Serican Journal of Medicine
2025, VOL. 2, NO. 3, 23747
https://doi.org/10.17161/sjm.v2i3.23747

Unraveling the Role of N^6-Methyladenosine in Prostate Cancer: Implications for Prognosis and Tumor Aggression

Xin Xu[1,#], Xinqiao Zheng[1], Housheng Hansen He[1,2,#]

[1]Princess Margaret Cancer Center, University Health Network, Toronto, Canada; [2]Department of Medical Biophysics, University of Toronto, Toronto, Canada. #Correspondence: xin.xu@uhn.ca, hansen.he@uhn.ca

ABSTRACT

The epitranscriptomic modification N6-methyladenosine (m^{6}A) has emerged as a central regulator of RNA metabolism, influencing diverse physiological and pathological processes. As the most abundant RNA modification in eukaryotic cells, m^{6}A dynamically modulates gene expression by regulating RNA processing, stability, and translation. Dysregulation of m^{6}A has been implicated in key oncogenic processes, including tumor initiation, progression, metastasis, therapy resistance, and interactions within the tumor microenvironment. Despite these advances, the role of m^{6}A in prostate cancer remains poorly understood, highlighting the need for further investigation. In a recent study, Xu et al. utilized refined m^{6}A meRIP-seq to profile 162 primary prostate cancer patient samples, unveiling novel insights into the epitranscriptomic landscape of this malignancy. These findings not only enhance our understanding of m^{6}A regulation in cancer biology but also underscore its potential to inform diagnostic, prognostic, and therapeutic strategies for prostate cancer.

ARTICLE HISTORY
Received: March 21, 2025
Revised: April 8, 2025
Accepted: April 10, 2025

KEYWORDS
Prostate cancer,
tumor aggression,
N^6-Methyladenosine

Introduction

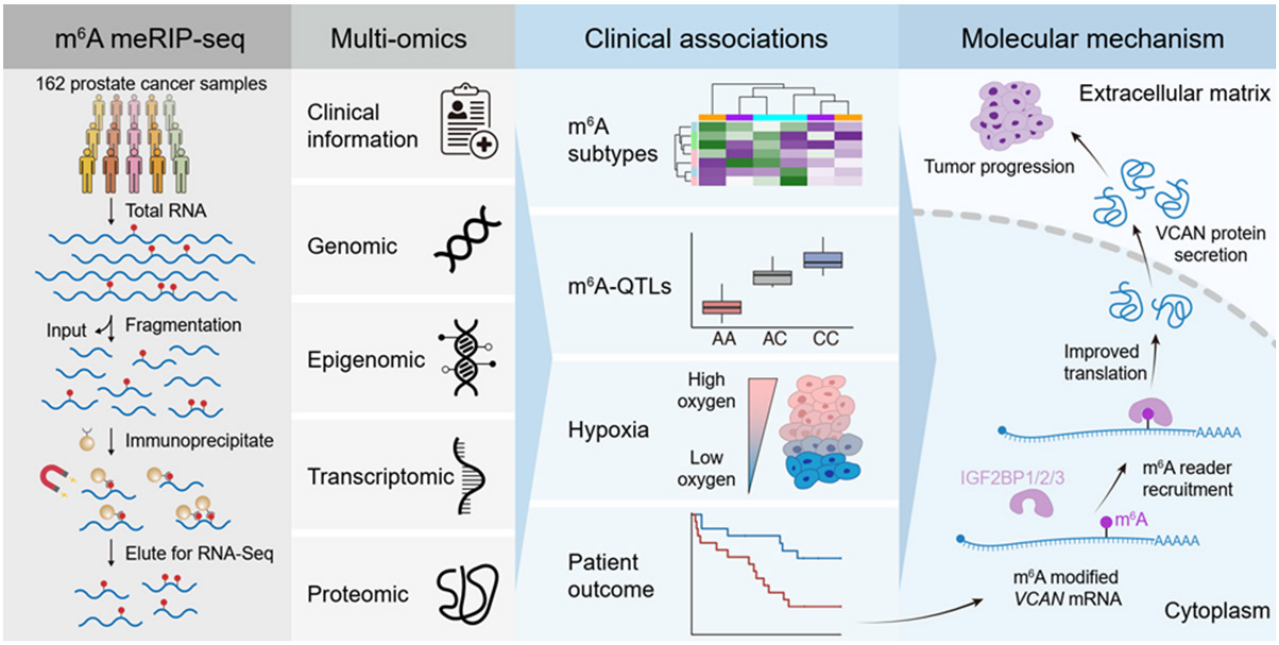
m^{6}A is the most abundant mRNA modification in eukaryotes, playing a critical role in regulating various aspects of RNA metabolism, including splicing, translation, and degradation [1, 2]. m^{6}A modifications are catalyzed by the "writer" methyltransferase complex, whose core components include METTL3, METT14, and WTAP [3]. Proteins that recognize these modifications, known as "readers", include YTH domain-containing proteins (YTHDF1/2/3 and YTHDC1/2), heterogeneous nuclear ribonucleoproteins (hnRNPs), and IGF2BP family members, among others [1, 4]. Each reader performs distinct roles during every step of the RNA lifecycle, thus fine-tuning gene expression.

