The dynamic epitranscriptome: Encoding the fate and function of mRNA with reversible nucleotide modifications

An emerging concept is that an “epitranscriptomic code” of diverse modified nucleotides is found within mRNA and long noncoding RNA, and control their fate and function in cells. This concept was initiated by our transcriptome-wide map of $N^6$-methyladenosine ($m^6$A) which revealed that $m^6$A levels are dynamic, located in at least a fourth of all mRNAs, and enriched in specific regions of the transcript body. Cellular stresses induce an altered pattern of $m^6$A in the transcriptome with notable enrichment in the 5′UTR. These 5′UTR-localized $m^6$A residues confer cap-independent translation to these mRNAs. Next to $m^6$A, the most prevalent modified nucleotide in mRNA is $N^6,2′$-O-dimethyladenosine ($m^6$Am), which is exclusively located at adjacent to the 7-methylguanosine-cap at the first encoded nucleotide in up to 40% of mRNAs. Our transcriptome-wide map of $m^6$Am revealed that $m^6$Am-initiated transcripts are markedly more stable than mRNAs beginning with other nucleotides by rendering the cap resistant to the mRNA-decapping enzyme DCP2. Notably, the fat mass and obesity-associated protein, FTO, demethylates $m^6$Am to 2′-O-dimethyladenosine ($A_m$). FTO shows a marked preference for $m^6$Am compared to $m^6$A, and switches off the stability of $m^6$Am-initiated mRNAs. These findings reveal that epitranscriptomic information is stored in both internal nucleotides and mRNAs caps.