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A Functional Dissection of the mRNA and Locally Synthesized Protein Population in Neuronal Dendrites and Axons

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local translation, RNA localization, neuronal processes, dendrites, axons, synaptic plasticity

Abstract

Neurons are characterized by a complex morphology that enables the generation of subcellular compartments with unique biochemical and biophysical properties, such as dendrites, axons, and synapses. To sustain these different compartments and carry a wide array of elaborate operations, neurons express a diverse repertoire of gene products. Extensive regulation at both the messenger RNA (mRNA) and protein levels allows for the differentiation of subcellular compartments as well as numerous forms of plasticity in response to variable stimuli. Among the multiple mechanisms that control cellular functions, mRNA translation is manipulated by neurons to regulate where and when a protein emerges. Interestingly, transcriptomic and translatomic profiles of both dendrites and axons have revealed that the mRNA population only partially predicts the local protein population and that this relation significantly varies between different gene groups. Here, we describe the space that local translation occupies within the large molecular and regulatory complexity of neurons, in contrast to other modes of regulation. We then discuss the specialized organization of mRNAs within different neuronal compartments, as revealed by profiles of the local transcriptome. Finally, we discuss the features and functional implications of both locally correlated—and anticorrelated—mRNA-protein relations both under baseline conditions and during synaptic plasticity.

INTRODUCTION

Neurons are fascinating cells. Neurons arguably possess some of the most complex morphologies, characterized by the intricate and branched tree-like structures of their dendrites and axons. This morphology is closely linked to function as dendrites and axons provide not only the tracks for information flow in nervous systems but also the functionalities to accelerate and decelerate traffic and to integrate and split stimuli. These functionalities are enabled by the specialization of subcellular compartments that can operate with biochemical and electrical autonomy, while maintaining communication and coordination within the whole cell through signals spanning intracellular domains. The superimposition of compartment-specific and neuron-wide processes is particularly apparent in the synapses formed by the axons and dendrites of different neurons, which can be individually potentiated or depressed while still contributing to dynamic responses of the entire neuron. Impressively, a typical neuron constantly computes the activity of tens of thousands of synapses across its dendritic and axonal arbors. Additionally, neurons seamlessly overcome the challenges of operating across the relatively large volumes and distances that accompany their extensive structures. The average volume of a neuron [$\sim$30,000 μm^3, BioNumbers identification number (BNID) 112496] is over 10,000 times that of most mammalian cells (e.g., average Cos7 cell volume is $\sim$2 μm^3, BNID 101666), while dendrites and axons usually extend distances of millimeters and centimeters, respectively.

THE NEURONAL TRANSCRIPTOME: AN UNPARALLELED DIVERSITY OF GENE PRODUCTS

Not surprisingly, the molecular machinery underlying these neuronal properties is equally fascinating and complex. This complexity commences at the level of transcription. Early RNA sequencing (RNA-seq) studies showed that the brain expresses over 70% of all genes and possesses an extremely complex transcriptome (139). In support of this, recent single-cell RNA-seq (scRNA-seq) studies have detected expression of >8,000 genes, on average, in individual neurons, which is approximately double the number of genes detected among nonneuronal single cells (161). This, however, is likely an underestimation as scRNA-seq methods only capture a snapshot of a cell's transcriptome, and even the most sensitive methods consistently fail to detect a significant percentage of messenger RNAs (mRNAs). Such complexity is further expanded by mechanisms that generate multiple isoforms per gene. Indeed, a recent profile of full-length transcripts in the hippocampus revealed that $\sim$72% of detected genes express multiple isoforms, with an average of 3.9 isoforms per locus (173). Events of alternative splicing, one of the mechanisms responsible for isoforms that encode different proteins, are more abundant in the brain compared to other tissues (113) and in neurons compared to other brain cell types (188). Other mechanisms such as alternative polyadenylation generate neuron-specific isoforms containing elements within untranslated regions that regulate when and where an mRNA is translated (6). As predicted by the transcriptome, the brain proteome is one of the most complex among all tissues (168), and neurons possess the most complex proteome among brain cells (153). However, the full complexity of the neuronal proteome is still obscure as current methods are unequipped to widely distinguish protein isoforms and detect posttranslational modifications (PTMs). Indeed, recent studies suggest that phosphorylation is highly abundant and dynamic in the brain proteome, particularly in synapses, for example, during sleep-wake cycles (18, 174). Additionally, compared to other cells, neurons exhibit unique glycosylation patterns in hundreds of surface membrane proteins (72).

SPECIALIZED NEURONAL COMPARTMENTS AND ORGANELLES

The diversity among the gene products of a neuron is exploited to customize its subcellular compartments including the soma, axons, dendrites, and synapses as well as their respective organelles (**Figure 1**). This process relies on the transport and recruitment of proteins to their proper organellar destinations and microenvironments, which may vary significantly according to the compartment. For example, the Golgi apparatus is mostly absent from neuronal processes (80), while other structures like microtubules and mitochondria are present throughout the neuron, but their organization, orientation and shape varies between somata, dendrites, and axons (135, 140, 181) (**Figure 1**). The translational machinery itself is also differentially organized between and within compartments. Ribosomes in cell bodies are more often arranged in polysomes (multiple ribosomes bound to a single transcript), while neuronal processes are enriched in monosomes (single ribosome bound to a transcript) (12). Additionally, within a dendrite, ribosomes appear in local hotspots spanning between 5 and 10 μm in length, which tend to coincide with neighborhoods of high synaptic density (26, 157). Furthermore, differences in local microenvironments (e.g., pH, salt concentration) may be conducive for protein interactions that generate liquid phase condensates, whose shapes and compositions are less stable than membrane organelles (25). Although we are still learning about the functions of these condensates, it is clear that they play essential roles in subcellular RNA localization (54) and the generation of critical synaptic structures, including the presynaptic active zone and postsynaptic density (PSD) (25). Consistent with the variable receptive and physiological properties of neuronal compartments, the subcellular localization of integral plasma membrane proteins is also tightly controlled. For example, at the microscale, the localizations of type 1 voltage-gated sodium channels and voltage-gated potassium channels KCNQ2/KCNQ3 are restricted to the axon initial segment and nodes of Ranvier (125), while the *N*-methyl-D-aspartate (NMDA) receptor (NMDAR) subunit GluN2B and the potassium channel HCN1 are mostly limited to the proximal and distal dendrites of CA1 pyramidal neurons, respectively (4, 107). At the nanoscale, glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPAR) in the PSD form multiple clusters (nanodomains), which align with glutamate release sites in the presynaptic terminal to form excitatory nanocolumns, while NMDA receptors group in a unique cluster at the center of the PSD (11, 64).

