Supplementary information S1: \( N^6 \)-methyladenosine in simpler life forms

\( N^6 \)-methyladenosine (\( m^6 \)A) has been found in numerous simpler life forms such as viruses and unicellular organisms. Recent findings illuminate its elusive functions in these organisms.

- **Viruses**
  The existence of \( m^6 \)A in viruses that integrate their genome into the host genome has been known since the discovery of \( m^6 \)A\(^1\)\(^,\)\(^2\). These viruses include SV40, adenovirus, herpes virus, Rous sarcoma virus, influenza virus (reviewed in REF. \(^3\)) and more recently, human immunodeficiency virus (HIV)\(^4\)\(^-\)\(^6\). One study reported that \( m^6 \)A is crucial for HIV gene expression and replication, as depletions of cellular \( m^6 \)A writers inhibit these processes\(^4\). Another study found that \( m^6 \)A at 3' untranslated regions of viral genes recruits YTH domain family (YTHDF) readers and facilitates viral gene expression and replication, which can be further enhanced by overexpressing YTHDF readers\(^5\). These results suggest \( m^6 \)A and its cognate factors have crucial roles in regulating virus life cycle and host-viral interactions.

- **Archaea**
  Little is known about \( N^6 \)-adenosine methylation in archaea. The existence of \( m^6 \)A was reported in tRNA from hyperthermophiles\(^7\) and later on in other archaea as well\(^8\), But the general function of \( m^6 \)A in archaea remains largely unknown.

- **Bacteria**
  \( m^6 \)A has been found in many RNA species in bacteria, including rRNA, tRNA, and most recently, mRNA\(^9\)\(^,\)\(^10\). A recent work discovered conserved yet distinct patterns of \( m^6 \)A in seven bacterial species including *Escherichia coli*, and associated \( m^6 \)A with respiration, amino acids metabolism, stress responses and small RNA regulation\(^10\).

- **Yeast**
  The abundance of \( m^6 \)A in yeast mRNAs is highly dynamic. First detected in sporulating *Saccharomyces cerevisiae*, \( m^6 \)A was shown to be present only during meiosis and to be required for meiosis progression and sporulation\(^11\). Budding yeast Ime4 (mammalian METTL3 homolog) is an \( m^6 \)A writer along with two auxiliary factors, Mum2 (mammalian WTAP homolog) and sporulation-specific with a leucine zipper motif protein 1 (Slz1), together forming the complex MIS (Mum2, Ime4, Slz1)\(^11\)\(^,\)\(^12\). Slz1 is crucial for the localization of \( N^6 \)-adenosine methyltransferase complexes at the nucleolus\(^13\). Only one YTH domain protein, methylated RNA-binding protein 1 (Mrb1), exists in yeast as a potential \( m^6 \)A reader\(^13\)\(^,\)\(^14\). Mrb1 regulates phosphate metabolism by destabilizing the *pho4* mRNA\(^15\).
although it is unclear whether this function is m^6A-dependent as the mRNA was not identified with the m^6A modification. Generally, m^6A is essential for yeast, as a functional MIS complex is required for normal progression through meiosis and regulates multiple developmental processes during nutrient starvation. A recent study also reported an enrichment of m^6A in ribosome-bound fractions of mRNA during starvation-induced meiosis, suggesting translation-promoting roles of m^6A in yeast.

References:


