New ribosomes for new memories?

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Widely thought to be a housekeeping process, the regulation and synthesis of rRNA emerges as a potentially central mechanism for the maintenance of synaptic plasticity and memory. We have recently shown that an essential component of late-phase synaptic plasticity is rRNA biosynthesis — the rate-limiting step in the production of new ribosomes. We hypothesize that a particular population of ribosomes is generated upon learning-associated neural activity to alter the rate of synthesis of plasticity factors at tagged synapses that will support the maintenance of synaptic plasticity and memory.

In 1950, Katz and Halstead first proposed that memory formation required new protein synthesis1 — a hypothesis that was not tested until decades later.2-4 It is now well accepted that for memory to become consolidated, new transcription must accompany new, activity-dependent protein synthesis.5,6 Persistent experience-evoked changes in synaptic efficacy are widely believed to form the basis of learning and memory (reviewed by).7 Long-term potentiation (LTP) is a persistent form of synaptic plasticity used to investigate the physiological basis of long-term memory (LTM) at the synaptic and cellular level. Like memory, LTP can be divided into a transient translation-independent phase and an enduring late phase (L-LTP) that requires new transcription and protein synthesis.7,8 Because of the crucial relevance of new transcription and protein synthesis for the transition between transient to consolidated memory, most efforts to understand experience-induced changes in neuronal gene expression have focused on the regulation and synthesis of RNA polymerase II transcripts, that is, precursor mRNA, snRNA and microRNA and their protein products.6,9

In a recent article we reported findings that provide new insight into the molecular mechanism of long-term synaptic plasticity. We demonstrated for the first time that nucleolar integrity—and specifically, new ribosomal RNA (rRNA) synthesis is required for the maintenance of LTP.10 rRNAs are the transcription products of RNA polymerase I (Pol I). Widely thought to be a housekeeping process, the regulation and synthesis of rRNA in learning and memory has remained largely unexplored until now when it emerges as a potentially central mechanism for the maintenance of synaptic plasticity.

Hypothesis

The rRNAs are essential components of ribosomes.11 The requirement of Pol I-dependent transcription during LTP suggests that during long-term synaptic plasticity pre-existing rRNAs, in pre-existing ribosomes, are not sufficient to sustain LTP expression. Our overarching hypothesis is based on a speculative model where Pol I-dependent gene expression is selectively regulated to produce new rRNA; hence, new ribosomes, to carry out the protein synthesis required to support long-term synaptic plasticity at learning-activated ("tagged") synapses (Fig. 1). To test our hypothesis we are addressing the following questions: 1) How does synaptic plasticity regulate the formation of new ribosomes? 2) Are these plasticity-induced new ribosomes functionally different from other ribosomes? 3) How do these new, and perhaps distinct, ribosomes support...
the maintenance of synaptic plasticity and memory? And 4) do all forms of plasticity and learning and memory require new ribosomes? The latter question becomes particularly relevant in light of a recent article in which Pol I transcription was disrupted in mouse hippocampal neurons by the conditional knockout of the nucleolar transcription factor TIF-1A. TIF-1A is required for Pol I directed rRNA transcription. In characterizing the effect of Pol I disruption 1 month or more after tamoxifen induced TIF-1A ablation, the authors observed impairment in tetanic induced LTP (early and L-LTP), but no changes in LTM as measured by performance in the Morris Water Maze (a hippocampus dependent spatial learning task). However, at different times after ablation the animals exhibited variable changes in spatial learning and re-learning skills, an apparent upregulation of the mTOR pathway, and increased neurogenesis in the Dentate Gyrus suggesting a robust activation of neuroprotective compensatory mechanisms as a result of the hippocampal TIF-1A ablation. An interesting question is whether the spatial learning tested in this study (Morris Water Maze) would be affected by acute disruption of Pol I activity.

Ribosome Diversity

In 2002, Mauro and Edelman proposed the “ribosome filter” hypothesis introducing the idea that differential binding of mRNAs to the ribosomal subunits may affect the efficiency of translation. Ribosomal subunits would act as regulatory elements that mediate interaction between particular mRNAs and components of the translational machinery. This notion suggests that ribosomes may not simply be the homogeneous indiscriminant arbiters of translation as traditionally assumed, but might exhibit sufficient heterogeneity to play a regulatory role in translation. Sources of ribosome heterogeneity include: 1) ribosomal protein composition (paralogues), 2) post-translational modification of ribosomal proteins and ribosome-associated factors, 3) post-transcriptional modification of rRNA, and 4) rRNA gene (rDNA) sequence variants.

In eukaryotes, rDNA exist as multiple tandem repeats totaling, in some cases, hundreds of copies. Each transcription unit produces a 45S precursor rRNA that contains highly conserved coding regions as well as variable ones. Length and sequence heterogeneity in the non-coding and coding regions of rDNA allows for the possibility of functional rRNA variants (v-rRNAs) as have been described for mice and humans. Therefore, it seems possible that rDNA variants might provide the structural and/or catalytic basis for specialized ribosomes and ribosomal diversity during plasticity and memory.

Recently, the existence of physiologically relevant v-rRNAs has been confirmed.
in organisms ranging from Arabidopsis thaliana to Homo sapiens.\textsuperscript{17,18} For example, in Arabidopsis, 4 v-rRNAs were identified that differed in their expression according to tissue type and stage of development.\textsuperscript{18} In mice, 7 v-rRNAs were cloned and characterized as being differentially expressed.\textsuperscript{16} As in the Arabidopsis study, the 7 v-rRNAs were found to be transcriptionally regulated in a manner corresponding to differences in DNA methylation sites. Interestingly, the epigenetic regulator poly(ADP-ribose)-polymerase-1 (PARP-1) has been shown to regulate DNA methylation patterns (reviewed by),\textsuperscript{19} chromatin availability and transcriptional activation in response to environmental cues (reviewed by),\textsuperscript{20} and ribosome biogenesis.\textsuperscript{21}

Many studies have noted an increase in RNA synthesis, including rDNA gene expression, in correlation with neural plasticity and learning and memory models (See for example).\textsuperscript{14,22-25} In our recent RNA synthesis, including rDNA gene cloning and characterization as being differentially expressed.\textsuperscript{16} As in the Arabidopsis study, 4 v-rRNAs were identified in Arabidopsis,\textsuperscript{2} and transcriptional activation in response to environmental cues (reviewed by),\textsuperscript{20} and ribosome biogenesis.\textsuperscript{21}

An important hallmark of neurodegenerative diseases is the occurrence of aberrations in the epigenetic code of acetylation, methylation and PARylation\textsuperscript{30} (reviewed by).\textsuperscript{31,32} Nucleolar impairment may be a common denominator in several neurodegenerative disorders such as Huntington’s, Parkinson’s and Alzheimer’s disease (reviewed by).\textsuperscript{33} Our data demonstrate that nucleolar integrity is necessary for long-term synaptic plasticity and strengthens the connection between the structure and function of the nucleolar complex. We suggest that the impairment of memory and cognition occurring in the above-mentioned neurodegenerative disorders manifest through nucleolar function deficits and aberrant nucleolar DNA methylation.

Nucleolar Integrity and Neurodegenerative Disorders

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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