Content available at: https://www.ipinnovative.com/open-access-journals

International Journal of Recent Innovations in Medicine and Clinical Research

Journal homepage: https://www.ijrimcr.com/

Short Communication

Epitranscriptomics in oncology: The double-edged role of RNA modifications in cancer and resistance

Harsh Nawal[1]*

[1]*Medical College & Hospital, Kolkata, West Bengal, India*

ARTICLE INFO

Article history:
Received 18-08-2024
Accepted 21-09-2024
Available online 11-11-2024

Keywords:
Genetic techniques
Nanopore sequencing
Drug development
Machine learning
Cancer progression
Epitranscriptomics

ABSTRACT

Epitranscriptomics, the study of RNA modifications such as N6-methyladenosine (m6A), has emerged as a pivotal field in cancer research. These chemical modifications influence gene expression, protein translation and cellular behavior, driving critical processes like tumor initiation, progression and metastasis. Furthermore, RNA modifications contribute to cancer stem cell plasticity, promoting survival and therapy resistance. Treatment resistance, a major obstacle in cancer therapy, is often driven by aberrant RNA modifications that affect the stability of coding and non-coding RNAs, leading to enhanced DNA repair, drug efflux and immune evasion. As a result, targeting RNA-modifying enzymes has gained attention as a novel therapeutic strategy. Inhibitors of "writers," "erasers" and "readers" of these modifications are currently being explored to restore sensitivity to conventional therapies. This commentary discusses the emerging role of RNA modifications in cancer progression and treatment resistance, highlighting the potential for novel therapeutic interventions in combatting drug-resistant cancers.

1. Introduction

The role of epitranscriptomics, the study of post-transcriptional RNA modifications, is gaining increasing attention in cancer biology. These modifications, including N6-methyladenosine (m6A), 5-methylcytosine (m5C) and pseudouridine, act as key regulators of gene expression and cellular processes. Recent advances have uncovered their profound impact on cancer progression, stem cell plasticity and treatment resistance, positioning them as critical players in tumor biology and potential therapeutic targets.

1.1. Cancer progression

RNA modifications such as m6A have proven to be pivotal in the regulation of gene expression, influencing numerous biological processes central to tumorigenesis, including cell proliferation, invasion and epithelial-mesenchymal transition (EMT). Notably, m6A methylation dynamically regulates the expression of both oncogenes and tumor suppressors, modulating pathways critical for tumor initiation and metastatic spread. This dynamic modification is highly responsive to the tumor microenvironment, providing cancer cells with the plasticity to adapt to stress, evade immune surveillance and enhance metastatic potential.[1–3]

For instance, m6A modifications in key regulatory genes influence signaling pathways like Wnt/β-catenin and PI3K/AKT, known drivers of cancer progression. By fine-tuning mRNA stability and translation, m6A methylation facilitates the expression of proteins that promote tumorigenic traits such as invasiveness and migration. Furthermore, the reversible nature of these modifications means that cancer cells can adapt dynamically, switching between proliferative and invasive states depending on external stimuli.[4,5]

* *Corresponding author*.
E-mail address: harshnawalatwork@gmail.com (H. Nawal).

https://doi.org/10.18231/j.ijrimcr.2024.065

Cancer stem cells (CSCs), often implicated in recurrence and therapy resistance, also exhibit distinct epitranscriptomic landscapes. The ability of CSCs to self-renew and differentiate is partly regulated by unique RNA modifications, which maintain their stemness and resistance to environmental stressors.[4,5] Unraveling the RNA modification patterns specific to CSCs offers new insights into cancer progression, potentially unveiling biomarkers for early cancer detection or novel therapeutic targets aimed at eradicating this aggressive cell population.

1.2. Treatment resistance

Treatment resistance is a primary obstacle in effective cancer therapy. Epitranscriptomic modifications, especially m6A, have been increasingly recognized as contributors to the development of resistance to chemotherapy, radiotherapy and even immunotherapy. For example, m6A modifications alter the stability and translational efficiency of mRNAs coding for proteins involved in drug resistance mechanisms. In patients treated with cisplatin or gefitinib, m6A-modified transcripts increase the expression of drug efflux pumps and anti-apoptotic proteins, ultimately driving chemoresistance.[3,6,7]

