N6-METHYLADENOSINE (M6A) RESTRICTS AXONAL GROWTH IN DROSOPHILA THROUGH REPROGRAMMING OF FMR1 TARGET SELECTION

Soldano A. (1), Worpenberg L. (2), Paolantoni C. (2), Longhi S. (1), Murloz M. (2), Lence T. (2), Notarangelo M. (1), Dassi E. (3), Wessels H. (4), Aiello G. (5), Edupuganti R. (6), Vermeulen M. (6), Ohler U. (4), Dieterich C. (7), Roignant J.Y. (2), Quattrone A. (1)

(1) Department CIBIO, University of Trento, Laboratory of Translational Genomics, Trento, (Italy)
(2) Institute of Molecular Biology (IMB) Laboratory of RNA Epigenetics, Mainz (Germany)
(3) Department CIBIO, University of Trento, Trento (Italy)
(4) Berlin Institute for Medical Systems Biology, Max-Delbrück-Center for Molecular Medicine, Berlin (Germany)
(5) Department CIBIO, University of Trento, Armenise-Harvard Laboratory of Brain Disorders and Cancer, Trento (Italy)
(6) Department of Molecular Biology, Faculty of Science, Radboud Institute for Molecular Life Sciences, Oncode Institute, Radboud University Nijmegen, Nijmegen (The Netherlands)
(7) Department of Internal Medicine III, University Hospital Heidelberg, Heidelberg, Germany; DZHK (German Centre for Cardiovascular Research), Partner Site Heidelberg, Mannheim, Heidelberg (Germany)

N6-methyladenosine (m6A) is the most common modification found in mRNA and regulates a variety of physiological processes through modulation of the RNA fate. m6A is particularly enriched in the nervous system of several species and its dysregulation has been associated with neurodevelopmental defects as well as neural dysfunctions. Using Drosophila melanogaster as a model organism we have found that impairment of the m6A pathway leads to axonal overgrowth of the Mushroom Body β-lobe as well as of the larval neuromuscular junctions. We have identified Ythdf as the main m6A reader in the nervous system required for limiting axonal growth. In particular, we have clarified that Ythdf interacts with Fmr1 and both proteins regulate common targets enriched for genes involved in nervous system development and cytoskeleton organization. Interestingly, different Fmr1 targets are required in the two systems: in fact, Profilin and Futsch seem to be the most relevant ones with regards to axonal growth regulation at the NMJ and MB, respectively. Altogether, this study suggests that m6A affects Fmr1 target selection to modulate axon growth both in the CNS and PNS via selection of different targets. Moreover, the results described highlights a concerted function of Ythdf and Fmr1 in the development of the nervous system in Drosophila melanogaster.