PLASTICITY MECHANISMS AND TIMESCALES

In addition to subcellular compartment specialization, the complexity among neuronal gene products enables tailored responses to diverse stimuli while also recording information about their nature. Remarkably, the molecular configuration of a neuron can track the number, nature (excitatory, inhibitory, and modulatory), strength, and subcellular localization of inputs occurring within variable time windows (27, 30, 147). Furthermore, this information can be retained (via plasticity mechanisms) from milliseconds to days and maybe much longer by a relay of spatially regulated molecular changes (**Figure 2**). Short-term changes in synaptic strength (milliseconds to minutes) rely mostly on the activity of kinases, phosphatases, and GTPases of various signaling pathways (126). In presynaptic terminals, for example, phosphorylation induced seconds after stimulation alters active zone proteins and is mainly driven by CaMK2A and ERK (48). Interestingly, recent work has also identified a set of phosphorylation sites in the neuronal proteome that exhibit reciprocal changes within minutes of treatments that induce synaptic up- and downscaling (38). At longer timescales (minutes to hours), changes in synaptic strength rely on changes to the proteome mediated by the synthesis and degradation of proteins (20, 159). In fact, a significant fraction of proteome remodeling happens locally, as is the case for brain-derived neurotrophic

Liquid phase condensate: a protein–protein or protein–RNA interaction that phase separates from the cytosol and generates liquid-like droplets

Active zone: a disc-like and electron-dense structure at the presynaptic plasma membrane where synaptic vesicles undergo exocytosis

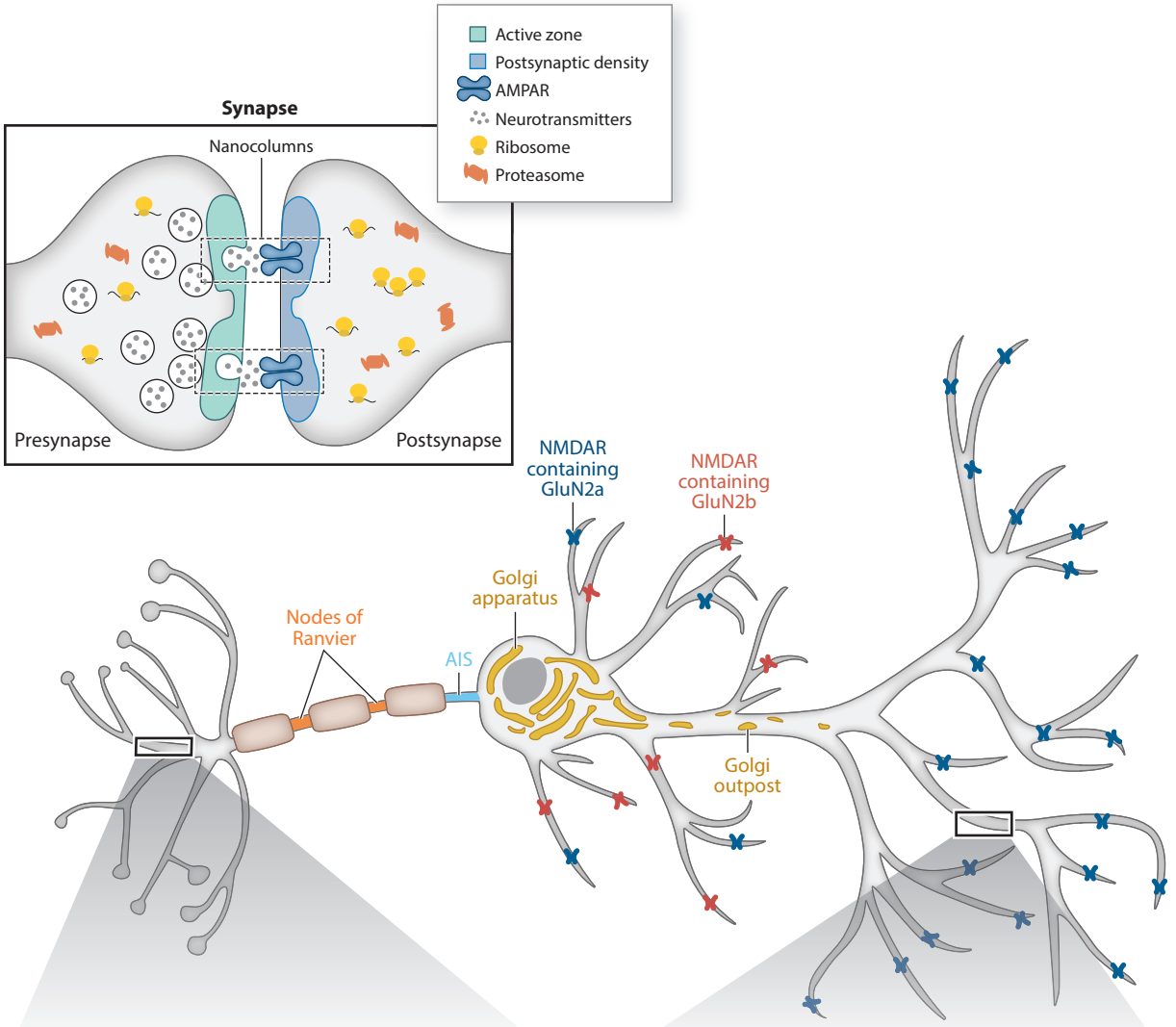
Postsynaptic density (PSD): a disc-like and electron-dense structure at the postsynaptic plasma membrane where neurotransmitter receptors are spatially and functionally organized

Axon initial segment: the compartment at the base of the axon, where action potentials are generated

Node of Ranvier: ~1-μm-long gap between myelin sheets that serves to facilitate the rapid conduction of action potentials

***N*-methyl-D-aspartate (NMDA):** an amino acid derivate that activates a specific type of glutamate receptor

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA): a compound that activates a specific type of glutamate receptor



Short and fast-moving mitochondria
Microtubules with the same orientation + TAU
Neurofilaments

Long and stable mitochondria
Microtubules with mixed orientation + MAP2

(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

Spatial organization of neuronal compartments and organelles. Neurons are characterized by high spatial organization. At the macro level, dendrites, the soma, and axons show specialized organelles (including the Golgi apparatus, cytoskeleton, and mitochondria). At the microscale, different receptors or channels can be found within axonal (AIS versus nodes of Ranvier) and dendritic (proximal versus distal) compartments. At the nanoscale, the spatial arrangement of several synaptic components is tightly regulated between the pre- and postsynapse, to maximize the release and reception of neurotransmitters, including the alignment of the glutamate release sites and clusters of AMPA receptors (see the section titled Specialized Neuronal Compartments and Organelles for more details). Abbreviations: AIS, axon initial segment; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NMDAR, *N*-methyl-D-aspartate receptor.

factor (BDNF)-induced potentiation, late-phase long-term potentiation (LTP), and metabotropic glutamate receptor (mGluR)-dependent long-term depression (LTD), which require protein synthesis and degradation in dendrites (74, 79, 94). Proteome-wide characterizations of turnover during these forms of plasticity are unclear but were recently described during homeostatic scaling (165), a different form of plasticity. Although the majority of regulated proteins exhibited a reduction in either their synthesis or degradation rates following scaling, a subset mainly composed of synaptic proteins exhibited an increase in synthesis or degradation (44). For plasticity to be sustained for hours onward, additional nuclear processes are required, including activity-induced transcription and chromatin modifications (24, 180). Because of its central location and fast induction, transcription changes may integrate neuron-wide information about activity, including the nature, frequency, duration, and location of stimuli. Indeed, transcriptional responses to various patterns of neuronal activity can be classified in three waves of gene activation, where the specific genes induced vary according to activity pattern (167). However, for transcriptional changes to persist well beyond plasticity-inducing stimuli, mechanisms that regulate loci accessibility to the transcriptional machinery are needed. Interestingly, in mice, memory retrieval after fear conditioning is normal when DNA methylation or nucleosome histone exchange are blocked in the

