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PREFACE

RNA Modifications and Epitranscriptomics



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More than 170 distinct chemical modifications have been identified in non-coding and coding RNAs. Accumulating evidence suggests that RNA modifications play pivotal roles at both the molecular and physiological levels. Dysregulation of RNA-modifying enzymes has been linked to various human cancers and developmental diseases. The expanding understanding of RNA modifications in molecular and cellular functions further suggests promising prospects for therapeutic applications. Recently, the creation of effective mRNA vaccines against coronavirus disease 2019 (COVID-19), based on RNA base modification, was honored with the Nobel Prize in Physiology or Medicine 2023 (<https://www.nobelprize.org/prizes/medicine/2023/press-release/>). Aiming to provide a forum for emerging advances in detection and functional studies of epitranscriptomic modifications, we have organized a special issue “RNA Modifications and Epitranscriptomics” for the journal *Genomics, Proteomics & Bioinformatics* (GPB). This special issue encompasses a wide range of topics, including: (1) dynamic landscapes of RNA modifications in various organisms, including animals, plants, and viruses; (2) mechanistic

regulation of m⁶A and m⁵C modifications in human diseases and plant responses to stresses; (3) an online platform for unveiling the context-specific m⁶A methylation and m⁶A-affecting mutation; and (4) the regulatory role of non-coding RNAs (ncRNAs), including tRNAs and circular RNAs (circRNAs), in gene expression regulation.

We are pleased to present 14 articles selected for publication in this special issue, comprising eleven original research articles, one review, one letter, and one database article. An overview of the studies included in this issue is provided as follows.

Yafen Wang and Xiang Zhou reviewed the writer, reader, and eraser proteins involved in m⁶A modification, describing their mechanism of action during viral replication and infection. Moreover, the authors provided an overview of current detection methods for m⁶A, shedding light on the development of vaccines and antiviral drugs by examining the role of epigenetic modifications in viral processes [1].

Yixian Cun et al. uncovered a novel role of serine/arginine-rich splicing factor 7 (SRSF7) in regulating m⁶A and its impact on glioblastoma (GBM) progression. The authors found that SRSF7 specifically influenced m⁶A levels on genes associated with cell proliferation and migration, exhibiting oncogenic roles by recruiting the m⁶A methyltransferase complexes. This study highlights the significance of RNA-binding protein (RBP)-mediated specific regulation of m⁶A in determining cellular functions [2].

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Xiao Han et al. presented the inaugural landscapes of dynamic DNA 5hmC and RNA m⁵C modifications across a variety of samples, including heart, kidney, liver, and lung, from human fetuses at 13–28 weeks. The authors identified 70,091 and 503 organ- and stage-specific differentially hydroxymethylated regions (DhMRs) and m⁵C-modified mRNAs, respectively. The integrated studies revealed a potential link between DNA modification and RNA methylation, illustrating the epigenetic dynamics during human fetal organogenesis [3].

Feng Yu et al. presented a study on the complexity of epitranscriptomic dynamics in rice by identifying RNA modifications using direct RNA sequencing (DRS) technology. Besides identifying tissue-specific genes and transcript expression, the authors also mapped the m⁶A and m⁵C modifications on RNA across six developmental tissues of rice, offering a thorough understanding of the rice transcriptome and epitranscriptome [4].

Peng Yu et al. explored the relationship between tRNA abundance and translational efficiency in mammals, as well as the contribution of tRNA expression to tissue-specific proteomes. The authors measured tRNA expression using demethylase-tRNA sequencing (DM-tRNA-seq) and mRNA translational efficiencies using ribosome-tagging sequencing (RiboTag-seq) in the mouse brain, heart, and testis. They showed tRNA expression variations among tissues and provided insights into the dynamics of tRNAs and their roles in translational regulation [5].

Shuai Chen et al. studied the presence and role of circRNAs in stress granules (SGs), which are cytoplasmic ribonucleoprotein assemblies formed under stress conditions. The authors used improved total RNA sequencing to identify both linear and circular RNAs in purified SG cores and found that circRNAs with higher SG-related RBP binding abilities are more likely to be enriched in SGs. They also identified differentially expressed SG-enriched circRNAs in hepatocellular carcinoma (HCC) and adjacent tissues, suggesting a regulatory role of circRNAs and SGs in HCC [6].

Bowen Song et al. presented m⁶A-TSHub, a comprehensive online platform designed to explore tissue-specific m⁶A RNA methylation patterns and related genetic mutations. This platform encompasses four core tools: m⁶A-TSDB, which curates extensive m⁶A site data from human tissues and tumors; m⁶A-TSFinder, a predictive server for tissue-specific m⁶A sites using deep learning; m⁶A-TSVar, evaluating genetic variant impacts on m⁶A modifications; and m⁶A-CAVar, cataloging mutations affecting m⁶A in various cancers. This serves as a pivotal resource for specialized m⁶A epitranscriptome studies [7].