Beyond protein-coding RNAs, non-coding RNAs such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) also undergo critical epitranscriptomic modifications that affect their function, stability and interactions with other molecules. These modified non-coding RNAs can regulate drug resistance pathways by modulating the expression of critical oncogenes or tumor suppressors.[6,8] For instance, m6A-modified lncRNAs have been shown to sequester tumor-suppressive miRNAs, thus promoting resistance to targeted therapies like tyrosine kinase inhibitors. Furthermore, epitranscriptomic alterations in non-coding RNAs can enhance DNA repair pathways, diminishing the efficacy of radiotherapy by allowing cancer cells to better survive DNA damage.[3,7]

The enzymes responsible for adding (writers), removing (erasers) and recognizing (readers) these modifications represent promising therapeutic targets. Inhibiting these enzymes could reverse the aberrant RNA modifications that support treatment resistance. For example, inhibitors of m6A writers like METTL3 or erasers like FTO may restore chemosensitivity and disrupt the adaptive resistance mechanisms cancer cells exploit to survive therapy.[2,9]

2. Therapeutic implications and future directions

The growing understanding of RNA modifications in cancer has spurred interest in developing small molecule inhibitors that target specific epitranscriptomic enzymes. These inhibitors offer the potential to reprogram the RNA landscape of cancer cells, restoring normal gene expression patterns and sensitizing tumors to conventional therapies.[2,9] The development of m6A inhibitors, for example, holds promise for reversing the oncogenic RNA modifications that contribute to drug resistance. Preclinical studies have demonstrated that targeting these modifications can enhance the efficacy of chemotherapy and immunotherapy, providing a novel strategy to combat refractory cancers.

In addition to enzyme inhibitors, identifying specific RNA modification signatures in various cancer types could facilitate the development of personalized treatment strategies. Tumor profiling based on the epitranscriptomic landscape can help predict responses to therapies and identify patients who may benefit from RNA modification-targeting drugs. With advancements in RNA sequencing technologies, we can now comprehensively profile the RNA modifications in tumor samples, providing valuable insights for precision medicine.[1,10]

Looking forward, the field of epitranscriptomics is poised to transform our understanding of cancer biology and therapeutic approaches. By harnessing the knowledge of RNA modifications and their regulatory networks, future research may unlock new ways to target treatment-resistant cancers, potentially leading to more durable therapeutic responses and improved patient outcomes.

3. Conclusion

Epitranscriptomic modifications, particularly m6A methylation, play a crucial role in the regulation of cancer progression and treatment resistance. As our understanding of these modifications deepens, so too does the potential to develop innovative therapies that disrupt the oncogenic RNA landscape. Targeting RNA modification pathways presents a promising frontier in cancer treatment, offering new hope in the battle against aggressive and resistant tumors.

4. Source of Funding

None.

5. Conflict of Interest

None.

References

1. Clevers H. Modeling development and disease with organoids. *Cell*. 2016;165(7):1586–97.
2. Huang Y, Huang Z, Tang Z, Chen Y, Huang M, Liu H, et al. Research progress, challenges, and breakthroughs of organoids as disease models. *Front Cell Dev Biol*. 2021;9:740574.
3. Corro C, Novellasdemunt L, Li VSW. A brief history of organoids. *Am J Physiol Cell Physiol*. 2020;319(1):C151–65.
4. Kim J, Koo BK, Knoblich JA. Human organoids: model systems for human biology and medicine. *Nat Rev Mol Cell Biol*. 2020;21(10):571–84.
5. Hofer M, Lutolf MP. Engineering organoids. *Nat Rev Mater*. 2021;6:402–20.

6. Pedrosa RS, Salgado AJ, Ferreira PE. Revolutionizing disease modeling: The emergence of organoids in cellular systems. *Cells*. 2023;12(6):930.
7. Lancaster MA, Huch M. Disease modeling in human organoids. *Dis Model Mech*. 2019;12(7):dmm039347.
8. Sayed IM, El-Hafeez AA, Maity PP, Das S, Ghosh P. Modeling colorectal cancers using multidimensional organoids. *Adv Cancer Res*. 2021;151:345–83.
9. Nuciforo S, Heim MH. Organoids to model liver disease. *JHEP Rep*. 2020;3(1):100198.
10. Azar J, Bahmad HF, Daher D, Moubarak MM, Hadadeh O, Monzer A, et al. The use of stem cell-derived organoids in disease modeling: An update. *Int J Mol Sci*. 2021;22(14):7667.

Author's biography

Harsh Nawal, MBBS Student https://orcid.org/0009-0000-1914-4037

Cite this article: Nawal H. Epitranscriptomics in oncology: The double-edged role of RNA modifications in cancer and resistance. *Int J Recent Innov Med Clin Res* 2024;6(4):134-136.