Long-term potentiation (LTP): a long-lasting increase in synaptic strength, induced by specific types of stimulation

Long-term depression (LTD): a long-lasting decrease in synaptic strength, induced by specific types of stimulation

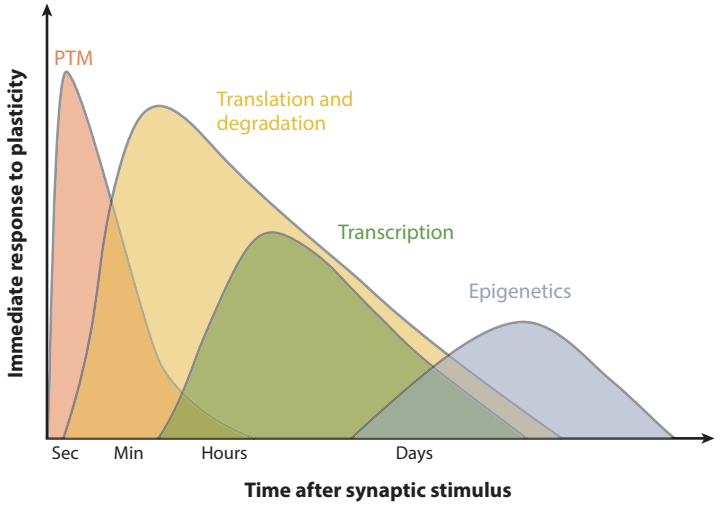


Figure 2

Simplified model of different temporal domains and mechanisms of gene regulation during synaptic plasticity. Short-term synaptic changes are mediated initially by posttranslational modifications, followed by regulation of the synthesis and degradation of proteins. Long-term synaptic plasticity often requires global changes implemented in the nucleus by transcription and epigenetic regulation. Abbreviation: PTM, posttranslational modification.

hippocampus just 2 days after training but abnormal when they are blocked 30 days after training (114, 189), indicating an extended window of transcriptional regulation during long-term memory. The specific contributions of chromatin modifications to neuronal function are still obscure, but there is much focus on the modified transcription of genes encoding synaptic proteins (24).

Together, the data discussed above highlight our growing understanding of how a neuron's rich repertoire of gene products enables some of its highly diverse operations. It is clear that the location and time frame of the operation strongly influence whether regulation occurs at the mRNA or protein level and which process it is driven by. Generally, fast responses begin locally through protein PTMs, while at the other extreme, neuron-wide responses are much slower and depend on transcriptional changes. Between these two poles are mRNA translation and protein degradation, which can be initiated locally at timescales between those of protein modifications and transcription. However, among the diverse set of neuronally expressed genes, what functions are best accommodated by each regulatory process? What factors influence the degree to which a gene function relies on a particular regulatory process? Here, we choose to focus these questions on translation as its spatial regulation can bridge fast and slow responses, as well as local and global operations. The scope of this article is not to summarize recent advancements in the field of neuronal translation, for which we refer the reader to valuable reviews (20, 79, 92). Instead, we build on the knowledge of the field to try to understand the impact of spatially regulated translation on different gene functions. We begin by discussing the relation between local transcriptomes and their respective translatomes and proteomes.

Homeostatic scaling: a neuronal response that counterbalances prolonged elevated or decreased activity, aiming to stabilize neuronal and circuit activity

Fear conditioning: a behavioral paradigm where an aversive stimulus is paired with a neutral stimulus, resulting in the expression of a fear response in the presence of the initially neutral stimulus alone

THE LOCAL TRANSCRIPTOME AND ITS RELATION TO THE LOCAL TRANSLATOME AND PROTEOME

To understand the role of translation across different neuronal compartments, we must first understand how the transcriptome varies from one compartment to another. Because the neuronal soma houses the source of transcription (the nucleus), its transcriptome provides the pool from which other subcellular transcriptomes are derived. Indeed, using scRNA-seq to separately profile the dendritic and somatic transcriptomes of single neurons, Perez et al. (132) detected ~14,000 genes expressed among somata sharing a cell identity, of which at least ~4,000 (~30%) were present among their respective dendrites. Additionally, the relative abundances between genes detected in the soma (e.g., gene A 4× more abundant than gene B) are by and large conserved in dendrites (22, 49, 132). Nevertheless, deviations from this pattern do occur as some mRNAs are significantly over- or underrepresented in dendrites and axons, relative to their somatic levels (132, 172). Thus, besides absolute values, local mRNA abundance can be evaluated in terms of enrichment relative to the somatic transcriptome. Transport of mRNAs from the soma to neuronal processes relies on a complex interplay between elements mainly in untranslated regions of targeted mRNAs, RNA-binding proteins, and the intracellular transport machinery (for reviews, see 35, 62). Interestingly, some of these components may also be used to prevent some transcripts from entering the processes (111).

As we will see, the patterns of mRNA localization can vary both between and within the dendrites and axons. However, a core set of mRNAs has been consistently found in the transcriptome of most neuronal compartments (96). Prominent among them are mRNAs encoding cytoskeletal and mitochondrial proteins, translation factors, and ribosomal proteins (RPs). Although all of these are locally abundant, mitochondrial and RP mRNAs are also enriched relative to the somatic transcriptome. Profiles of axonal projections (containing both axons and terminals) have revealed significant differences according to developmental stage, where mRNAs encoding cytoskeletal and cell cycle proteins are enriched in embryonic but not adult projections, while mRNAs encoding

inflammation and immune regulators are enriched in adult but not embryonic projections (67). Significant differences may also exist between the axon shaft and its terminals. Recently, high-resolution spatial transcriptomics has revealed strikingly low complexity in axon shafts compared to somata and dendrites in culture, with mRNAs encoding kinesin motors and kinesin-related proteins making up the majority of the axon shaft transcriptome (172). Terminals, however, exhibit a more complex transcriptome. During development, an axon's growth cone is enriched for a few hundred mRNA species that, besides the common set outlined above, encode regulators of growth and of homophilic interactions (136). By adulthood, the transcriptome of terminals becomes tuned to presynaptic functions as it is enriched for mRNAs encoding proteins of the active zone and of locally active signaling pathways (69, 149). To characterize the dendritic transcriptome, our group has taken advantage of the CA1 neuropil, where the dense organization of the dendrites of pyramidal neurons constitutes most of the cellular matter (22). Transcriptome-wide analyses of this region revealed an enrichment of mRNA encoding postsynaptic proteins, including components of the PSD, neurotransmitter and neuromodulator receptors, and an extensive set of signaling proteins. Strikingly, within dendrites, the mRNA distribution varies according to function, with regions proximal, intermediate, and distal from the soma exhibiting variable combinations of mRNAs encoding receptors, PSD components, kinases, and phosphatases, among others (1, 22, 100, 172). Moreover, certain mRNAs, like *Shank1*, may be specifically enriched within spines, while others, such as *Camk2a* and *Ddn*, appear to reside in the dendritic shaft (1).