Zidong Liu et al. uncovered the m⁶A modification dynamics during porcine spermatogenesis. Analyzing m⁶A distribution across spermatogonia, spermatocytes, and round spermatids, they identified a globally conserved m⁶A pattern in genes related to spermatogenesis. Enrichment of m⁶A in genes encoding metabolic enzymes and regulators was observed, showcasing its regulatory role. This study provides novel insights into the transcriptional regulation of lifelong male fertility in non-rodent mammals, enhancing our understanding of spermatogenesis in large animals [8].

Lorane Le Franc et al. employed the methylated RNA immunoprecipitation sequencing (MeRIP-seq) method to map m⁶A RNA methylomes during oyster development. Their analysis revealed dynamic and stage-specific m⁶A modifications in mRNA and lncRNA classes, displaying unique methylation

patterns compared to transposon transcripts. The observed shifts in methylation profiles corresponded to expression changes across developmental stages such as cleavage, gastrulation, and organogenesis. These findings highlight the potential regulatory role of m⁶A in oyster development, offering novel insights into the control and evolution of developmental processes in lophotrochozoan organisms [9].

Ying Lv et al. deciphered the pattern and function of m⁶A modification during sexual reproduction in *Chlamydomonas* and also revealed its frequent occurrence in the DRAC motif and its main enrichment in the 3' untranslated region (UTR) of mRNAs. The study found that m⁶A levels negatively correlate with gene expression, particularly affecting the microtubule-associated pathway. This study offers evolutionary insights into the role of m⁶A in *Chlamydomonas* and sheds light on its evolutionary significance in plant sexual reproduction [10].

Dan Song et al. highlighted that HCC tissues exhibit increased m⁵C methylation, particularly influencing phosphoinositol signaling pathways. NOP2/Sun RNA methyltransferase (NSUN2) is notably overexpressed in HCC, impacting the expression of several genes and HCC cell sensitivity to the drug sorafenib. The study revealed innovative insights into the impact of RNA epigenetic modification on HCC progression, which might help to discover more effective HCC treatment targets and strategies [11].

Boyang Shi et al. employed the psoralen analysis of RNA interactions and structures method (PARIS) to map RNA structures in non-small cell lung cancer (NSCLC) cells, shedding light on epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) resistance mechanisms. They found that RNA structures, particularly in UTRs, correlate with translation efficiency, and the RNA structure of the gene encoding yrdC N⁶-threonylcarbamoyltransferase domain containing (YDRC) impacts EGFR-TKI sensitivity by modulating its translation. Disrupting the RNA structure in YRDC 3' UTR with antisense oligonucleotide (ASO) presents a potential therapeutic strategy. This unveils a novel RNA structure-driven mechanism controlling EGFR-TKI resistance, providing valuable therapeutic perspectives [12].

Chen Zhu et al. explored the m⁶A-mediated regulatory impact on tea flavor-related metabolic pathways during solar-withering processes. Through integrated transcriptome analysis, the study revealed that two m⁶A erasers control global m⁶A levels, influencing terpenoid biosynthesis and spliceosome pathways. This m⁶A-mediated mechanism affects volatile terpenoid accumulation and flavonoid content. This study uncovered a novel epitranscriptomic layer in tea flavor formation, enhancing our understanding of tea flavor evolution during solar-withering [13].

Yongsheng Wang et al. systematically explored circRNAs in moso bamboo seedlings, especially in relation to gibberellin (GA) and auxin (NAA) treatments. They also developed a custom degradome sequencing method to detect microRNA-mediated cleavage of circRNAs. Their study revealed insights into the biogenesis, function, and microRNA-mediated degradation of circRNAs, emphasizing their significance in regulating hormone metabolism. The findings provided a deeper understanding of the role of circRNAs in plant biology, especially in moso bamboo [14].

These 14 articles in this special issue collectively broaden our understanding of RNA epitranscriptomics. They elucidate

the roles of RNA modifications in gene regulation, diseases, and developmental processes across a range of organisms and tissues. We envision that new breakthrough in epitranscriptomics will underscore the complexity and importance of RNA modifications in determining cellular functions and hint at potential novel clinical applications.

Completing interests

Both authors have declared no competing interests.

CRedit authorship contribution statement

Chengqi Yi: Conceptualization, Writing – original draft, Writing – review & editing. **Jianhua Yang:** Conceptualization, Writing – original draft, Writing – review & editing. Both authors have read and approved the final manuscript.

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