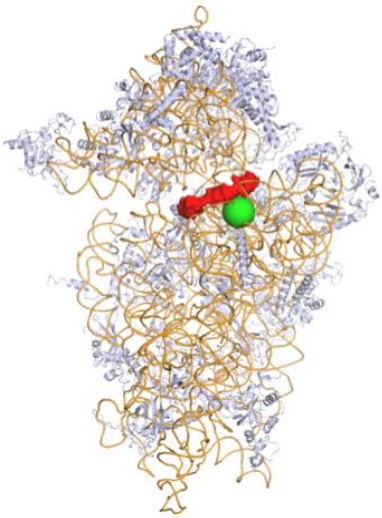
From one brain to another : the devil is in the methyl !

Protein synthesis is performed by the ribosome, a highly complex macromolecule decorated with many chemical modifications whose biological functions remain enigmatic. Two recent studies published in *Nucleic Acids Research* and *EMBO Reports* journals describe the identification of the enzyme responsible for a methylation located within the ribosome decoding center, also considered as its « brain ». This enzyme is important for the normal development of animal brain and for normal walking behavior in fruit-fly.



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In living organisms, the translation of messengers RNA (mRNA) into proteins is realized by the ribosome assisted by many translation factors and transfer RNAs (tRNA). The ribosome is a nano-machine whose synthesis in eukaryotic organisms is a very complex and highly coordinated process requiring more than 200 assembly proteins and many noncoding RNAs. Some of these ribosome biogenesis factors are responsible for essential post-transcriptional maturation steps by decorating ribosomal RNA (rRNA) with many chemical groups (mostly methyl groups). Ribosome biogenesis defects can either be embryonic lethal or result in blood diseases (mostly bone marrow defects, termed ribosomopathies) or in cancers. If most of the chemical modifications decorating human rRNA are known for more than 40 years, the identification of the enzymes responsible for those modifications is in progress. This prevents us from studying the physiological role of these enzymes and of these modifications in physiopathology.

Through an international collaboration with the Université libre de Bruxelles, the University of Lausanne and the Institute for Molecular Biology from Mainz, scientists have shown that the METTL5 methyltransferase is essential for the formation of the N6-methyladenine (m^6A) base at position 1832 of the small subunit 40S of the human ribosome, a modification initially described

in 1986. Thanks to a study performed in archaea (prokaryotic micro-organisms, which translation machinery is close from eukaryotic one), they have identified TRMT112 protein, an allosteric activator of several methyltransferases modifying factors (tRNAs, rRNAs and proteins) involved in protein synthesis, as a partner of METTL5 protein.

This modified base is located in the ribosome decoding center, which role is important for the pairing between the mRNA codon and the tRNA specific for this codon and then for translation fidelity. This ribosomal functional center is commonly considered as the ribosome « brain ». The researchers have also inactivated the gene coding for METTL5 in *Drosophila melanogaster* fly and observed that flies inactivated for this gene display abnormal walking behavior.

These studies highlight the importance of a ribosome modification as small as a methyl group in gene expression and in animal behavior. They are echoing other very recent studies that identified mutations within METTL5 gene as responsible for human intellectual disorders as well as microcephaly and cranio-facial anomalies in animals.

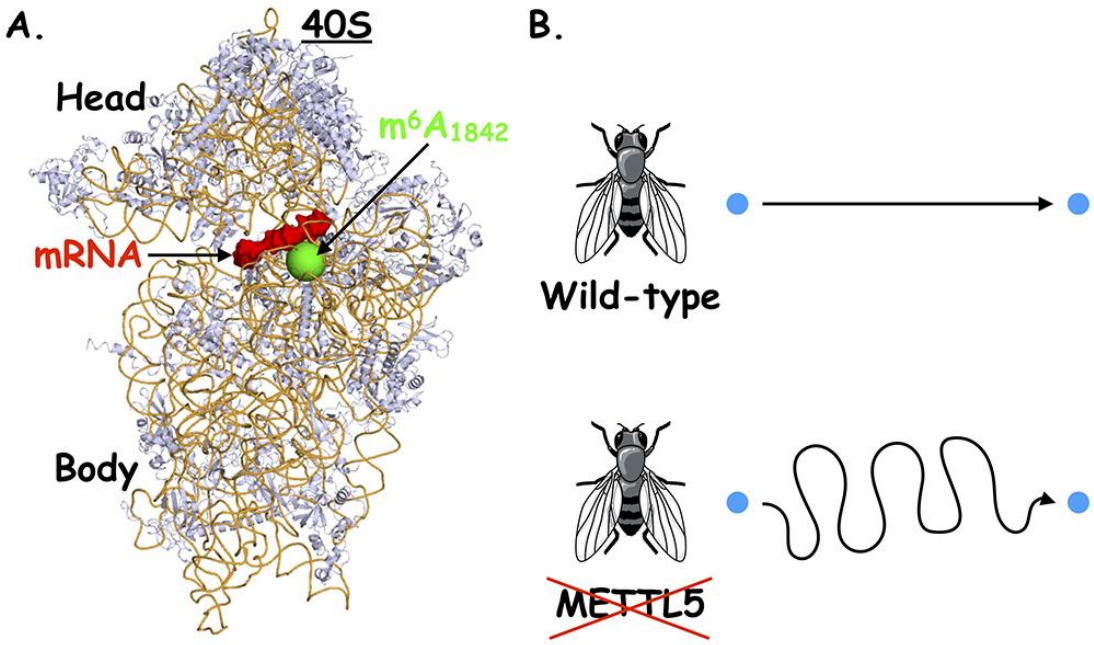

Figure : The lack of m^6A_{1832} modification located within the decoding center of the small ribosomal subunit leads to walking behavior defects in fruit-fly. (A) View of the human small ribosomal subunit (proteins in blue and rRNA in orange). The mRNA being decoded in shown in red. The m^6A_{1832} modified nucleotide located below the mRNA in the decoding center is shown as a green sphere.(B) The inactivation of the METTL5 gene in *Drosophila melanogaster* results in a neurological defects as illustrated by abnormal walking behavior.

More informations:

The human 18S rRNA m6A methyltransferase METTL5 is stabilized by TRMT112.
van Tran N, Ernst FGM, Hawley BR, Zorbas C, Ulryck N, Hackert P, Bohnsack KE, Bohnsack MT, Jaffrey SR, Graille M, Lafontaine DLJ.
Nucleic Acids Res. 2019 Sep 5;47(15):7719-7733. doi: 10.1093/nar/gkz619.

The 18S ribosomal RNA m^6A methyltransferase Mettl5 is required for normal walking behavior in *Drosophila*.
Leismann J, Spagnuolo M, Pradhan M, Wacheul L, Vu M.A.; Musheev M, Mier P, Andrade-Navarro MA, Graille M.; Niehrs C.; Lafontaine DLJ, Roignant JY
Embo reports, e49443. doi: 10.15252/embr.201949443

Contact :

Marc Graille
Directeur de Recherche (DR1) CNRS
Email: marc.graille@polytechnique.edu
+33 1 69 33 48 90
Twitter : @GrailleLab

Laboratoire de Biologie Structurale de la Cellule (BIOC) - (CNRS/ Ecole Polytechnique)
91128 Palaiseau Cedex