To understand the significance of local transcriptome patterns, it is necessary to ask the following: How much do mRNA levels explain those of local proteins? Besides local mRNA abundance, local protein levels depend on the rates of local translation, protein degradation, and protein transport in and out of compartments (52), all of which are poorly understood compared to mRNA levels. In the CA1 neuropil, transcription levels can explain ~70% of the variability in translation rates and over 75% of translation differences between neuropil and somata (61), suggesting that translation activity largely reflects local mRNA levels. In contrast, the local transcriptome or translatome explains only 26% or 33% of the variability in the local proteome, respectively (12). Similar modest correlations between the transcriptome and proteome were observed for neurites in culture, as well as in the growth cone (136, 185). A high correlation between local transcriptome and translatome, but modest correlation between either one and the local proteome, may be explained by a combination of factors (19). Technical differences in the handling of RNAs and proteins likely add noise to these comparisons and may systematically reduce correlations. Physiologically, regulated protein degradation simultaneously sculpts the local proteome while also removing excesses in the production of particular proteins (90, 159). Indeed, brain mRNA abundance and protein turnover appear to be uncorrelated in vivo (55), suggesting that regulation of protein degradation could partially explain the modest correlation between translation and protein levels. Additionally, some proteins may be somatically synthesized and transported to a compartment, while others may be locally synthesized and then transported out of a compartment (120). Finally, the local presence of an mRNA (or even its association with ribosomes) may better reflect the future local proteome rather than the current one. For example, circadian oscillations in the synaptic transcriptome are reflected in the synaptic proteome 2–4 h later (127).

Importantly, the power of mRNA levels to predict protein levels can significantly vary according to the gene, indicating that different functions rely more or less on local translation versus posttranslation regulation. Conceptually, local translation provides multiple non-mutually exclusive advantages for protein regulation (79). First, a neuron can preserve energy by transporting mRNAs that produce multiple local proteins, instead of transporting the same number of proteins. Second, local translation can produce a protein at the specific place of need and in environments suitable for proper folding and macromolecular complex assembly, thus forgoing undesired

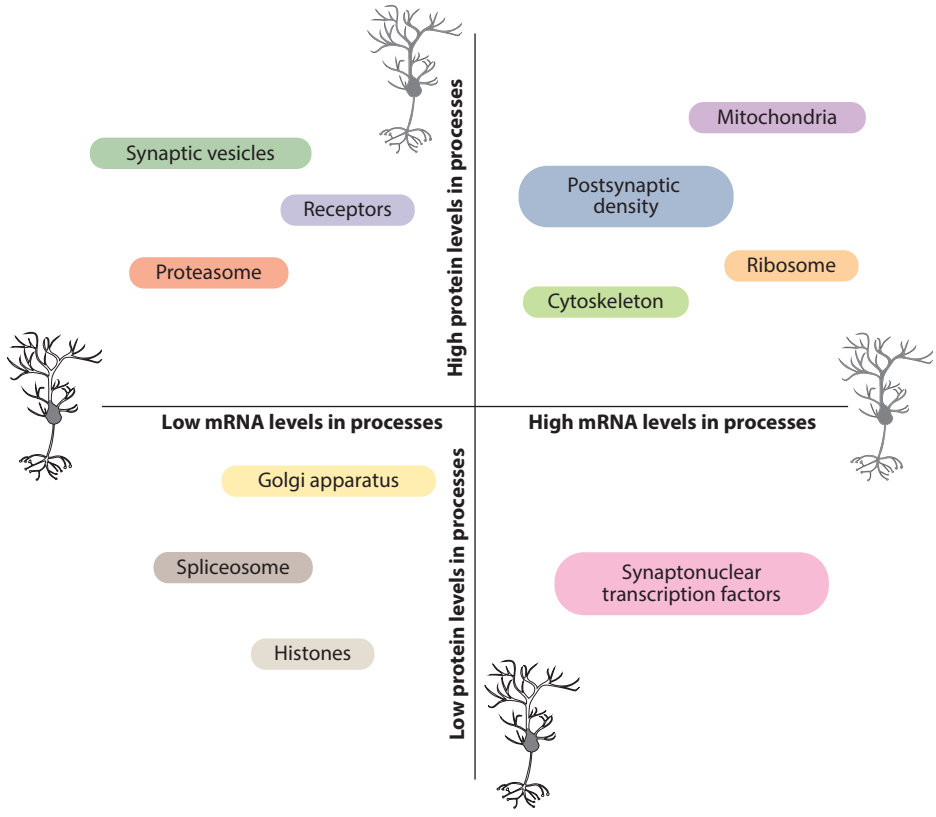


Figure 3

The relation between mRNA and protein levels in neuronal processes for several gene categories. Both the mRNA and protein of components of the spliceosome, Golgi apparatus, and the histones tend to be restricted to the cell body, while both the mRNA and protein of components of the cytoskeleton, mitochondria, ribosome, and postsynaptic density are abundant in neuronal processes. The mRNAs of other categories, including components of the proteasome, synaptic vesicle membrane proteins, and AMPARs, tend to be de-enriched in processes, although the proteins are abundant there. Finally, the mRNAs of some transcription factors are abundant in processes even though their encoded proteins are rarely found there. The functional consequences of local translation (or lack thereof) of some of these groups are described in the main text. Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; mRNA, messenger RNA.

protein interactions during trafficking or the required transport machinery to specifically target the protein to its final destination. Finally, local translation enables fast local responses to extracellular stimuli, as discussed in the section titled Functional Contributions of Local Translation to Long-Term Plasticity. This leads to the question, Which cellular functions are better accommodated by local translation in neuronal processes and which are not? To address this question, we select some examples of functional gene groups belonging to categories defined by the local relation of their mRNAs and proteins and consider how local translation, or lack thereof, affects these functions (**Figure 3**). First, we consider gene groups for which both the mRNAs and corresponding proteins are locally enriched. Then, we discuss gene groups for which the mRNAs are not locally enriched but the corresponding proteins are. Finally, we examine gene groups for which the mRNAs are locally enriched but the corresponding proteins are not.

