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In Vivo Investigation of microRNA Expression and Function at the Mammalian Synapse by AGO-APP

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Abstract : MicroRNAs (miRNAs) are short 20-23 nucleotide long non-coding RNAs; there are 2605 miRNA in humans and 1936 miRNA in mouse in total (miRBase). The nervous system expresses the most abundant miRNA and most diverse. MiRNAs play a role in many steps during neurogenesis, like cell proliferation, differentiation, neural patterning, axon pathfinding, etc. Moreover, in vitro studies suggested a role in the regulation of local translation at the synapse, thus controlling neuronal plasticity. However, due to the specific structure of miRNA molecules, an in-vivo confirmation of the general role of miRNAs in the control of neuronal plasticity is still pending. For example, their small size and their high level of sequence homology make difficult the analysis of their cellular and sub-cellular localization in-vivo by in-situ hybridization. Moreover, it was found that only 40% of the expressed miRNA molecules in a cell are included in RNA-Induced Silencing Complexes (RISC) and, therefore, involved in inhibitory interactions while the rest is silent. Definitively, the development of new tools is needed to have a better understanding of the cellular function of miRNAs, in particular their role in neuronal plasticity. Here we describe a new technique called in-vivo AGO-APP designed to investigate miRNA expression and function in-vivo. This technique is based on the expression of a small peptide derived from the human RISC-complex protein TNRC6B, called T6B, which binds all known Argonaute (Ago) proteins with high affinity allowing the efficient immunoprecipitation of AGO-bound miRNAs. We have generated two transgenic mouse lines conditionally expressing T6B either ubiquitously in the cell or targeted at the synapse. A comparison of the repertoire of miRNAs immuno-precipitated from mature neurons of both mouse lines will provide us with a list of miRNAs showing a specific activity at the synapse. The physiological role of these miRNAs will be subsequently addressed through gain and loss of function experiments.

Keywords : RNA-induced silencing complexes, TNRC6B, miRNA, argonaute, synapse, neuronal plasticity, neurogenesis
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