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Cancer Epigenetics Beyond DNA Methylation: Role of RNA Modifications (m6A, m5C) in Tumor Initiation and Therapy Resistance

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Abstract

Epigenetic regulation has turned out to be a key factor in the formation and progression of cancer. Histone modifications and DNA methylation have traditionally been considered to be the key epigenetic processes that mediate oncogenesis. Recent discoveries, however, emphasize the importance of other types of RNA modifications, i.e. N6 -methyl adenosine (m6A) and 5 -methyl cytosine (m5C) that creates an extra layer of gene control in malignant settings. These changes are dynamically coordinated by methyltransferases, demethylases and reader proteins to mediate important facets of RNA metabolism such as splicing, stability, translation and subcellular localization. Aberrant RNA methylation is one of the largest contributory factors to tumor formation, disease pathogenesis, immune-survival, and resistance to therapy. The imbalance between m6A and m5C disrupts the regular RNA metabolism, thus promoting oncogenic signalling, stem-cell-like behaviour of cancer cells, and immune escape. Consequently, growing data suggest that the development of aberrant RNA methylation is associated with chemotherapy, radiotherapy, targeted therapy, and immunotherapy resistance. m6A/m5C perturbations activating particular molecular pathways involve increased DNA repair ability, metabolic repositioning and changed dynamics of antigen-presentation. The review summarizes the existing literature on the molecular processes

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controlled by m6A and m5C in cancer, and provides two summary tables one listing the canonical regulators of these RNA modifications as involved in oncogenesis, and the other listing their role in therapeutic resistance. Also, we discuss new therapeutic approaches which focus on the inhibition of RNA modification machineries, including inhibitors of major methyltransferases and reader proteins. Lastly, we touch on the future clinical uses of epitranscriptomic data in cancer, and how novel biomarkers and targeted therapies can improve the patient outcomes.

Keywords: Cancer epigenetics, RNA modifications, N6-methyladenosine (m6A), 5-methylcytosine (m5C), Tumor initiation, Therapy resistance, Oncogene regulation, Cancer stemness.

1. Introduction

The epigenetic regulation controls the expression of the genes without the change of the basic DNA code, thus maintaining cell identity and function. In the past, cancer epigenetics research has focused on DNA methylation and histone decoration as the key regulators of chromatin structure and transcription. However, more recent advances in high-throughput sequencing technologies have discovered the epitranscriptome a dynamic component of RNA modifications that impose post-transcriptional regulation of gene expression [1]. N6 -methyl adenosine (m6A) and 5 -methyl cytosine (m5C) are the most common and functional consequences of RNA modifications in eukaryotic cells. Methyltransferases (also known as writers e.g. METTL3, NSUN2) deposit these modifications, demethylases (also known as erasers e.g. FTO, ALKBH5) remodel them and RNA-binding proteins (also known as readers e.g. YTH domain family members) decode them [2]. Their responses to developmental and environmental stimuli alter the metabolism of RNA in a number of different ways, such as splicing, stability, translation, and subcellular location [3].

M6A and m5C deregulation is emerging as a typical feature of oncogenesis, which leads to tumor formation, spread, and resistance to treatment [4]. The proteins, METTL3, and NSUN2 have been shown to be overexpressed to support malignant transformation, and the loss of control over the activity of FTO and ALKBH5 has been associated with drug resistance and immune evasion [5]. This review of the literature explores the complex functions of RNA modifications in cancer biology, and in particular, their treatment potential. RNA-modifying enzyme targeting could provide new biomarkers and individual treatment options, which will provide an opportunity to enhance clinical outcomes in cancerous malignancies [6].

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2. RNA Modifications in Cancer

The manner in which RNA is modified has become key regulators of gene expression that go well beyond the traditional models of DNA and histone modifications. These covalent chemical modifications that are collectively known as the epitranscriptome coordinate various facets of RNA biology such as splicing, stability, subcellular localization and translational efficiency, and hence modulate cellular phenotype [7]. Irrational epitranscriptomic phenotypes have come to be linked with oncogenesis, metastatic spread, and therapeutic resistance. Some of the most studied marks include N6-methyladenosine (m6A) and 5-methylcytosine (m5C), which have different but similar impacts on tumorigenic processes **(Figure 1)** [8].