Dysregulation of these regulators has been closely linked to tumorigenesis and cancer progression, underscoring the pivotal role of m^{6}A in controlling cellular and pathological states [5-9]. Elucidating the precise molecular mechanisms of m^{6}A modifications remains a critical area of research, with significant implications for understanding cancer biology and developing therapeutic strategies. Dysregulation of m^{6}A modification has been implicated in diverse cancer-related processes such as tumorigenesis, metastasis, and chemoresistance [10-12]. Altered levels of m^{6}A have been observed in several types of cancer, including gastric, bladder, and colon cancer [10, 13, 14]. Recent studies have shed new light on the epitranscriptomic landscape of pancreatic [15] and lung cancers [16], revealing significant enrichment at genes involved in cell adhesion and migration, highlighting the importance of mRNA regulation in tumorigenesis.

Results and Discussion

Despite a growing understanding of prostate cancer biology, there remains a knowledge gap regarding the epitranscriptomic landscape of this disease. Previous studies have profiled the genomic [17, 18], transcriptomic [19, 20], and proteomic features of prostate cancer [21], but these efforts have not fully elucidated the underlying mechanisms driving tumorigenesis. As a critical layer of gene regulation, m^{6}A warrants further investigation in this context. To address this gap, Xu *et al.* present a comprehensive

Figure 1. Overview of m⁶A mapping, multi-omics integration, and functional validation. A refined meRIP-seq method was applied to 162 localized primary prostate cancer samples to detect m⁶A peaks, which were then integrated with multi-omic data to define m⁶A subtypes linked to tumor aggressiveness, genomic instability, and biochemical recurrence (BCR), with *VCAN*, a significant BCR-associated peak, validated to demonstrate that m⁶A stabilizes its mRNA via IGF2BP proteins and that tumor hypoxia alters m⁶A profiles.



analysis of the m⁶A landscape in 162 localized primary prostate tumors [19]. This research sheds light on the translational implications of m⁶A modifications for understanding tumor biology, aggressiveness, and clinical outcomes in prostate cancer, an area of growing interest given the intricate role of epitranscriptomics in cancer progression.

By integrating the meRIP-seq data and the previously released multi-omics data, the authors affirmed that patient subtypes determined by m⁶A profiles exhibit distinct clinico-molecular features, including tumor aggressiveness, genomic instability, and relapse rate, and m⁶A subtypes reveal specific somatic CNA patterns in m⁶A regulators, partially overlapping with established DNA and RNA subtypes (**Fig 1**). The team evaluated the germline risks by identifying genome-wide m⁶A modifications on quantitative trait locus (m⁶A-QTL). It revealed allelic imbalances at active m⁶A sites and identified m⁶A-QTLs linked to prostate cancer risk and clinical outcomes, including RNA and protein abundance changes in driver genes. Notably, the discovery of m⁶A-QTLs linked to prostate cancer risk and clinical outcomes supports and extends earlier reports on the existence and importance of m⁶A-QTLs in human disease [22, 23]. Another breakthrough in this study was the demonstration that tumor hypoxia can directly alter m⁶A profiles. Mutationally quiet subtypes were found to exhibit more normoxic m⁶A profiles, providing new insights into tumor biology. Further exploration of the underlying mechanisms driving these hypoxia-m⁶A interactions could provide valuable insights into their functional roles and potential therapeutic implications. Interestingly, frequent somatic mutations in genes that regulate m⁶A modifications were found in prostate cancer tumors, providing prognostic insights into biochemical recurrence and highlighting pathways implicated in disease progression. These findings demonstrate the potential of integrating epitranscriptomic data with clinical and genomic insights to advance precision medicine in prostate cancer.

