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m6A RNA Methylation and Cancer Progression: Pathogenesis, Implications, and Therapeutic Potential

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Abstract

N6-methyladenosine (m6A) is a prominent internal modification of eukaryotic messenger RNA (mRNA) and has garnered significant attention due to its regulatory role in various biological processes, particularly in cancer. As a dynamic and reversible modification, m6A is orchestrated by three key players: Writers, primarily methyltransferases like METTL3 and METTL14, add m6A marks to mRNA, influencing processes such as RNA stability and translation. Erasers, such as FTO and ALKBH5, remove these marks, enabling the fine-tuning of mRNA functions. Readers, including YTH domain-containing proteins (e.g., YTHDF1, YTHDF2), recognize and bind to m6A-modified mRNA, directing its fate in terms of degradation, translation efficiency, or cellular localization. In cancer, m6A modifications have been implicated in promoting tumor progression by affecting gene expression at the post-transcriptional level. The dysregulation of m6A machinery can lead to aberrant expression of oncogenes or tumor suppressors, thereby driving oncogenesis Furthermore, m6A modifications play a crucial role in modulating the tumor microenvironment (TME) and immune evasion. By altering the expression of cytokines, chemokines, and immune checkpoint molecules, m6A can influence immune cell infiltration and activation, impacting the anti-tumor immune response. This modulation of the TME not only aids in tumor progression but also presents challenges and opportunities for cancer immunotherapy. Given its profound impact on cancer biology, targeting the m6A machinery holds therapeutic potential. Small molecules or inhibitors designed to modulate m6A writers, erasers, or readers could offer new avenues for cancer treatment, making m6A a promising target in the fight against cancer.

Keywords: *Cancer Progression, erasers, Gene Expression Regulation, m6A Writers, mRNA Modification, N6-Methyladenosine (m6A), Oncogenesis, Post-Transcriptional Regulation, Readers, Tumor Microenvironment (TME).*

Introduction

N6-methyladenosine (m6A) RNA methylation is one of the most prevalent and dynamic epigenetic modifications in eukaryotic messenger RNA (mRNA), playing a crucial role in the regulation of various biological processes [1]. This post-transcriptional modification involves the methylation of the nitrogen atom at the sixth position of adenosine within mRNA, significantly influencing RNA metabolism, including its stability, splicing, translation, and decay. m6A methylation is mediated by a complex machinery of "writers" (methyltransferases), "erasers" (demethylases),

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and "readers" (RNA-binding proteins), each of which plays a critical role in fine-tuning gene expression [2]. Emerging evidence suggests that dysregulation of the m6A epitranscriptome is closely associated with the development and progression of various human cancers [3].

In recent years, m6A RNA methylation has gained considerable attention in the field of cancer research. Increasing evidence suggests that dysregulation of m6A methylation is closely associated with cancer initiation, progression, and metastasis [4]. Aberrant m6A modification has been linked to multiple oncogenic processes, such as uncontrolled cell proliferation, tumorigenesis, and the development of resistance to chemotherapy [5]. By modulating key oncogenic pathways, m6A RNA methylation facilitates tumor progression and contributes to the pathogenesis of various cancers, including leukemia, glioblastoma, hepatocellular carcinoma, and lung cancer [6]. Furthermore, m6A modification has been shown to impact the tumor microenvironment and the immune response, potentially influencing the efficacy of cancer immunotherapy [7].

The discovery of m6A's role in cancer has not only expanded our understanding of the molecular mechanisms underlying tumorigenesis but has also opened new avenues for therapeutic intervention [8]. Targeting m6A regulatory proteins—writers, erasers, and readers—offers a promising approach to modulating oncogenic pathways and reprogramming the tumor microenvironment (TME) [9].

This article aims to provide an overview of the current understanding of m6A RNA methylation in cancer, focusing on its role in cancer progression, tumor microenvironment reprogramming, immune evasion, and therapeutic potential. By elucidating the complex regulatory networks governed by m6A, we can pave the way for novel, personalized cancer therapies.

m6A Writers: The Methylation Machinery

The installation of m6A marks on mRNA is mediated by a multicomponent complex consisting primarily of methyltransferase-like 3 (METTL3), METTL14, and their cofactors such as WTAP (Wilms' tumor 1-associating protein) [10]. This "writer" complex catalyzes the methylation of adenosine residues, primarily in the consensus sequence DRACH (D = A/G/U, R = A/G, H = A/C/U). METTL3 and METTL14 function synergistically to regulate mRNA fate, impacting processes such as mRNA splicing and stability [11].