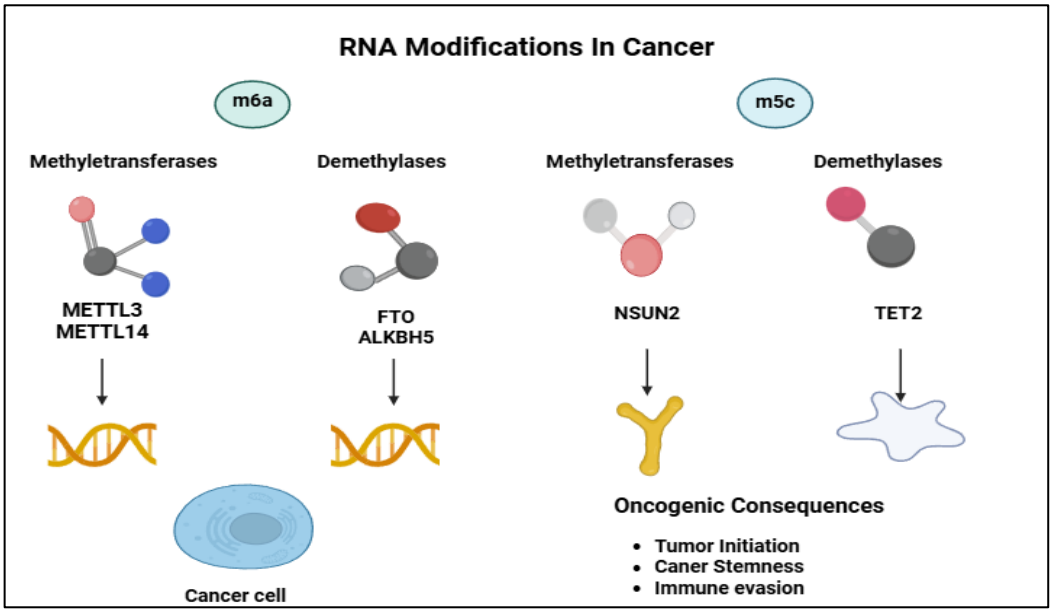

Figure 1: RNA modifications in cancer.

This figure shows how the changes in RNA, namely m6A and m5C, participate in the pathogenesis of cancer by means of the important enzymes such as methyltransferases (METTL3, METTL14, NSUN2) and demethylases (FTO, ALKBH5, TET2) in cancer cells. It emphasizes the oncogenic effects of these epitranscriptomic alterations including tumor formation, stemness and immune evasion.

2.1 N6-Methyladenosine (m6A)

The most common internal modification in eukaryotic messenger RNA is m6A. Deposition is catalysed by METTL3/METTL14 methyltransferase complex, its removal is

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promoted by demethylases like FTO and ALKBH5 and its recognition is mediated by YTH domain family reader proteins [9]. The m6A dynamic regulation to cellular stressors and cellular developmental cues underscores the role of the m6A in regulating the metabolism of RNA with precision. Aberrant m6A signalling plays a role in tumor initiation and resistance to treatment in neoplastic disease [10]. As an example, hyper-expression of METTL3 increases translational expression of cancer-promoting transcripts such as MYC and BCL2, which enhances proliferative competence. In contrast, an increased FTO and ALKBH5 activity increases the stability of mRNAs which promote cell cycle initiation and immune evasion [11]. Moreover, m6A changes also have an impact on important metastatic characteristics, including cancer stemness and epithelial-mesenchymal transition (EMT). Anti-tumor effects of pharmacologic inhibition of demethylases, in particular FTO antagonists have been shown in preclinical models, and therefore provide a promising therapeutic option [12].

