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The discovery that reversible mRNA modifications provide a tuneable layer regulating gene expression has galvanized the field of epitranscriptomics. Now, Mauer *et al.* report that one of the most prevalent modified bases, $N^6$,2′-*O*-dimethyladenosine ($m^6A_m$), found in 30% of mRNAs, is a dynamic and reversible modification that confers mRNA stability.

In contrast to internal base modifications such as $N^6$-methyladenosine ($m^6A$), $m^6A_m$ is found at the 5′ end of mRNAs, when the first nucleotide following the 5′ cap is a 2′-*O*-methyladenosine that is modified by additional $N^6$-methylation. Although the prevalence of $m^6A_m$ had been known for some time, its function remained elusive.

The demethylase FTO was previously linked to the demethylation of $m^6A$, but the team suspected that FTO-regulated peaks in transcriptome-wide maps might reflect $m^6A_m$ rather than $m^6A$. The authors incubated a synthetic oligonucleotide, in which $m^6A_m$ was positioned following a 5′ cap, with FTO, which readily demethylated $m^6A_m$, as assessed by high-performance liquid chromatography. Competition with another oligonucleotide containing $m^6A$ showed that FTO had higher activity towards $m^6A_m$ than $m^6A$, suggesting that $m^6A_m$ is the preferred substrate of this enzyme. This finding was confirmed *in vivo* using HEK293T cells transfected with a tagged FTO. Transfection led to significantly reduced levels of $m^6A_m$, which could be decreased further by inducing the cytosolic translocation of FTO. By contrast, knockdown or knockout of FTO expression increased the amount of $m^6A_m$ *in vivo*, but had no effect on $m^6A$ levels.

Interestingly, mRNAs beginning with $m^6A_m$ were found to be substantially more stable, showing an average increase in half-life of ~2.5 h, and exhibited higher transcript levels than mRNAs starting with any other nucleotide. Manipulation of $m^6A_m$ levels through FTO overexpression or knockdown indicated that demethylation of this RNA modification reduces mRNA stability, whereas increasing $m^6A_m$ levels enhances the stability of mRNAs beginning with this modified nucleotide.

Given that mRNA degradation often involves decapping, the authors set out to determine whether this process is affected by $m^6A_m$. *In vitro* experiments found that RNAs with a 5′ cap followed by $m^6A_m$ exhibited significantly reduced decapping mediated by the mRNA-decapping enzyme DCP2. Furthermore, levels of $m^6A_m$ mRNAs did not change as dramatically as those of other mRNAs in DCP2-deficient HEK293T cells compared with controls, which suggests that $m^6A_m$ confers protection from DCP2-mediated degradation.

The findings raise a number of questions that the authors hope to address going forward. "Many aspects of extended cap methylation are yet to be explored," says lead author Jan Mauer (Weill Cornell Medicine, Cornell University). "For example, how does $m^6A_m$ affect ribosome binding? Or what physiological stimuli activate demethylation of $m^6A_m$?" The preference of FTO for $m^6A_m$ also raises doubts over some of the previously established dynamics of the $m^6A$ modification.

Overall, the study clearly demonstrates that the location of modified nucleotides along the mRNA and the exact combination of modifications on the nucleotide all play a crucial part in modulating epitranscriptome function. "Our findings suggest that the mRNA cap does not simply serve as a docking platform for the translation machinery, but can actually carry information encoded by the modification state of the first nucleotide," concludes Mauer.

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**ORIGINAL ARTICLE** Mauer, J. *et al.* Reversible methylation of $m^6A_m$ in the 5′ cap controls mRNA stability. *Nature* http://dx.doi.org/10.1038/nature21022 (2016)
**FURTHER READING** Frye, M. *et al.* RNA modifications: what have we learned and where are we headed? *Nat. Rev. Genet.* **17**, 365–372 (2016)