Recent studies have underscored the oncogenic role of aberrant m6A methylation in various cancers, including leukemia, glioblastoma, and hepatocellular carcinoma (HCC). In HCC, for instance, overexpression of METTL3 promotes cancer cell proliferation and tumorigenesis by stabilizing oncogenic mRNA. Additionally, METTL3 has been implicated in enhancing mRNA translation efficiency in cancer cells by interacting with the eukaryotic initiation factor eIF3 [12-14].

m6A Erasers: Reversible Regulation

The dynamic nature of m6A methylation is controlled by two key demethylases, also known as "erasers": fat mass and obesity-associated protein (FTO) and AlkB homolog 5 (ALKBH5) [15]. These enzymes reverse m6A methylation, thus modulating the stability and translation of target mRNAs. FTO, for example, has been linked to oncogenic processes by influencing cancer cell metabolism and immune responses. In acute myeloid leukemia (AML), FTO-driven demethylation stabilizes oncogenes such as MYC and CEBPA, promoting leukemogenesis [16].

ALKBH5, on the other hand, has been shown to play a crucial role in maintaining cancer stem cell properties. In breast cancer, hypoxia-induced ALKBH5 expression enhances the stemness and tumorigenicity of cancer stem cells (CSCs), contributing to

chemoresistance and tumor progression. These findings suggest that targeting m6A erasers may represent a promising therapeutic strategy in cancer treatment [17].

m6A Readers: Translating the Epigenetic Code

m6A readers are RNA-binding proteins that recognize and bind to m6A-modified mRNAs, thereby influencing their fate. The YTH domain-containing proteins (YTHDF1-3, YTHDC1-2) are among the most well-characterized m6A readers. YTHDF1, for instance, enhances mRNA translation, while YTHDF2 promotes mRNA degradation, thus exerting opposite regulatory effects on gene expression [18, 19].

Other reader proteins, such as IGF2BP1-3 (insulin-like growth factor 2 mRNA-binding proteins), also play pivotal roles in cancer progression. IGF2BPs promote the stability and expression of m6A-modified oncogenic mRNAs, driving tumorigenesis [20]. The dysregulation of m6A readers has been implicated in various cancers, including lung cancer, where YTHDC2 exhibits a tumor-suppressive role (Table 1). The multifaceted functions of m6A readers highlight their importance in cancer biology and present new avenues for therapeutic intervention [21]. Figure 1 represents the dynamic process of m6A RNA modification by m6A writers, readers and erasers.

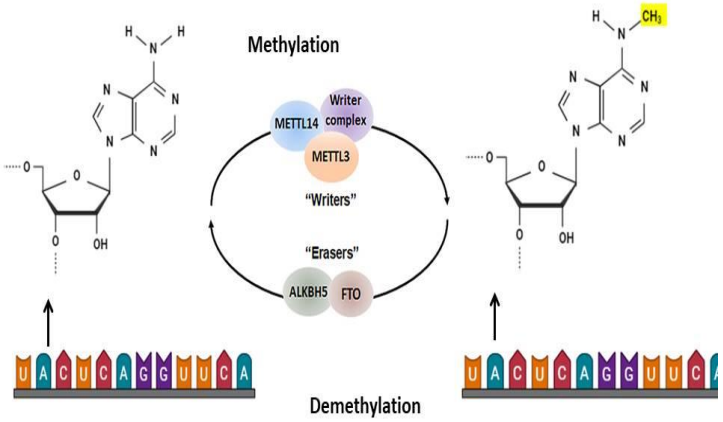

Figure 1. The Dynamic Process of RNA m6A Modification Involves the Regulation of m6A Marks, which can be Controlled by Various m6A Methyltransferases and Demethylases

m6A Methylation and Tumor Microenvironment (TME) Reprogramming

Tumor Microenvironment (TME) and m6A Methylation

The tumor microenvironment (TME) is a complex and dynamic network that surrounds and interacts with cancer cells, profoundly influencing tumor progression, metastasis, and resistance to therapy. The TME consists of various cell types, including immune cells, fibroblasts, endothelial cells, and pericytes, as well as extracellular matrix components, signaling molecules, and metabolic factors. Recent studies have demonstrated that m6A RNA methylation significantly impacts the reprogramming of the TME, contributing to tumor growth, immune evasion, and therapeutic resistance [6].