LOCALIZED mRNA AND LOCAL PROTEIN FUNCTION

Mitochondrial Proteins

The many enzymatic operations performed across a neuron's large structure engender a high energetic cost. These energetic demands vary across cellular compartments, with synaptic transmission using as much as 44% of the available adenosine triphosphate (ATP) (73). To address these demands, neuronal mitochondria are distributed throughout the entire cell, providing local ATP sources for ongoing intracellular and extracellularly imposed demands (141). Distal compartments receive sufficient supply of this organelle through active transport and mitochondrial fission and fusion dynamics. However, to maintain a healthy local pool that adapts to local energetic demands, efficient protein turnover must be locally available to replace old and damaged mitochondrial proteins (116). To address this issue, the mRNAs of hundreds of nuclear genes encoding mitochondrial proteins are transported to neuronal processes where their translation products replace degraded proteins (58, 98). In fact, these mRNAs are localized to the mitochondrial surface, where they are translated and, presumably, immediately integrated into the organelle (29). Consistent with the high energy expenditure of synapses, mitochondrial proteins are one of the most enriched gene groups in both the axonal and dendritic transcriptomes (69, 132, 149, 162).

Mitochondria exhibit distinct morphologies according to cell type and subcellular compartment that tailor their functions to variable cellular conditions (60). In neurons, axonal mitochondria are relatively small (~3 μm), motile, and largely restricted to the presynaptic terminals (36, 135). Furthermore, highly active terminals tend to have larger mitochondria with increased crista density and folding, features associated with increased energy production (34). By contrast, dendritic mitochondria form long interconnected filaments (~30 μm) and are mostly stationary in dendritic shafts (36, 135). These features are correlated with increased coordination over larger distances between mitochondria and local environments (60). In presynaptic terminals, the ATP burden is divided between mitochondria and glycolysis. It is known, however, that in postsynaptic compartments local translation is solely powered by mitochondria, and it is unclear whether glycolysis meaningfully contributes to other local processes (141). These observations correlate with quantitative differences in the proteome of somatic and presynaptic mitochondria (171), but whether local protein synthesis contributes to these differences is still unexplored.

It is also worth noting that local protein synthesis in neurons is also highly dependent on mitochondrial function. This is evident in the overlapping distribution of mitochondria and translationally active spots in both developing axons and mature dendrites (29, 140, 154). Additionally, in developing axons, the depletion of mitochondria abolished the overlapping local translation and diminished axonal branching (154). In dendrites, the elimination of individual mitochondria blocked the upregulation of local translation and structural changes of neighboring spines that are normally induced by synaptic plasticity (140). Finally, such interdependent relationships between mitochondria and local protein synthesis may amplify deficiencies in either process and eventually lead to disease. Indeed, recent studies suggest that mutations in genes related to either function negatively affect the other function and play a key role in neurological diseases such as Charcot-Marie-Tooth (29) and Fragile X syndrome (102), among others (103).

Ribosomal Proteins

The presence of RP mRNAs has been one of the most consistent findings of transcriptomic studies of axons and dendrites, detected in a variety of cell types and organisms, including excitatory and inhibitory neurons as well as sensory and motor neurons from invertebrate, amphibian, and mammalian species. Moreover, RP mRNAs have also been reported in the perisynaptic processes

of astrocytes (112, 145) and in the protrusions of mesenchymal cells (37, 110) and the intestinal epithelium (119). These observations suggest that the localization of RP mRNAs to cellular processes is a common feature of polarized cells.

5′ terminal oligopyrimidine (TOP) motif: a 6–12-pyrimidine-long sequence at the 5′ end of an mRNA, found in mRNAs encoding factors required for protein translation (ribosomal proteins and translation factors)

The detection of RP mRNA in remote cellular locations is difficult to reconcile with our current understanding of ribosome biogenesis. Eukaryotic ribosomes are made from ~79 RPs and 4 ribosomal RNA (rRNA) species. Much of the research over the last 45 years has shown that RPs are incorporated into ribosomes in a process that mostly takes place in the nucleus as rRNAs are transcribed (15, 164). However, the canonical view of ribosome biogenesis cannot explain the heterogeneity in ribosome stoichiometry shown in an emerging cohort of work (reviewed in 47).

Many axonal/dendritic transcriptomic studies have detected a large majority of the ~79 RP mRNAs in the dendrites or axons (96). Despite differences in absolute dendritic abundance, dendritic enrichment relative to the soma is uniform across RP mRNAs, suggesting a common mechanism might regulate their localization (132). The 5′ terminal oligopyrimidine (TOP) motif that has been shown to control translation of all RPs as a functional group (101) has also been recently implicated in regulating their localization (136, 150). Interestingly, some RNA-binding proteins that are known to specifically bind this motif have also been detected in distal processes, suggesting they could be responsible for RP mRNA localization (37, 124, 169). Finally, recent studies have demonstrated that RP mRNAs bound to translating ribosomes in tissues enriched for neuronal processes (12, 149) and nascent RPs have been directly visualized in the dendrites of hippocampal neurons (57), together indicating that RP mRNAs are localized and translated in axons and dendrites.

What are the functional consequences of localizing and translating RP mRNAs in distal processes? In developing *Xenopus* neurons, a subset of RPs was shown to be locally synthesized and incorporated into assembled ribosomes in axons that were physically severed from their cell bodies (150). Another study found 12 of the 80 RPs in rat neurons can rapidly incorporate into mature ribosomes, even when ribosome biogenesis is pharmacologically inhibited (57). In this study, the 12 identified RPs largely occupy surface positions on the ribosome and exhibit fast and dynamic incorporation into neuronal ribosomes. Another recent study suggested that in migrating cells RPs synthesized at protrusions travel to the nucleus, where they enhance ribosome biogenesis (37). These data, taken together with data from other systems, challenge the dominant view of ribosomes as stable and monolithic machines and suggest a more dynamic picture.

What function might locally remodeled ribosomes serve in axons, dendrites, and other cellular locales? In the subsections below, we describe some potential functions.

Activation of ribosomes in local translational hotspots. There is active debate about the translational status of localized mRNAs and ribosomes in dendrites and axons (79). If some dendritic/axonal ribosomes exist in a premature state, the local synthesis of some RPs could serve to switch on an otherwise incompetent translational machinery. This could be used to rapidly regulate the translation capacity of individual neighborhoods by the in situ maturation of ribosomes. The maturity status of the ribosomes present in processes remains to be investigated, although a few ribosome biogenesis factors have been detected in the growth cone (150).

Maintenance and repair of damaged ribosomes. The ribosome is one of the most complicated macromolecular assemblies present in cells, and its assembly in the nucleus and subsequent transport to the periphery are energetically costly (65, 175). As such, replacing individual RPs when damaged would be especially advantageous in neuronal processes to sustain protein synthesis. It is currently believed that ribosomes are degraded as a whole complex by specialized forms of autophagy and proteasomal degradation (3). However, site-specific ubiquitylation events of

individual RPs have been reported (78, 89), and in neurons the half-life of RPs spans between 4 and 10 days (45, 55).

