreatic cancer, an m6A demethylase that regulates gene expression by removing m6A modifications from mRNA. In pancreatic cancer, the downregulation of ALKBH5 is associated with chemoresistance and poor clinical outcomes. Bo Tang and colleagues found that overexpression of ALKBH5 could make pancreatic ductal adenocarcinoma (PDAC) cells more sensitive to chemotherapeutic drugs, while the silencing of ALKBH5 increased the proliferation, migration, and invasion capabilities of PDAC cells. These effects are related to ALKBH5's regulation of the Wnt signaling pathway. Specifically, ALKBH5 reduces m6A modification on Wnt inhibitory factor 1 (WIF-1) mRNA, increasing WIF-1 expression, thereby inhibiting the activity of the Wnt signaling pathway. The Wnt signaling pathway plays a key role in cell proliferation, migration, and chemoresistance of tumor cells. Therefore, the tumor-suppressing role of ALKBH5 is related to its ability to regulate m6A modifications and the Wnt signaling pathway. In contrast, Huiying Han et al. (2020) [17] discovered that piRNA-30473 modulates the global level of m6A by affecting WTAP, thereby promoting the progression of DLBCL. piRNA-30473 is a small non-coding RNA that increases the expression of m6A mRNA methylation enzyme WTAP and the global level of m6A by binding to the 3' untranslated region (3' UTR) of WTAP. m6A modification is a chemical modification that adds a methyl group to mRNA, regulating gene expression by affecting mRNA stability, splicing, transport, and translation. In DLBCL, high expression of piRNA-30473 supports the invasive phenotype of tumors and is significantly associated with the overall survival (OS) of patients. Huiying Han and colleagues found that the depletion of piRNA-30473 reduced the proliferation of DLBCL cells and induced cell cycle arrest, and the inhibition of piRNA-30473 in a xenograft DLBCL model reduced tumor growth. Additionally, piRNA-30473 affects the global level of m6A by regulating WTAP, thereby enhancing the expression of its key target gene HK2 and promoting the progression of DLBCL. These studies not only provide new perspectives for understanding the role of RNA methylation in tumors but also offer potential targets for future therapeutic strategies.

5. THE POTENTIAL OF RNA METHYLATION IN TUMOR THERAPY

5.1. RNA Methylation as a Biomarker for Tumor Diagnosis and Prognosis Assessment

RNA methylation is a chemical modification process that adds methyl groups to RNA molecules and has shown great potential in the field of tumor therapy in recent years. This modification is not only involved in the regulation of gene expression but is also closely related to the occurrence, development, and prognosis of tumors. As a biomarker for tumor diagnosis and prognosis assessment, the abnormal expression of RNA methylation is associated with the invasiveness and drug resistance of various tumors. For example, it was pointed out that N6-methyladenosine (m6A) RNA methylation, as a common internal post-transcriptional modification, is significant in tumor therapy and drug resistance. Moreover, the abnormal changes in m6A modification are increasingly related to the occurrence of human tumors and drug resistance [18].

5.2. RNA Methylation Regulators as Potential Therapeutic Targets

RNA methylation regulators, especially the proteins acting as "writers," "erasers," and "readers," provide new targets for tumor therapy. m6A inhibitors such as rhein and R-2HG show anti-tumor

activity in leukemia and glioma by competitively binding to the catalytic domain of the FTO protein, inhibiting its activity (Su et al., 2018) [19]. m7G regulators, such as METTL1 and WDR4, also play a role in tumor development by affecting the stability and translation efficiency of RNA. Researchers have conducted extensive studies on the potential of RNA methylation in tumor therapy, finding differences in expression and function across various tumor types. For instance, Shi et al. (2019) [20] emphasized the context-dependent functions of RNA methylation writers, readers, and erasers in tumor development. Ma et al. (2021) [21] found that the expression of the m6A reading protein YTHDC2 in lung cancer is related to the occurrence and progression of tumors. These studies not only reveal the multifaceted role of RNA methylation in tumor therapy but also provide a theoretical basis for the development of new treatment strategies.

5.3. The Role of RNA Methylation in Tumor Immunotherapy

In tumor immunotherapy, RNA methylation is equally important. For example, METTL3-mediated m6A modification of PD-L1 mRNA enhances the ability of tumor cells to evade immune surveillance, and inhibiting METTL3 or its reading protein IGF2BP3 can improve the anti-tumor immune response (Wan et al., 2022) [22]. Additionally, ALKBH5 affects the response to anti-PD-1 therapy by regulating the accumulation of lactate and immune-suppressive cells in the tumor microenvironment (Li et al., 2020) [23].

6. CONCLUSION

RNA methylation is a post-transcriptional modification that adds methyl groups to RNA molecules and significantly impacts the regulation of gene expression. In recent years, RNA methylation, especially N6-methyladenosine (m6A) modification, has received widespread attention for its role in the occurrence and development of tumors. Studies have shown that RNA methylation is involved in regulating the proliferation, migration, and apoptosis of tumor cells by affecting processes such as mRNA stability, splicing, transport, and translation. Moreover, the abnormal expression of RNA methylation modifiers, demethylases, and recognition proteins is closely related to the invasiveness and drug resistance of various tumors, providing new biomarkers and potential targets for tumor diagnosis and therapy.

Although RNA methylation has shown great potential in tumor research, the understanding of its functions and biological consequences is still limited. Future research needs to delve deeper into the specific mechanisms of RNA methylation in different types of tumors, as well as its interaction with the tumor microenvironment. In addition, the regulatory network of dynamic changes in RNA methylation, its role in tumor immune escape, and the maintenance of tumor stem cell characteristics are also important directions for future research.

With the development of high-throughput sequencing technologies and the discovery of RNA methylation regulators, the application prospects of RNA methylation in tumor therapy are becoming increasingly clear. The development of small molecule inhibitors targeting RNA methylation regulators may provide new strategies for tumor therapy. At the same time, the regulatory role of RNA methylation in tumor immunotherapy also offers possibilities for the development of new immunotherapies. In summary, as a new field in tumor research, the mechanism of action of RNA methylation in tumor occurrence and its potential for clinical application deserve further in-depth study.

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