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A Dicing Machine for Micrornas in Neurons

Christian Barbato*

Department of Sense Organs, Institute of Cell Biology and Neurobiology (IBCN), National Research Council (CNR), University Sapienza of Rome, Rome, Italy

***Corresponding author:** Barbato C, Department of Sense Organs, Institute of Cell Biology and Neurobiology (IBCN), National Research Council (CNR), University Sapienza of Rome, Rome, Italy, Tel: +39-06501703236; E-mail: christian.barbato@cnr.it

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Editorial

Recent neurobiology studies on microRNA-mediated gene silencing, opens a new frontier in deciphering the regulation of neuronal gene expression in normal and pathological conditions. In the nervous system, the transcriptional and post-transcriptional gene regulation mechanisms manage synaptic plasticity, memory formation and cognition. MicroRNAs (miRNAs) are coming on the scene as important players in post-transcriptional regulation in the brain, and it was evidenced that the miRNAs might cooperate in the formation and conservation of such brain complexity [1,2]. MiRNAs are small non-coding regulatory RNAs, double-stranded RNAs (dsRNAs) of 22 nucleotides, which co-work with RISC (RNA-Induced Silencing Complex) to inhibit the target mRNA translation by an imperfect pairing between miRNAs/3′UTRs of the mRNA targets [3]. MiRNAs are refined regulators expressed at different layers with a neuronal specific-type modality, in a spatially and temporally definied regulation in the nervous system [4]. Recent in vitro and in vivo studies aimed to explore the functional role of miRNA, suggested that miRNAs are engaged in regulating neuronal specification, differentiation, dendritic spine architecture, synaptic plasticity and local protein synthesis.

Axons and dendrites meet at the synapses, change their structure and function adapting to a changing environment. Neuronal, morphological and biochemical changes that occur during synaptic plasticity are necessary for the information storage capacity of the brain. According to the de novo protein synthesis theory of memory formation, long term memories are inferred to be saved as modifications in synaptic connections in the brain. The dendritic localization of selected mRNA and polyribosomes was proposed to be a route for rapid dendritic protein synthesis, triggered by synaptic activity, aimed to long-term plasticity at specific synapse. The memory formation requires neuronal protein synthesis, and the localization of synaptic miRNAs suggests that the post-transcriptional regulation of gene expression may contribute to the regulation of dendrites and spine architecture by modulating the expression of site-specific mRNAs associates with learning and memory.

In neurodegenerative disease and dementia, the recent memories are progressively lost and it is conceivable an involvement of miRNA regulation, directly/indirectly, on mRNA target protein synthesis, or protein synthesis machinery. In adult brain, the oldest memories are less dependent on extensive protein synthesis. A miRNAs malfunctions on selected target mRNA involved in Alzheimer's Disease [5,6], as APP or tau genes, might explain a selected cognitive impairment of recent memories. The involvement of RISC in memory formation in Drosophila melanogaster and hippocampal neurons was reported [7,8]. The effect of RISC/Ago2 complex inactivation in the mouse brain was investigated [9]. Five different siRNA targeting Ago2 mRNA and inducing Ago2 down-regulation were injected into the hippocampus of C57BL/6 mice. After one week, the treated mice subjected to hippocampus-related tasks, showed that Ago2 silencing impaired both short-term memory and long-term contextual fear memory [9]. Moreover, when Ago2 expression levels were rescued three weeks after Ago2 silencing, memory was recovered, indicating that the memory deficiency was not due to a broad-spectrum impairment in hippocampal activity. This study showed a role for the RISC/Ago2 pathway in mammalian memory formation in vivo. On the other hand, the inducible deletion of Dicer in the adult mouse brain showed amelioration in several learning and memory tests, twelve weeks following Dicer deletion [10], or an enhanced contextual fear memory and impairment in fear memory extinction [11]. From these evidences emerged that 'less microRNAs' support an 'enhanced memory', but the exact relationship between miRNAs pathway and molecular component of memory it is to be explored [10-12]. MicroRNAs emerged in the neuronal regulation scene of gene expression and they have helped many neurobiologists to partially understand one of the most fascinating phenomena of neuronal cell biology: the local protein synthesis. The small non coding-RNAs represent a versatile molecule that participates in an articulated network of regulatory mechanisms involved during all phases of neuronal development, differentiation, synaptic plasticity, memory formation and cognitive functions. Studies in animal models showed that RISC, mainly Dicer and Ago2 proteins, and specific miRNAs might be recruited supporting learning, memory and cognition. A major curiosity driven research will be needed to define the role of RNA-mediated gene-silencing machinery in neurons, the neuronal miRNA targets, and specific components of RISC that are relevant in the development and progression of neurological and psychiatric diseases [6]. The exploration of a new frontier of miRNAs biology in the nervous system likely represents just the tip of the iceberg compared to what we expect to learn in the next decade.

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