On-demand specialization of the translational machinery. One potential function for local translation in neurons is the site-specific translational regulation of different mRNAs, depending on the pattern and nature of local synaptic activity. Neurons could use the local dynamic incorporation of RPs to change the stoichiometric composition of their translational machinery. Ribosomes with different compositions could differentially engage with specific mRNAs (47). Interestingly, three RPs that have shown a dynamic incorporation profile into neuronal ribosomes [RPL38, RACK1, and RPS26 (57)] have been reported to direct mRNA-specific translation in other systems (50, 109, 179). In addition, the axonal pool of mRNAs encoding some RPs has been reported to be sensitive to neuronal stimulations (178). Whether this results in a differential composition of ribosomal particles remains to be investigated.

mRNA NOT LOCALIZED WHILE PROTEIN FUNCTIONS LOCALLY: PROTEASOMAL PROTEINS

As discussed above, after an initial phase (seconds) driven mostly by PTMs, neurons respond to external stimuli by remodeling the synaptic proteome via local synthesis and degradation of proteins. In fact, dendrites and axons contain not only the translational machinery but also components for the regulated degradation of proteins. The turnover of organelles and membrane proteins is performed by the autophagy-lysosome system, while the ubiquitin-proteasome system degrades proteins. Both systems are present in dendrites and axons (13, 23, 97, 131). In fact, recent publications have even suggested that some proteasomes may be bound directly to the neuronal plasma membrane where they respond to synaptic calcium signaling (137, 138). The presence and activity of local proteasomes are dynamically regulated to maintain the synaptic proteome (159) and are required for several forms of synaptic plasticity (23, 70, 75), as well as for learning and memory (51, 99, 106). Interestingly, most mRNAs coding for the proteasome components are de-enriched in dendrites and axons (61, 132, 136). Hence, the proteasome is an example of the transcript class where the encoded proteins, but not the mRNAs, are abundant in processes.

The 26S proteasome is composed of 33 proteins, arranged in a core particle (20S) that possesses proteolytic activity and a regulatory particle (19S) that recognizes, unfolds, and translocates ubiquitinated proteins to the catalytic core. The two particles are assembled independently and—after conformational changes mediated by dedicated chaperones—the 19S and 20S are joined (122, 144). To ensure protein homeostasis, proteasome levels are tightly regulated at the transcription level (in mammals mainly via the transcription factor NRF1); however, less is known about post-transcriptional and translational regulation of the proteasome (121, 144). At the mRNA level, it is interesting to note that the proteasome is one of the most enriched gene categories among transcripts that possess a single 3′ untranslated region (UTR) in hippocampal neurons (166). As distally localized genes usually have multiple 3′-UTRs with distinct localization domains, the presence of only one 3′-UTR in proteasome mRNAs may be one of the reasons for the de-enrichment of proteasome subunit mRNAs in processes. Surprisingly, only two proteasome transcripts were detected at higher levels in the dendritic arbors of hippocampal neurons: the ones coding for the β6 and β7 subunits, which are among the last proteins to be incorporated in the core particle (132). In particular, β7 incorporation leads to the dimerization of two half-proteasomes (15S) and formation of the 20S (95). Whether the half-proteasomes (15S) are present in distal processes and the local translation of β7 is used to complete proteasome assembly in dendrites remains to be investigated.

Local levels of proteasomes at synapses are also regulated by active transport. For example, after neuronal depolarization, the proteasome is rapidly sequestered in dendritic spines (13), owing to its association with CaMKIIα (14). In the opposite direction, the retrograde transport of proteasomes from the growing axon to the soma, mediated by protein kinase A (PKA), has been shown to establish the asymmetric proteostasis required for axon formation (81). Recently, the adaptor protein PI31 was reported to couple axonal proteasomes to a specific dynein motor protein. This interaction, regulated by p38 MAPK phosphorylation, mediates the bidirectional movement of the proteasome between somata and axons and is required for normal presynaptic morphology (104). These and other examples show how neurons dynamically regulate proteasomal localization, often through activity-dependent PTMs of the proteasome itself or of interacting proteins.

PTMs, particularly phosphorylation, of its core subunits can also regulate the activity state of a proteasome (68). Historically, it was believed that the degradation of a protein was defined merely by its ubiquitination and that—once recruited to the proteasome—protein degradation was inevitable. Recent developments, however, have revealed a regulatory role for the proteasome itself in determining whether a ubiquitinated protein is degraded or not (31). Related to this, in hippocampal neurons under baseline conditions, 80% of the 26S proteasome appears not to be engaged in substrate processing (5). In neurons, two kinases have been shown to regulate proteasomal activity: PKA [reported first in *Aplysia* (75)] and CaMKII (more often described in mammals). For example, CaMKII-mediated phosphorylation increased proteasomal activity after synaptic plasticity (42) as well as during memory retrieval and learning (84, 85). Interestingly, proteasome phosphorylation not only can regulate on/off activity but can also impact the selection of substrates. For example, in other systems, proteasome phosphorylation by PKA specifically increases the degradation of short-lived proteins, which often are regulatory proteins (105). Altogether, these observations suggest that neurons may rely more on PTMs and active transport of the proteasome, rather than on local translation of its components, to regulate proteasomal degradation at synapses.

Finally, to sustain protein homeostasis, changes in protein degradation are often coordinated with changes in protein synthesis and vice versa. For example, proteasome inhibition in neurons leads to a decrease in protein synthesis (2). During aging, loss of proteasomal activity in the brain results in ribosome stoichiometry alterations and aggregation (93). In fact, several forms of synaptic plasticity as well as memory retrieval require a coordinated action of both translation and degradation of plasticity-related proteins, and when only one of these two mechanisms is inhibited, the phenotype is impaired (53, 94, 99). Ribosomes and proteasomes can also directly regulate one another. For example, during axon guidance, the proteasome degrades the translational suppressor FMRP and thus enhances the local synthesis of specific proteins (160). Proteasomal degradation is also responsible for the reduction of ribosome levels observed in axons after synaptic formation (32). Although the coordinated regulation between ribosomes and proteasomes is characterized to some extent at the protein level, it remains unclear if crosstalk also occurs at the transcription level. It would be particularly interesting to explore whether the different levels of mRNAs coding for RPs or proteasomal subunits in distal processes are connected by feedback regulatory mechanisms.

mRNA LOCALIZED AND PROTEIN FUNCTIONS SOMATICALLY: TRANSCRIPTION FACTORS

As discussed in previous sections, the molecular repertoire of neurons provides a rich palette not only to differentiate subcellular compartments but also to simultaneously define temporal states in response to external stimuli. Neuronal responses to synaptic plasticity usually include a relatively

late phase (minutes to hours after the stimulus), which entails changes in gene transcription. This phase begins with the activity-dependent transcription of immediate early genes (IEGs). Most IEGs encode transcription factors that go on to induce the expression of downstream genes that can regulate size and number of synapses (180). In another form of plasticity, transcriptional changes are essential for neuronal survival after stresses such as axonal lesions (142). In both of these cases, distal events in the dendrites or axons must be reported back to the nucleus to activate the appropriate transcriptional response. One of the ways neurons accomplish this task entails the context-dependent local synthesis of transcription factors that are immediately subjected to retrograde transport and nuclear translocation. Thus, these transcription factors are examples of genes whose mRNAs are locally abundant but whose proteins act centrally in the nucleus.