Building upon these findings, the authors conducted an in-depth mechanistic study on one of three m⁶A peaks associated with biochemical recurrence (BCR) and discovered that the m⁶A modification status of *VCAN* serves as a superior biomarker compared to its mRNA and protein abundance. They revealed that the positive association between this peak and tumor risk factors is driven by m⁶A-mediated stabilization of *VCAN* mRNA and enhanced translation into protein, mediated by IGF2BP reader proteins. This discovery exemplifies how epitranscriptomic regulation contributes to prostate cancer initiation

and progression, offering new insights and potential targets for the diagnosis and treatment of this disease.

From a methodological perspective, the study employs several innovative approaches. The authors developed the algorithm HistogramZoo, which integrates sample-level peaks into cohort-level joint peaks, providing a rationalized framework for identifying m^{6}A modification sites. Their refined meRIP-seq approach enables deep and high-coverage sequencing from minimal sample input [24]. Notably, their findings demonstrated strong concordance with results obtained using the state-of-the-art single-nucleotide resolution method m^{6}A-selective allyl chemical labeling and sequencing (SAC-seq [25]), while achieving even higher coverage. Furthermore, the dCasRx/METTL3 programmable site-specific editing tool was used to install m^{6}A modifications, allowing investigation into the impact of m^{6}A alterations on mRNA stability and translation.

The study by Xu et al. marks an important step forward in our understanding of the epitranscriptomic landscape of prostate cancer. The findings highlight the potential for targeting m^{6}A-mediated gene regulation as a novel approach to treating this disease. However, further research is needed to fully elucidate the mechanisms underlying m^{6}A modification and its impact on prostate cancer biology. Future studies should aim to validate these findings in larger cohorts and explore the therapeutic implications of targeting m^{6}A modification in prostate cancer.

Future studies hold significant promise in several areas. One potential direction is the inclusion of additional patient samples, such as normal or metastatic prostate cancer tissues, alongside primary tumor samples used in this study. This would enhance the robustness of the findings and provide a more comprehensive understanding of the role of m^{6}A modifications across different stages of disease. Moreover, the identification of additional functional m^{6}A peaks would greatly enrich our understanding of m^{6}A-driven cancer progression and open new therapeutic possibilities. Many m^{6}A regulators, for which inhibitors have already been reported [26-28], show considerable potential as drug targets, offering exciting opportunities for targeted therapies. Additionally, exploring m^{6}A modifications in the context of hypoxia could uncover novel mechanisms in tumor biology, shedding light on how the tumor microenvironment influences m^{6}A regulation and cancer progression. These directions represent exciting future opportunities for advancing the understanding and treatment of prostate cancer.

In conclusion, this study provides valuable insights into the m^{6}A landscape in localized primary prostate cancer, highlighting its potential to enhance patient management. By elucidating the complex interplay between m^{6}A modifications and tumor characteristics, these findings contribute to a deeper understanding of prostate cancer biology. As research in epitranscriptomics advances, translating these findings into actionable insights for personalized patient care remains a crucial goal.

Acknowledgments

The author gratefully acknowledges the support of the Prostate Cancer Foundation Young Investigator Award (21YOUN06), Terry Fox New Frontiers Program Project Grant, and the Tier 1 Canada Research Chair in RNA Medicine.

Declaration of interests

The author has no conflict of interest to declare.

References

1. Yang Y, Hsu PJ, Chen YS, Yang YG: **Dynamic transcriptomic m(6)A decoration: writers, erasers, readers and functions in RNA metabolism**. *Cell Res* 2018, **28**(6):616-624; doi:10.1038/s41422-018-0040-8; PMC5993786.
2. Zhao BS, Roundtree IA, He C: **Post-transcriptional gene regulation by mRNA modifications**. *Nat Rev Mol Cell Biol* 2017, **18**(1):31-42; doi:10.1038/nrm.2016.132; PMC5167638.
3. Shi H, Wei J, He C: **Where, When, and How: Context-Dependent Functions of RNA Methylation Writers, Readers, and Erasers**. *Mol Cell* 2019, **74**(4):640-650; doi:10.1016/j.molcel.2019.04.025; PMC6527355.
4. Zou Z, He C: **The YTHDF proteins display distinct cellular functions on m(6)A-modified RNA**. *Trends Biochem Sci* 2024, **49**(7):611-621; doi:10.1016/j.tibs.2024.04.001; PMC11227416.
5. Panneerdoss S, Eedunuri VK, Yadav P, Timilsina S, Rajamanickam S, Viswanadhapalli S, Abdelfattah N, Onyeagucha BC, Cui X, Lai Z *et al*: **Cross-talk among writers, readers, and erasers of m(6)A regulates cancer growth and progression**. *Sci Adv* 2018, **4**(10):eaar8263; doi:10.1126/sciadv.aar8263; PMC6170038.
6. Lin S, Choe J, Du P, Triboulet R, Gregory RI: **The m(6)A Methyltransferase METTL3 Pro-**

motes Translation in Human Cancer Cells. *Mol Cell* 2016, **62**(3):335-345; doi:10.1016/j.molcel.2016.03.021; PMC4860043.