2.2 5-Methylcytosine (m5C)

m5C is found in numerous species of RNA such as mRNA, transfer RNA, and non-coding RNAs and is put in by the NSUN family of methyltransferases, and the NSUN2 is one of the key catalysts [13]. This alteration trails the RNA stability, translational ideality and fidelity and immune voltage. NSUN2 overexpression in malignancies is associated with poor prognosis, increasing proliferative abilities and giving cancer cells immunotherapy-resistance [14]. m5C changes in non-coding RNAs have the potential to regulate the expression of immune checkpoint receptors, promoting immune escape of a tumor. Oncogenic mRNAs and the survival of tumors in cytotoxic stress are enhanced by translationally by NSUN2-mediated methylation **(Table 1)**. The current evidence points to the idea that the m5C levels can be used as a prognostic marker and become a potential target of future therapeutic intervention [15].

Table 1: Consolidated summary of the key regulators and oncogenic functions of m6A and m5C is presented in below table.

Sr. No.	Modifications	Writers	Erasers	Readers	Oncogenic Functions	References
1.	m6A	METTL3, METTL14, WTAP, VIRMA	FTO, ALKBH5	YTHDF1–3, YTHDC1/2, IGF2BPs	RNA stability, EMT, cancer	[16]

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					stemness, immune evasion	
2.	m5C	NSUN2, NSUN3, DNMT2	TET2	ALYREF, YBX1	Oncogene stabilization, ribosome biogenesis, immune escape	[17]

3. RNA modifications in tumor initiation

RNA modifications of oncogenes are increasingly recognized as important tumor developmental regulators. In particular, these chemical marks (including N6-methyladenosine (m6A) and 5-methylcytosine (m5C)), instruct RNA metabolism, such as splicing, stability, translation and localization, and thereby affect gene-expression programs that are important for oncogenic transformation [18]. Mis regulation of these modifications changes cellular plastic nature, stemness, and immune evasion, and thus leading to early phases of carcinogenesis. In the next part short and long, the importance of m6A and m5C in tumor initiation is analysed in a variety of cancer types [19].

3.1 m6A in Oncogenesis

RNA modifications have been a hot topic, with its role in tumor biology only beginning to pick up steam, and N6-methyladenosine (m6A) is a notably successful example of a post-transcriptional controller directly linked to oncogenesis [20]. m6A is the most common internal mRNA modification in eukaryotes, and regulates various RNA metabolism processes including splicing, export, stability, and translation, METTL14 are controlled to determine the functional role of m6A methylation (**Figure 2**) [21]. Disruption of a single component of this machinery can carry serious pathophysiological implications in tumor development and progression. The interaction between functional outcome of m6A methylation and the reader (e.g., YTHDF and IGF2BP families), erasers (e.g., FTO, ALKBH5) and writers (e.g., METTL3 [22].

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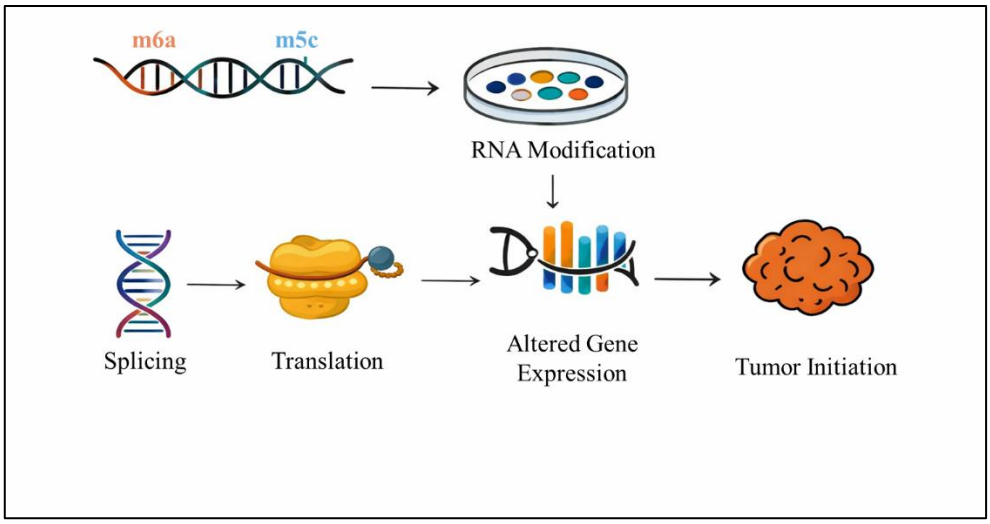