Hypoxia-Induced m6A Regulation in the TME

Hypoxia, a characteristic feature of solid tumors, arises due to abnormal vascularization and increased oxygen consumption by rapidly proliferating cancer cells. This low-oxygen environment leads to the stabilization and activation of hypoxia-inducible factors (HIFs), which orchestrate cellular responses to hypoxic stress, including angiogenesis,

metabolic reprogramming, and immune modulation. m6A methylation has been identified as a critical regulator of hypoxia-driven changes in the TME. For instance, hypoxia-induced downregulation of METTL3 in hepatocellular carcinoma (HCC) reduces m6A levels on FOXO3 mRNA, resulting in decreased mRNA stability and contributing to chemoresistance. This finding highlights the role of m6A in mediating hypoxia-induced therapeutic resistance, a common challenge in cancer treatment [22, 23].

Moreover, hypoxia increases the expression of ALKBH5, an m6A demethylase, in breast cancer stem cells. ALKBH5-dependent demethylation maintains the stemness and tumorigenicity of these cells, thereby promoting tumor progression and resistance to chemotherapy. The interplay between hypoxia and m6A methylation suggests that targeting the hypoxic TME and associated m6A alterations could improve the efficacy of cancer therapies [9].

Immune Modulation in the TME via m6A Methylation

Immune cells within the TME play a dual role in cancer, either promoting tumor elimination or facilitating immune evasion depending on the context. Tumors often exploit various mechanisms to evade immune surveillance, including the suppression of cytotoxic T cells and the recruitment of immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) [24]. Recent research has shown that m6A methylation contributes to immune modulation within the TME, influencing the outcome of the anti-tumor immune response [8].

One of the key mechanisms by which m6A methylation affects immune evasion is through the regulation of immune checkpoint molecules, such as programmed death-ligand 1 (PD-L1). Hypoxia-induced m6A modifications can enhance the expression of PD-L1 on tumor cells and immune-suppressive cells like MDSCs, thereby inhibiting the activation of cytotoxic T cells and promoting immune evasion. This highlights the potential of targeting m6A methylation to enhance the efficacy of immune checkpoint inhibitors in cancer therapy [25].

Additionally, m6A methylation influences the infiltration and function of various immune cell populations in the TME. For instance, elevated m6A levels in cancer cells have been associated with reduced infiltration of effector T cells, leading to a more immunosuppressive TME. These findings suggest that m6A modifications could serve as therapeutic targets to modulate the immune landscape of tumors, making them more susceptible to immune-mediated destruction [26].

Metabolic Reprogramming and m6A Methylation in the TME

The metabolic landscape of the TME is another critical factor influencing cancer progression and therapeutic resistance. Cancer cells undergo metabolic reprogramming to support their rapid growth and survival under stressful conditions such as nutrient deprivation and hypoxia. m6A methylation has been shown to play a key role in regulating metabolic pathways in the TME, thereby influencing tumor cell behavior and interactions with the surrounding microenvironment (Table 2).

For instance, m6A modifications can regulate the expression of enzymes involved in glycolysis, lipid metabolism, and oxidative phosphorylation, thus modulating the metabolic phenotype of cancer cells. By influencing mRNA stability and translation, m6A methylation controls the metabolic flexibility of cancer cells, allowing them to adapt to the fluctuating conditions within the TME. Targeting m6A-driven metabolic reprogramming could enhance the vulnerability of cancer cells to metabolic stress and improve therapeutic outcomes [27].

Therapeutic Potential and Future Directions

The discovery of the critical role of m6A methylation in cancer progression has spurred interest in targeting the m6A machinery for therapeutic purposes in various cancers including cervical cancer [28]. Inhibitors of m6A writers, erasers, and readers are being explored as potential anticancer agents. For instance, small-molecule inhibitors of FTO and ALKBH5 have shown promising preclinical results in reducing tumor growth and enhancing the efficacy of chemotherapy.