The local translation of transcription factor mRNAs has been mostly described in axons. Diverse stimuli induce not only the local translation of multiple transcription factors but also the necessary machinery for their nuclear relocation. For example, lesions in axons of the dorsal root ganglia induce the local synthesis of the transcription factor STAT3 (10), as well as the local translation of Vimentin and RANBP1, two factors necessary for the retrograde transport of STAT3 (133, 184) and Importin β1, which is essential for STAT3 nuclear translocation (134). In a different system, the injection of β-amyloid to the dentate gyrus induces loss of forebrain neurons. This effect requires the axonal synthesis and transcription factor activity of ATF4; inhibition of ATF4's local translation reduces neuronal loss (7). Axonal translation of transcription factors has also been reported to play an important role during development. Nerve growth factor (NGF) induces the local synthesis and retrograde traffic of CREB in developing axons of the dorsal root ganglia, which is necessary for their survival (33). NGF also induces the axonal translation of two dynein cofactors that increase local retrograde transport (170). In addition, axonal translation of transcription factors can help determine cell identity of developing neurons. Neurons of the trigeminal ganglia, which control facial movements, are differentiated into subtypes as their axons reach their destination. This specification is determined by the presence of BDNF at the innervation site: BDNF has been reported to induce the local synthesis of three SMAD transcription factors and BMP4, which induces their retrograde transport to the nucleus where they regulate cell-type-specific transcription (86).

Several transcription factors are also known to localize to synapses and undergo activity-dependent translocation to the nucleus (76). Compared to other activity-dependent transcription factors, these proteins have a delayed effect on transcription due to the time required for transport from synapse to nucleus. Thus, if combined with other indicators of activity (e.g., a back-propagating action potential), the nuclear translocation of these transcription factors may allow neurons to compute both the frequency and location of stimulation. Additionally, since the level of translocated factors should be proportional to the number of activated synapses, neurons could also integrate this information in transcription (187). Most synaptonuclear transcription factors have been observed in the postsynapse, and their translocation is dependent on intracellular increases in calcium. It is still unclear whether local translation plays a role in their function, but the mRNAs of two of these transcription factors, RNF10 and NSMF (Jacob), were recently observed to be significantly enriched in the dendrites of single neurons (132). RNF10 translocation is induced by the stimulation of NMDARs and is essential for LTP (41). NSMF nuclear localization is also induced by NMDARs but is differentially phosphorylated and promotes different transcription programs depending on whether the interacting receptors are synaptic or extrasynaptic (40). CTBP1 is unique among synaptonuclear proteins because it localizes to presynaptic terminals and acts as a transcriptional repressor. Also, in contrast to other synaptonuclear factors, CTBP1 is translocated to the nucleus under basal conditions, and synaptic activity induces its presynaptic

retention through interactions with Bassoon and Piccolo (83). Interestingly, *Ctbp1* mRNAs are significantly enriched in the presynaptic terminals of excitatory neurons (69).

Excitatory postsynaptic potential (EPSP): a graded change in the membrane potential of a neuron that leads to a higher probability of action potential firing

A role for dendritic translation was recently demonstrated for *Npas4*, an IEG whose activation is specifically induced by depolarization. Brigidi et al. (16) observed that NPAS4 levels were increased by both action potentials and excitatory postsynaptic potentials (EPSPs) but that, in the latter case, newly synthesized NPAS4 derived from dendritic translation. Dendritically synthesized NPAS4 was able to locally form a distinct heterodimer with ARNT1 (also locally synthesized), which possesses unique transcriptional activity once translocated to the nucleus (16). These results demonstrate how local protein synthesis can directly regulate activity-dependent transcription.

FUNCTIONAL CONTRIBUTIONS OF LOCAL TRANSLATION TO LONG-TERM PLASTICITY

As discussed in the section titled Plasticity Mechanisms and Timescales, a striking diversity of molecular mechanisms allow neurons to record information across short (seconds), intermediate (minutes to hours) and long (hours to days) timescales (**Figure 2**). Experiments using inhibitors have revealed requirements for protein synthesis in synaptic and behavioral plasticity on the scale of minutes (91) to hours (56) to days (123). Most experiments demonstrating a role for protein synthesis have bath-applied or perfused chemical inhibitors of polypeptide elongation, like anisomycin, puromycin, or cycloheximide. Because these drugs have equal access to central and local protein synthesis sources, the site of translation cannot be resolved. We note that the recent development of genetically encoded protein-based inhibitors (77, 151) that could ultimately be targeted to specific subcellular domains might resolve the source of protein. In addition, the compartment-specific functionalization of protein synthesis inhibitors with light (46, 63) could be exploited. Nevertheless, experiments using time-resolved in situ imaging and physical separation of cell bodies and neurites have shown that local translation certainly contributes to plasticity in or near synapses during intermediate timescales (minutes to hours). Below, we highlight some post- and presynaptic protein functions that rely on local translation during long-term plasticity and some that do not.

Postsynaptic Mechanisms

In postsynaptic compartments, the detection of different stimuli can potentiate or depress the synapse, adjusting its sensitivity to subsequent stimuli for the following minutes to hours. At excitatory synapses, the relation between a given stimulus and the postsynaptic response is complex and depends on the nature of the stimulus, its duration and frequency, and the history of plasticity of both the synapse and the neuron. However, all of this complexity converges on the state of a single entity: the AMPAR, whose surface abundance and glutamate detection increases during potentiation and decreases during depression (30, 82). Accordingly, the four subunits composing AMPARs, GluA1–GluA4, are extensively regulated in a context-dependent manner (39). This includes differences in the specific subunits that make up the functional tetramer, dynamic alterations of the cytosolic C termini with a combination of PTMs, and variable interactions with AMPAR auxiliary subunits. Differences in these parameters alter the receptor's ion permeability, as well as the duration and probability of channel opening. Furthermore, these modifications make AMPARs more or less likely to be recruited to the synaptic membrane from either extrasynaptic membrane locations or via endocytosis and receptor recycling. As might be expected, different

types of synaptic plasticity induce characteristic patterns of AMPAR modifications, trafficking, and dwell times in the postsynaptic compartment.

Given the high degree of posttranslational regulation of AMPARs, it is fair to ask whether local translation of its subunits makes meaningful contributions to plasticity. In fact, local mRNA profiles reproducibly show that mRNAs encoding AMPA subunits are present in dendrites but de-enriched relative to the soma; in addition, the soma is a dominant site of AMPAR synthesis (61, 96, 132). However, activity-dependent local synthesis of one AMPAR subunit, GluA1, has been observed in dendrites (87, 88, 158). Interestingly, upregulation in the local synthesis of GluA1 occurs during a period of rapid synaptic upscaling and results in the exchange of the Ca^{2+} impermeable GluA1+,GluA2+ AMPARs with the Ca^{2+}-permeable GluA1-only AMPARs (158). Ca^{2+}-permeable AMPARs have larger conductance and can engage Ca^{2+}-sensitive signaling pathways that regulate plasticity. Thus, these results suggest that dendritic translation may enable local changes to the subunit stoichiometry of functional complexes. How are these observations reconciled with the reported local de-enrichment of GluA1–GluA4 mRNAs? The answer may lie in the distinction between relative and absolute values of local mRNAs. Although mRNAs encoding AMPAR subunits are locally de-enriched relative to their somatic abundance, their absolute numbers in dendrites may be sufficient to induce fast, activity-dependent responses.