7. Choe J, Lin S, Zhang W, Liu Q, Wang L, Ramirez-Moya J, Du P, Kim W, Tang S, Sliz P *et al*: **mRNA circularization by METTL3-eIF3h enhances translation and promotes oncogenesis**. *Nature* 2018, **561**(7724):556-560; doi:10.1038/s41586-018-0538-8; PMC6234840.
8. Zhang S, Zhao BS, Zhou A, Lin K, Zheng S, Lu Z, Chen Y, Sulman EP, Xie K, Bogler O *et al*: **m(6)A Demethylase ALKBH5 Maintains Tumorigenicity of Glioblastoma Stem-like Cells by Sustaining FOXM1 Expression and Cell Proliferation Program**. *Cancer Cell* 2017, **31**(4):591-606 e596; doi:10.1016/j.ccell.2017.02.013; PMC5427719.
9. Vu LP, Pickering BF, Cheng Y, Zaccara S, Nguyen D, Minuesa G, Chou T, Chow A, Saletore Y, MacKay M *et al*: **The N(6)-methyladenosine (m(6)A)-forming enzyme METTL3 controls myeloid differentiation of normal hematopoietic and leukemia cells**. *Nat Med* 2017, **23**(11):1369-1376; doi:10.1038/nm.4416; PMC5677536.
10. Wang Q, Chen C, Ding Q, Zhao Y, Wang Z, Chen J, Jiang Z, Zhang Y, Xu G, Zhang J *et al*: **METTL3-mediated m(6)A modification of HDGF mRNA promotes gastric cancer progression and has prognostic significance**. *Gut* 2020, **69**(7):1193-1205; doi:10.1136/gutjnl-2019-319639.
11. Chang G, Shi L, Ye Y, Shi H, Zeng L, Tiwary S, Huse JT, Huo L, Ma L, Ma Y *et al*: **YTHDF3 Induces the Translation of m(6)A-Enriched Gene Transcripts to Promote Breast Cancer Brain Metastasis**. *Cancer Cell* 2020, **38**(6):857-871 e857; doi:10.1016/j.ccell.2020.10.004; PMC7738369.
12. Sun Y, Shen W, Hu S, Lyu Q, Wang Q, Wei T, Zhu W, Zhang J: **METTL3 promotes chemoresistance in small cell lung cancer by inducing mitophagy**. *J Exp Clin Cancer Res* 2023, **42**(1):65; doi:10.1186/s13046-023-02638-9; PMC10022264.
13. Gu C, Wang Z, Zhou N, Li G, Kou Y, Luo Y, Wang Y, Yang J, Tian F: **Mettl14 inhibits bladder TIC self-renewal and bladder tumorigenesis through N(6)-methyladenosine of Notch1**. *Mol Cancer* 2019, **18**(1):168; doi:10.1186/s12943-019-1084-1; PMC6876123.
14. Pan J, Liu F, Xiao X, Xu R, Dai L, Zhu M, Xu H, Xu Y, Zhao A, Zhou W *et al*: **METTL3 promotes colorectal carcinoma progression by regulating the m6A-CRB3-Hippo axis**. *J Exp Clin Cancer Res* 2022, **41**(1):19; doi:10.1186/s13046-021-02227-8; PMC8744223.
15. Li R, Zhao H, Huang X, Zhang J, Bai R, Zhuang L, Wen S, Wu S, Zhou Q, Li M *et al*: **Super-enhancer RNA m(6)A promotes local chromatin accessibility and oncogene transcription in pancreatic ductal adenocarcinoma**. *Nat Genet* 2023, **55**(12):2224-2234; doi:10.1038/s41588-023-01568-8.
16. Wang S, Zeng Y, Zhu L, Zhang M, Zhou L, Yang W, Luo W, Wang L, Liu Y, Zhu H *et al*: **The N6-methyladenosine Epitranscriptomic Landscape of Lung Adenocarcinoma**. *Cancer Discov* 2024, **14**(11):2279-2299; doi:10.1158/2159-8290.CD-23-1212; PMC11528209.
17. Fraser M, Sabelnykova VY, Yamaguchi TN, Heisler LE, Livingstone J, Huang V, Shiah YJ, Yousif F, Lin X, Masella AP *et al*: **Genomic hallmarks of localized, non-indolent prostate cancer**. *Nature* 2017, **541**(7637):359-364; doi:10.1038/nature20788.
18. Taylor BS, Schultz N, Hieronymus H, Gopalan A, Xiao Y, Carver BS, Arora VK, Kaushik P, Cerami E, Reva B *et al*: **Integrative genomic profiling of human prostate cancer**. *Cancer Cell* 2010, **18**(1):11-22; doi:10.1016/j.ccr.2010.05.026; PMC3198787.
19. Xu X, Zhu H, Hugh-White R, Livingstone J, Eng S, Zeltser N, Wang Y, Pajdzik K, Chen S, Houlahan KE *et al*: **The landscape of N(6)-methyladenosine in localized primary prostate cancer**. *Nat Genet* 2025, **57**(4):934-948; doi:10.1038/s41588-025-02128-y; PMC11985349.
20. Cancer Genome Atlas Research N: **The Molecular Taxonomy of Primary Prostate Cancer**. *Cell* 2015, **163**(4):1011-1025; doi:10.1016/j.cell.2015.10.025; PMC4695400.
21. Sinha A, Huang V, Livingstone J, Wang J, Fox NS, Kurganovs N, Ignatchenko V, Fritsch K, Donmez N, Heisler LE *et al*: **The Proteogenomic Landscape of Curable Prostate Cancer**. *Cancer Cell* 2019, **35**(3):414-427 e416; doi:10.1016/j.ccell.2019.02.005; PMC6511374.
22. Xiong X, Hou L, Park YP, Molinie B, Consortium GT, Gregory RI, Kellis M: **Genetic drivers of**

