

N6-methyladenosine modification destabilizes developmental regulators in embryonic stem cells.

Journal: Nat Cell Biol

Publication Year: 2014

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PubMed link: 24394384

Funding Grants: Type III CIRM Stem Cell Research Training Program

Public Summary:

N6-methyladenosine is a modification found on messenger RNAs decades ago. But how this modification is catalyzed and what functional roles it plays are largely unknown. Our work for the first time identified an enzyme complex for N6-methyladenosine formation. And importantly we found this modification is essential to make embryonic stem cells at ground state.

Scientific Abstract:

N(6)-methyladenosine (m(6)A) has been identified as the most abundant internal modification of messenger RNA in eukaryotes. m(6)A modification is involved in cell fate determination in yeast and embryo development in plants. Its mammalian function remains unknown but thousands of mammalian mRNAs and long non-coding RNAs (lncRNAs) show m(6)A modification and m(6)A demethylases are required for mammalian energy homeostasis and fertility. We identify two proteins, the putative m(6)A MTase, methyltransferase-like 3 (Mettl3; ref.), and a related but uncharacterized protein Mettl14, that function synergistically to control m(6)A formation in mammalian cells. Knockdown of Mettl3 and Mettl14 in mouse embryonic stem cells (mESCs) led to similar phenotypes, characterized by lack of m(6)A RNA methylation and lost self-renewal capability. A large number of transcripts, including many encoding developmental regulators, exhibit m(6)A methylation inversely correlated with mRNA stability and gene expression. The human antigen R (HuR) and microRNA pathways were linked to these effects. This gene regulatory mechanism operating in mESCs through m(6)A methylation is required to keep mESCs at their ground state and may be relevant to thousands of mRNAs and lncRNAs in various cell types.

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