Figure 2: Mechanism of RNA modifications driving tumor initiation.

This figure demonstrates that tumor initiation can be triggered by RNA-modifications such as m6A and m5C that influence the process of splicing and translation, which results in changes in gene expression. These modifications in the RNA epigenetics are important in initiating cancer as they facilitate deregulation of cellular processes.

3.1.1 Acute Myeloid Leukaemia (AML)

In AML, the RNA m6A methyltransferase METTL3 has a strong oncogenic effect due to its implication in methylation of mRNAs such as MYC and BCL2 [23]. These post-transcriptional factors raise the stability and translational efficiency of mRNA, which is involved in furthering hematopoietic stem cell division and stopping differentiation. METTL3 also promotes cap-independent translation via its interaction with eIF3, and thereby increases the oncogenic signalling [24]. Pharmacologic or genetic inhibition of METTL3 negatively affects the growth of leukemic cells as well as to retrieve their differentiation potential, indicating the therapeutic relevance of METTL3 in AML. Meanwhile, METTL3 promotes leukemic stem-cells self-renewal and promotes disease persistence and relapse, and its overexpression is related to bad prognosis, suggesting it is a potential biomarker and target for epitranscriptomic therapy in sap cancer [25].

3.1.2 Glioblastoma

Glioblastoma stem-like cells have a high expression of the m6A demethylase ALKBH5, which demethylates transcripts that control stemness and invasion, namely, FOXM1 and NANOG mRNAs. For instance, demethylation enhances RNA stability, induces self-renewal, supports tumor growth, and cell resistance to radiotherapy [26]. ALKBH5 also regulates hypoxia

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- induced signalling pathways and thus contributes to glioma cell survival under stress conditions. Loss of ALKBH5 antagonizes stem-like traits and sensitizes glioblastoma cells to treatment and identifies this enzyme as an ideal candidate in tumorigenesis [27]. Moreover, ALKBH5 represses cytokine expression and manipulates the tumor microenvironment and induce immune evasion and angiogenesis. These results place ALKBH5 as being a dual regulator of intrinsic tumor growth and extrinsic tumor promoting states [28].

3.1.3 Lung Cancer

In lung cancer, m6A modification regulates epithelial-mesenchymal transition (EMT), which is an important process involved in metastasis. Methyltransferase-like or METTL)3 (METTL3) mediated methylation increases the translation of EMT regulators such as ZEB1, SNAIL, and TWIST leading to cellular plasticity and invasiveness [29]. Methylation of immune checkpoints leads to immune escape. m6A can also modulate immune checkpoints expression. Dysregulation of m6A signalling is associated with a poor prognosis and resistance to immunotherapy. Metastasis can also be inhibited and the clinical outcomes changed through therapeutic modulation of m6A pathways [30]. In addition, m6A marks are linked to tumor suppression, where m6A marks either influence expression of tumor suppressive genes or non-coding RNAs and thereby contribute to tumor heterogeneity. The dynamism of m6A regulation to environmental stress elicits its expediency in precision oncology as a target [31].

3.2 m5C in Oncogenesis

An important epitranscriptomic modification of RNAs includes 5-methylcytosine (m5C), which is common in messenger RNAs (mRNAs), transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), and long noncoding RNAs (lnc RNAs). NSUN2 primarily mediates cytosine base methylation and has mainly been reported to mediate oxidation of m5C by DNMT2, although TET2 has also been reported as an eraser by oxidizing cytosine bases to potentially be removed. Proteins like ALYREF and YBX1, which affect RNA stability and transport, perform the interpretation of this modification, or its reading. Aberrant m5C modification has been strongly associated with cancer formation and progression, enabling the activation of oncogenic gene programs, promoting ribosome biogenesis, enabling adaptation to changing environments, and enabling immune evasion [32].

