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RNA

Expanding the mRNA epitranscriptome

“m^{1}A mRNA modification … might have a functional role in promoting translation of methylated transcripts”

Cells chemically modify DNA in a dynamic manner, leading to changes in gene expression profiles, and it is likely that mRNA epigenetic modification pathways, including reversible methylation, have evolved to expand the cellular toolbox to regulate gene expression post-transcriptionally. However, the key regulatory functions of many such pathways are not well understood. Notably, it was recently shown that N^6-methyladenosine (m^{6}A) is a widespread modification in the mammalian transcriptome that affects mRNA stability, localization and translation. Decades ago, another adenosine methylation mark, m^{1}A, was identified in total RNA and later shown to be a prevalent modification in non-coding RNAs such as tRNAs, but whether this methyl mark is present in mRNA was unknown. Owing to its positive charge at physiological pH and the added methyl group that affects Watson–Crick base-pairing, m^{1}A could significantly alter secondary and/or tertiary RNA structure and protein–RNA interactions. Now, two new studies report the identification and comprehensive analysis of the m^{1}A mRNA modification, showing that this modification mark is enriched at the 5′ untranslated regions (UTRs) of mRNAs and might have a functional role in promoting translation of methylated transcripts.

Dominissini *et al.* and Li *et al.* used quantitative mass spectrometry analysis of purified mRNA and found that m^{1}A is present in transcripts of several human and mouse cell lines, albeit to a lesser extent than m^{6}A. To obtain high-resolution transcriptome-wide m^{1}A maps, they adapted an antibody-based approach, methylated RNA immunoprecipitation sequencing. Dominissini *et al.* identified 7,154 methylated positions (m^{1}A peaks) in 4,151 coding and 63 non-coding gene transcripts in human cells and determined that 35% of expressed genes carry the m^{1}A mark. Similarly, Li *et al.* identified 901 peaks in 841 coding and 46 non-coding transcripts, suggesting that m^{1}A is a prevalent mRNA modification. Dominissini *et al.* went on to show that m^{1}A levels varied between different mouse tissues, with kidney and brain possessing the highest m^{1}A levels.

When investigating the distribution of m^{1}A along the transcript, both groups found that although m^{1}A peaks can be detected in the 5′ UTR, the coding sequence and the 3′ UTR, they are clustered at highly structured, GC-rich regions at the 5′ UTR near the start codon in several human and mouse cell lines. This distribution pattern is in stark contrast to the distribution of m^{6}A, which is mostly located in the vicinity of the stop codon at the 3′ UTR. Dominissini *et al.* further showed that m^{1}A resides close to both canonical and non-canonical translation initiation sites (TISs) found mostly upstream of the first splice site in human mRNA, suggesting that the first splicing reaction guides the deposition of the methyl mark. The association of m^{1}A with TISs in transcripts with structured 5′ UTRs suggests a regulatory role in translation initiation. In agreement with this, Dominissini *et al.* report that m^{1}A correlated with increased protein expression and higher translation efficiency.

Furthermore, exposing cultured cells to different stress conditions, such as starvation, heat shock or H_2O_2 treatment, resulted in changes in m^{1}A levels, which suggests that m^{1}A is a dynamically regulated mRNA mark in response to physiological conditions.

Finally, cells overexpressing or lacking the demethylase ALKBH3 had increased or decreased m^{1}A levels in mRNA, respectively. These data imply that m^{1}A could be a reversible modification and that methylated mRNA could be a substrate for ALKBH3.

Taken together, these studies increase our so far limited understanding of the mRNA epitranscriptome and reveal a new prevalent mRNA modification that might be involved in post-transcriptional gene regulation. However, future work is now required to uncover the dynamic regulation of this methyl mark, how it affects translation and its impact on biological processes.

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ORIGINAL ARTICLES Dominissini, D. *et al.* The dynamic N^1-methyladenosine methylome in eukaryotic messenger RNA. *Nature* **530**, 441–446 (2016) | Li, X. *et al.* Transcriptome-wide mapping reveals reversible and dynamic N^1-methyladenosine methylome. *Nat. Chem. Biol.* http://dx.doi.org/10.1038/nchembio.2040 (2016)

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