The intricate interplay between m6A methylation and the TME presents exciting opportunities for therapeutic intervention in cancer. By modulating key processes such as immune evasion, metabolic reprogramming, and stromal interactions, m6A methylation contributes to the aggressive behavior of tumors and their resistance to treatment. Therapeutic strategies that target the m6A machinery, either alone or in combination with existing therapies hold promise for reprogramming the TME and improving cancer treatment outcomes.

As the field of m6A methylation in cancer continues to evolve, a deeper understanding of the spatiotemporal regulation of m6A and its context-dependent functions in the TME will be crucial. Integrating m6A-related biomarkers with other genomic and immunological features of the TME may enable the development of more personalized and effective cancer therapies.

Future research should focus on elucidating the context-specific roles of m6A methylation in different components of the TME and identifying biomarkers that predict responses to m6A-targeted therapies. By unraveling the complex regulatory networks of m6A methylation within the TME, we can pave the way for the development of novel, personalized therapeutic approaches that harness the full potential of epigenetic reprogramming in cancer therapy.

Conclusion

In conclusion, the emerging field of m6A methylation research has uncovered its critical role in modulating the tumor microenvironment and driving cancer progression. This epitranscriptomic modification regulates key processes such as immune evasion, metabolic reprogramming, and interactions with the stromal components of the tumor microenvironment, thereby contributing to tumor aggressiveness and treatment resistance. Furthermore, m6A methylation is implicated in various inflammatory diseases, including periodontitis and osteoporosis [29, 30] highlighting its broader significance in disease pathology.

Table 1. Key Components of m6A Methylation Machinery and their Roles in Cancer

Category	Component	Role in m6A Methylation	Involvement in Cancer
Writers	METTL3	Catalyzes the methylation of adenosine in mRNA	Promotes cancer cell proliferation and tumorigenesis in cancers such as hepatocellular carcinoma (HCC) by stabilizing oncogenic mRNA.
	METTL14	Works synergistically with METTL3	Regulates mRNA splicing and stability, contributing to cancer progression.
	WTAP	Cofactor that assists METTL3/METTL14 complex	Supports methylation activity, implicated in various cancers.
Erasers	FTO	Demethylates m6A-	Stabilizes oncogenes in acute myeloid leukemia

		modified mRNAs	(AML), promoting leukemogenesis and influencing metabolism and immune responses
	ALKBH5	Demethylates m6A marks, reversing methylation	Maintains cancer stem cell properties in breast cancer, contributing to tumorigenicity and chemoresistance.
Readers	YTHDF1	Binds to m6A-modified mRNAs, enhances translation	Influences gene expression, driving cancer progression by enhancing translation of oncogenes.
	YTHDF2	Promotes degradation of m6A-modified mRNAs	Regulates mRNA stability, playing roles in different cancers.
	IGF2BP1-3	Stabilizes m6A-modified oncogenic mRNAs	Drives tumorigenesis by promoting the stability and expression of oncogenic mRNAs in various cancers.

Table 2. Influence of m6A Methylation on the Tumor Microenvironment (TME)

Aspect of TME	**Role of m6A Methylation**	**Impact on Cancer Progression**
Hypoxia	Hypoxia-induced m6A modulation affects mRNA stability and expression under low oxygen conditions.	Contributes to chemoresistance in hepatocellular carcinoma (HCC) by decreasing m6A levels on specific mRNAs (e.g., FOXO3).
Immune Evasion	Regulates expression of immune checkpoint molecules (e.g., PD-L1) and cytokines, altering immune cell function.	Promotes immune evasion by suppressing cytotoxic T cell activity and enhancing the recruitment of immunosuppressive cells (e.g., MDSCs).
Cancer-Associated Fibroblasts (CAFs)	Modulates fibroblast growth factor receptor (FGFR) signaling and extracellular matrix production in CAFs.	Supports tumor progression by remodeling the stroma, promoting angiogenesis, and facilitating immune evasion.
Metabolic Reprogramming	Regulates expression of enzymes involved in glycolysis, lipid metabolism, and oxidative phosphorylation.	Enhances cancer cell survival by supporting metabolic flexibility in response to the fluctuating conditions within the TME.

Conflict of Interest

The authors declare no potential conflict of interest.

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