3.2.1 Colorectal Cancer

In colorectal cancer the methyltransferase NSUN2 which catalyses methylation of oncogenic mRNAs is overexpressed and can catalyse methylation of PHGDH, ENO1 and CDK1 mRNAs [33]. Taken together, cyclins and p53 have a role in metabolism regulation

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by interacting to stabilize and increase translational product of RNA, which aid in metabolic reprogramming and cell cycle advancement. NSUN2 also binds RNA binding proteins like YBX1 contributing to positive feedback of oncogenic signalling [34]. Knockdown of NSUN2 in vivo eventuated in hindrance of tumor formation and chemosensitizers cells to chemotherapy, and thus, it is a suitable therapeutic target. Furthermore, the NSUN2-mediated m5C methylation has been associated with resistance to oxidative stress, which averts cancer malignancy cells from arming up during neoplastic developments and in hostile microenvironments, and upholds a proliferative benefit during early tumorigenesis [35].

3.2.2 Liver Cancer

Hepatocellular carcinoma (HCC) is associated with high methylating m5C of long non-coding RNAs (lnc RNAs) including HULC, MALAT1 and PVT1 responsible for regulating apoptosis, proliferation and immune modulation. m5C regulates RNA export and subcellular localization of these lnc RNAs which enhances their oncogenic functions promote through NSUN2-mediated methylation which in turn stabilises these lnc RNAs, promoting tumor heterogeneity. Conclusion: High expression of m5C in HCC is associated with advanced stage, vascular invasion, and poor overall survival, which revealed the diagnostic and therapeutic value of m5C. Moreover, the m5C-modified lnc RNAs have been reported to interact with chromatin-remodelling complexes, and thus to adjust gene-expression map and facilitate epigenetic reprogramming biased toward tumour initiation and immune inhibition in liver cancer [36].

3.2.3 Breast Cancer

In breast cancer, specifically aggressive types of cancer (e.g. triple negative breast cancer, TNBC), high levels of m5C mice were linked to poor prognosis and increased metastatic potential. Although m5C controls immune checkpoints through immune evasion, m5C can also regulate transcripts such as HGH1 and FOSL1, thus leading us to proliferation and invasion [37]. NSUN2 expression is correlated with tumor grade and lymph-node metastasis, and thus it is a potential candidate biomarker. Moreover, m5C methylation has been reported to be involved in endocrine resistance through altered estrogen receptor signalling pathways, which consequently results in therapeutic failure [38]. Indeed, the role of m5C had further been linked to cellular flexibility and the capacity mediating oncogenic networks by playing interconnection with microRNA biogenesis [39].

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4 RNA Modifications and Therapy Resistance

4.1 Chemotherapy Resistance

The modification of RNAs and m6A and m5C in particular is becoming more and more involved in cancer chemotherapy resistance mechanisms, making treatment more difficult and affecting patient survival [40]. These epitranscriptomic marks assist the cancer cells to endure the typically-lethal actions of major chemotherapy which relies on to deliver the new treatment interference directives. In the case of m6A, the studies have determined that a methyl transferase, METTL3, is central to developing resistance to cisplatin [41]. Cisplatin, which is used as a first-line chemotherapeutic agent in various solid tumors (including lung, ovarian and bladder cancers), induces cell death in cancerous cells through DNA damage. Nevertheless, the increased expression of METTL3 increases m6A modifications of mRNAs, which encode DNA repair factors [42]. These m6A-marked transcripts are more stable and better translated leading to high levels of DNA repair proteins in the cell. This leaves cancer cells with the ability to repair the DNA damage caused by cisplatin rapidly, and to survive, allowing them to keep replicating, making the treatment less efficient [43].