m(6)A methylation in human brain, lung, heart and muscle. *Nat Genet* 2021, **53**(8):1156-1165; doi:10.1038/s41588-021-00890-3; PMC9112289.

23. Zhang Z, Luo K, Zou Z, Qiu M, Tian J, Sieh L, Shi H, Zou Y, Wang G, Morrison J *et al*: **Genetic analyses support the contribution of mRNA N(6)-methyladenosine (m(6)A) modification to human disease heritability**. *Nat Genet* 2020, **52**(9):939-949; doi:10.1038/s41588-020-0644-z; PMC7483307.
24. Zeng Y, Wang S, Gao S, Soares F, Ahmed M, Guo H, Wang M, Hua JT, Guan J, Moran MF *et al*: **Refined RIP-seq protocol for epitranscriptome analysis with low input materials**. *PLoS Biol* 2018, **16**(9):e2006092; doi:10.1371/journal.pbio.2006092; PMC6136692.
25. Wang G, Li H, Ye C, He K, Liu S, Jiang B, Ge R, Gao B, Wei J, Zhao Y *et al*: **Quantitative profiling of m(6)A at single base resolution across the life cycle of rice and Arabidopsis**. *Nat Commun* 2024, **15**(1):4881; doi:10.1038/s41467-024-48941-7; PMC11161662.
26. Yankova E, Blackaby W, Albertella M, Rak J, De Braekeleer E, Tsagkogeorga G, Pilka ES, Aspris D, Leggate D, Hendrick AG *et al*: **Small-molecule inhibition of METTL3 as a strategy against myeloid leukaemia**. *Nature* 2021, **593**(7860):597-601; doi:10.1038/s41586-021-03536-w; PMC7613134.
27. Su R, Dong L, Li Y, Gao M, Han L, Wunderlich M, Deng X, Li H, Huang Y, Gao L *et al*: **Targeting FTO Suppresses Cancer Stem Cell Maintenance and Immune Evasion**. *Cancer Cell* 2020, **38**(1):79-96 e11; doi:10.1016/j.ccell.2020.04.017; PMC7363590.
28. Micaelli M, Dalle Vedove A, Cerofolini L, Vigna J, Sighel D, Zaccara S, Bonomo I, Poulentzas G, Rosatti EF, Cazzanelli G *et al*: **Small-Molecule Ebselen Binds to YTHDF Proteins Interfering with the Recognition of N (6)-Methyladenosine-Modified RNAs**. *ACS Pharmacol Transl Sci* 2022, **5**(10):872-891; doi:10.1021/acsptsci.2c00008; PMC9578143.