In format provided by Zhao *et al.* (doi:10.1038/nrm.2016.132)

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

N^6-methyladenosine (m^6A) 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^6A in viruses that integrate their genome into the host genome has been known since the discovery of m^6A[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^6A is crucial for HIV gene expression and replication, as depletions of cellular m^6A writers inhibit these processes[4]. Another study found that m^6A 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^6A 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^6A was reported in tRNA from hyperthermophiles[7] and later on in other archaea as well[8], But the general function of m^6A in archaea remains largely unknown.

- Bacteria

m^6A 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^6A in seven bacterial species including *Escherichia coli*, and associated m^6A with respiration, amino acids metabolism, stress responses and small RNA regulation[10].

- Yeast

The abundance of m^6A in yeast mRNAs is highly dynamic. First detected in sporulating *Saccharomyces cerevisiae*, m^6A 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^6A 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^6A reader[13,14]. Mrb1 regulates phosphate metabolism by destabilizing the *pho4* mRNA[15],

although it is unclear whether this function is m^{6}A-dependent as the mRNA was not identified with the m^{6}A modification [13]. Generally, m^{6}A is essential for yeast, as a functional MIS complex is required for normal progression through meiosis[13] and regulates multiple developmental processes during nutrient starvation[12]. A recent study also reported an enrichment of m^{6}A in ribosome-bound fractions of mRNA during starvation-induced meiosis, suggesting translation-promoting roles of m^{6}A in yeast[16].

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