Clinical evidence shows that high levels of METTL3 are also associated with a poor response to cisplatin and low survivability of cancer patients. METTL3 inhibition or disruption of the m6A modification network has emerged as a very promising treatment strategy to restore cisplatin sensitivity and increase chemotherapy effectiveness [44]. Similarly, the methyltransferase mediated m5C-modification also contributes to 5-fluorouracil (5-FU) resistance in colorectal cancer. NSUN2 modifies some cytosines of mRNAs, which enhances their stability, and translation, especially in cell survival, in response to drug detoxification, and metabolism [45]. High levels of NSUN2 have been associated with reduced efficacy of chemotherapy based on 5-FU; cancer cell with a high level of NSUN2-mediating m5C marks can endure the cytotoxic stress and survive [46].

4.2 Radio Therapy Resisitance

Radiotherapy continues to play an important role in the treatment of most cancer types, yet radiation resistance is a major issue limiting radiotherapy in cancer treatment. The role of epitxtomic modifications (m6A and m5C) and radio resistance in cell survival and DNA repair: Epicentromic modifications (m6A and m5C) and radio resistance play vital roles in cell survival and DNA repair activities [47]. Demethylase ALKBH5 is one of the m6A regulators that have been found to make a significant contribution to the resistance to radiotherapy in glioblastoma, a highly aggressive and treatment-resistant brain tumor [48].

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ALKBH5 removes m6A marks on mRNAs encoding key DNA repair proteins, stabilizes such transcripts and enables their translation. This maintains a continuous presence of DNA repair machinery in glioblastoma cells, and they can respond well and quickly to radiation-induced DNA damage [49].

High expression of ALKBH5 is closely linked to the improvement of cancer stem-like cell survival and proliferation that occurs post-radiotherapy and encourages tumor growth and recurrence. Knockdown of ALKBH5 in glioblastoma increases cell vulnerability to radiation, compromising cell repair capacity, and cell survival- underscoring the value of ALKBH5 as a pharmacologic target in overcoming radio resistance [50]. Likewise, radiation tolerance has been proposed to be caused by m5C modification, which mainly occurs under the influence of the methyltransferase NSUN3. NSUN3 is an RNA (ribosomal RNA) methylator that influences both the biology of ribosome biogenesis and fidelity to translation, which are key components of cellular adaptation and survival to stressful environments such as radiation therapy [51]. Increased rRNA methylation through NSUN3 stimulates the production of turbine proteins in order to restore and replace damaged cellular structures that allow tumor cells to survive and regenerate after radiation assault. High NSUN3 activity has been linked to resistance to radiotherapy and poor treatment of cancer in a range of different types of cancer [52].

4.3 Immunotherapy resistance

Immunotherapy, and by extension immune checkpoint blockade has revolutionized the approach to the treatment of cancer through the use of the immune system inside the body to kill tumors. However, some cancer cells develop resistance to these therapies and this renders canaries' clinical insignificance [53]. Recently, RNA modifications m6A and m5C have been proposed as one of the most critical epitranscriptomic processes that control immunotherapy resistance through the modulation of immune response pathways and tumor-immune interactions [54].

The m6A demethylase FTO is central in suppression of the anti-tumor immune response. FTO erases the m6A marks formed on mRNAs that encode key interferon response genes, resulting in their reduced expression. As interferon signalling plays a vital role in the activation of immune cells and their recognition of tumor antigens, the down regulation of these genes leads to the compromised immune response against cancer cells [55]. This inhibits the effect of immunotherapies against programmed cell death protein 1 (PD-1) blockage, which demands the proper activation of the immune system to rid the body of tumors.FTO has been identified as a tumor-associated gene in tumors with resistance to PD-1 inhibitors, and is a potential immunotherapy target that could be exploited to overcome immunotherapy resistance [56].

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4.4 Targeted Therapy Resistance

Immunotherapy and particularly immune checkpoint blockade have completely changed the way cancers are treated because they have taken over the role of the body immune system to destroy cancers [57]. There is, however, a problem of resistance of many cancers to these therapies, which limits their clinical usefulness. Recent studies have identified RNA modifications (m6A and m5C) as important epitranscriptomic events involved in immunotherapy resistance by modulating immune response pathways and tumor-immune interactions [58].

The deactivation of the anti-tumor immune system involves the demethylase FTO m6A. FTO removes m6A methylations in mRNAs encoding major interferon response genes, causing them to be under-expressed. Because interferon signalling plays a crucial role in the activation of immune cells and stimulating tumor antigen recognition, suppression of these genes leads to a low immune response to cancer cells [59]. This is when the effects of programmed cell death protein 1 (PD-1) blockade therapy is relatively weakened because the establishment of an efficient immune response is a priority in the killing of the tumors. High levels of FTO in tumors are associated with lack of responsiveness to PD-1 inhibitors and it is suggested that FTO may potentially become a therapeutic target to reverse immunotherapy resistance **(Table 2)** [60].

Table 2: RNA modifications and their contributions to therapy resistance is provided in below table.

Sr. No.	Therapy Type	m6A Role	m5C Role	Example Cancers	References
1.	Chemotherapy	METTL3 enhances cisplatin resistance via DNA repair	NSUN2 promotes 5-FU resistance	Lung, Colorectal	[61]
2.	Radiotherapy	ALKBH5 stabilizes DNA repair genes	NSUN3 modifies rRNA for radiation tolerance	Glioblastoma	[62]

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3.	Immunotherapy	FTO reduces interferon response, PD-1 resistance	m5C disrupts antigen presentation	Melanoma, HCC	[63]
4.	Targeted therapy	m6A stabilizes *EGFR/KRAS* → TKI resistance	m5C enhances survival pathways	Lung, Breast	[64]

5. Therapeutic Targeting of RNA Modifications

A novel therapeutic approach to cancer is targeting an RNA modification, particularly, m6A. The demethylase FTO and the methyltransferase METTL3 have received particular attention due to their participation in the development and resistance to therapy of tumors [65]. Preclinical success was being achieved with methylthiazide blockers such as STM2457. STM2457 selectively inhibits the functions of METTL3 as a methyltransferase that silences the m6A mRNA oncogenes in mRNAs [66]. This results in diminished stability and translation of cancer-pro promoting transcripts repressing tumor cell proliferation and increasing sensitivity to conventional treatment options. STM2457 has shown efficacy in cancer as well as acute myeloid leukaemia and solid tumors [67].

On the other hand, FTO inhibitors (R-2-hydroxyglutarate, R-2HG and meclofenamic acid analogs) may prevent the removal of m6A marks and augment the target RNA methylation [68]. This increased degree of methylation turns off the expression of oncogenes, inhibiting the growth of tumors. The FTO inhibitors are also able to overcome chemotherapy and immunotherapy resistance, so it could be provided as a combination therapy [69]. These METTL3 and FTO inhibitors are together a novel type of epitranscriptomic cancer therapy. They provide promising mechanisms to defeat the problem of drug resistance and improve the fate of ailing individuals by altering the m6A RNA modifications [70].

5.1 m5C targeting

Inhibiting the methyltransferase NSUN2 to target the mC RNA modification is also a growing treatment method in cancer therapy. NSUN2-mediated m5C modification of multiple types of RNA in isolated tumors influences RNA stability, translation, and cellular processes that promote tumor development and treatment resistance [71]. The first preclinical

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data suggest that the inhibition of NSUN2 may reduce the m5C level on oncogenic transcripts, lead to a reduction in tumor cell proliferation, and an increase in tumor cell vulnerability to chemotherapy [72]. NSUN2 inhibition impacts translation of cancer cell survival and proliferation genes, disrupting the homeostasis of cancer cells. Besides this, the metabolic adjustment of the tumor to the stress induced by the therapy methods caused by NSUN2 blockage may be missed [73]. Recent research involving NSUN2 is very new and has massive potential to identify new anti-cancer drugs which can be combined with the existing drug to reverse the m5C oncogenic effect. More research is needed on potent, selective NSUN2 inhibitors and determining their safety and efficacy in treatment [74].

5.2 Combination therapies

Integrating therapies that modulate RNA with more traditional cancer modalities like chemotherapy, radiotherapy or immunotherapy is an encouraging approach to addressing resistance to therapy [75]. To evade immunotherapy, cancer cells often acquire resistance through exploiting RNA modifications such as m6A and m5C, which control important cellular functions such as DNA repair, gene regulation, and immune evasion [76].

This may be achieved by preventing the expression of survival genes, such as DNA repair, by impairs the activity of pathway signalling enzymes such as the methyltransferases METTL3 and NSUN2 [77].

Similarly, the direct targeting of the demethylase FTO can enhance an anti-inflammatory response to promote immunotherapies such as PD-1 blockade. Such dual targeting interferes with several different processes by which cancer cells can withstand treatment stress, potentially resulting in improved tumor control and reduced relapse [78].

Additionally, the RNA modification inhibitors will also enable reduction of doses of traditional therapy avoiding toxicity and side effects. On-going research and clinical trials on optimal combinations of treatment and optimum characteristics to apply when choosing patients are conducted [79]. Personalised combination therapies consisting of RNA modification targeting are showing remarkable promise to improve clinical outcomes and establish new standards in precision oncology [80].

6. Future Perspectives

RNA epigenetics can be viewed as a relatively new field of study that has a significant potential to both develop cancer research and develop therapeutic options. The recent studies of RNA post-transcriptional modifications, including N6-methyladenosine (m6A) and

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methylcytosine (m5C) have revealed new layers of regulation that can regulate the tumor phenotype, treatment response, and disease progression. These chemical modifications affect cellular stress-response programs, immune signalling cascades and oncogenic signalling pathways in a way that they pose themselves as attractive oncological targets. One such highly promising translational use is the generation of biomarkers based on RNA methylation pattern. Differentiating methylation patterns could be used to forecast disease outcomes and predict therapeutic sensitivity; chemoresistance and reduced immunotherapeutic efficacy in relation to dysregulation of m6A modulators, including METTL3 and FTO. These broad characterizations of epitranscriptomic perturbations would therefore be useful in aiding finer patient stratification and designing personalized treatment protocols. The other research area which is vital and crucial in terms of research is the development of selective inhibitors to enzymes which explain RNA modification. Although the small -molecule m6A writers and erasers antagonists have been shown to be therapeutically effective in preclinical systems, specific subtype -inhibition and off-target toxicity abatement remain significant challenges. Conclusively, CRISPR-based RNA editing technologies, such as Cas13 and engineered ADAR enzymes, are genome-safe and reversible therapeutic interventions which can specifically correct disease-related RNA transcripts. Such technologies have quite high potential in the future of cancer treatment.

7. Conclusion

RNA modifications, namely N6 -methyl adenosine (m6A) and 5 -methyl cytosine (m5C), have been identified as critical post-transcriptional regulators of gene expression, including splicing, transcript stability, nuclear export and translation. Mutations in these changes restructuring the transcriptomic and proteomic structure of cancer cells, transition of cancer, metastasis, and evolution of drug resistance contribute to the formation of tumors. The enzymes that install, remove or read these marks, i.e. METTL3, FTO, ALKBH5 and NSUN2, have context-dependent oncogenic or tumor-suppressive activity as in METTL3-mediated methylation of MYC and BCL2 in leukemic cells or NSUN2-mediated m5C modifications in colorectal cancer. These findings highlight the complexity of the epitranscriptomic regulation and its role in cancer stem cell behaviours and signal pathways. With the ongoing advancement of the field, the concept of preventing RNA-modifying enzymes is promising a highly selective therapeutic avenue with high potential of clinical transfer and the improvement of patient outcomes.

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