Significant regulation via local synthesis has been described for several proteins within the biochemical cascades that regulate AMPAR levels and are responsible for long-term forms of plasticity. Most of these cascades are triggered by NMDAR-dependent Ca^{2+} entry, which interacts with and activates Calmodulin. As an aside, one of the three mRNAs encoding Calmodulin, *Calm1*, is particularly abundant in dendrites where it is also locally translated (61, 132). Activated Calmodulin triggers the kinase activity of CaMK2, which is simultaneously translocated from dendritic shaft to synapse following Ca^{2+} influx. Active CaMK2 phosphorylates various targets essential for LTP, including AMPARs and their auxiliary subunits (9). Furthermore, because of its autophosphorylation at residue T286, CaMK2 can sustain its activity independently of calcium for up to a minute, and this sustained activity is an essential feature for LTP induction. Four separate genes encode variants of CaMK2, including *Camk2a*, whose mRNAs are localized and translated in dendrites, and *Camk2b*, whose mRNAs are localized and translated in the soma (21, 61). Both proteins are present in the postsynapse; however, *Camk2b* is the dominant variant in weakened or inactive synapses (128). These observations have led to a model where synaptic potentiation induces *Camk2a* local translation and newly synthesized CaMK2A replaces CaMK2B, effectively providing a tag for synaptic activity (9). Consistent with this model, whereas full deletion of *Camk2a* impairs induction of LTP, deletion of only the 3′-UTR responsible for its dendritic localization affects the maintenance of LTP (115, 152).

Various forms of long-term plasticity induce structural changes in the synapse that are correlated with learning and memory. In dendritic spines, for example, BDNF-dependent LTP and low extracellular Ca^{2+} LTD induce spine enlargement and shrinkage, respectively (126). These structural changes rely on remodeling of the actin cytoskeleton and seem to require the coordinated local synthesis of many of the proteins that regulate this process. Actin remodeling is controlled by a signaling cascade between several kinases and small GTPases (126). In structural LTP (sLTP), active CaMK2A or BDNF-stimulated TRKB receptor induce the activity of several small GTPases, including RHOA and CDC42, whose mRNAs are localized and translated in dendrites (17, 28). For *RhoA*, local translation is induced by BDNF, but whether the same is true for *Cdc42* remains to be determined. Interestingly, these two GTPases exhibit contrasting patterns during sLTP. RHOA is necessary only for an early transient phase of sLTP, and its activity spreads out to neighboring synapses, while CDC42 is required for sustained sLTP, and its activity is restricted to the stimulated spine (126). Both GTPases indirectly regulate the activity of Lim Kinase 1

Calyx of Held: a giant synapse in the mammalian auditory central nervous system

(LIMK1), which phosphorylates and inhibits the actin depolymerization factor Cofilin. Local repression of *Limk1* mRNA by miR-134 is alleviated during BDNF-induced sLTP, resulting in its local translation (148). Finally, sLTP induces dendritic localization and translation of β-actin itself (182). Strikingly, within minutes of sLTP induction, mobile β-actin mRNAs are trapped at the base of the stimulated synapse, where they are locally translated.

The above examples highlight how local translation enables the generation of functions with high subcellular precision and stimuli specificity. In addition, however, local translation can also allow the activation and cessation of functions within precise time windows. This concept is best captured by the regulation of ARC, an enigmatic protein important for long-term plasticity. Under baseline conditions, both the mRNA and protein of *Arc* are low, but its transcription is quickly induced by neuronal activity. *Arc* mRNAs are then quickly transported and located at previously active synapses where they are locally translated (156, 176). After translation *Arc* mRNA is degraded, and less than an hour later ARC protein is also degraded (59, 108). What is the functional benefit of such temporally restricted expression? ARC participates in multiple forms of synaptic plasticity, including mGluR-LTD and homeostatic scaling, where it weakens synapses by promoting AMPAR endocytosis (128, 155, 176). A surprising development, however, has come from the realization that *Arc* originated from the genomic insertion of retrotransposons, and it encodes a protein that can self-assemble into virus-like capsids that encapsulate mRNAs (including those of *Arc* itself) and are transported between neurons (71). The functional significance of such regulation is unknown, but it is tempting to speculate that it may allow the exchange of mRNAs across the synapse or between different synapses.

Presynaptic Mechanisms

Long-term changes in synaptic plasticity can also be driven by regulation of neurotransmitter release from the presynaptic terminal (118). Synaptic strength can be increased or decreased and can occur in both excitatory and inhibitory synapses. Central to these forms of plasticity are interactions between integral vesicle proteins, the cytoskeletal matrix, and the active zone, which regulate the number, density, and proximity of synaptic vesicles to the active zone, where they are docked and primed for release, and the alignment of vesicle release sites to AMPAR clusters in the postsynaptic surface. Recently, multiple groups observed ribosomes in adult presynaptic terminals, suggesting that local translation may regulate these processes (69, 129, 146, 149, 183). Brief metabolic labeling of isolated presynaptic terminals (synaptosomes) showed that ~40% of both excitatory and inhibitory nerve terminals exhibited active protein synthesis (69). Indeed, inhibition of local translation in GABAergic terminals of the hippocampus impairs endocannabinoid-induced inhibitory LTD (iLTD) (183). In addition, blocking protein synthesis in the excitatory projections to the calyx of Held synapse increases spontaneous neurotransmitter release and reduces LTD (146). Direct visualization of protein synthesis in isolated nerve terminals indicated that treatment of GABAergic terminals with an endocannabinoid receptor agonist induced protein synthesis, while application of BDNF induced protein synthesis in both GABAergic and glutamatergic terminals (69).

Which proteins are locally synthesized during these forms of plasticity is still unclear, but clues are emerging. Global changes in protein turnover during endocannabinoid-receptor-mediated iLTD were recently characterized (117). Increased synthesis was observed for RPs, along with peptidases and components of the protein degradation machinery, while increased degradation was observed for actin regulators, active zone proteins, and mitochondrial proteins. iLTD requires protein ubiquitination but not degradation by the proteasome (117). Whether the newly synthesized peptidases participate in the observed patterns of degradation, and whether these changes occur

within presynapses, remains to be tested. Changes in the proteome during iLTD are consistent with modifications of the axonal translatome in mice undergoing Pavlovian conditioning. Projections to the lateral amygdala in mice that learned to associate a sound with electrical shocks exhibit increased translation of mRNAs encoding RPs and mitochondrial proteins as well as translation and transcription factors, and exhibit reduced translation of those encoding cytoskeletal proteins (129). Interestingly, the translation of mRNAs encoding components of the neurotransmitter release machinery is mostly downregulated, including that of Bassoon and Munc18-1, two active zone proteins known to be locally synthesized under basal conditions (69, 130).

Additional insights regarding which proteins may be locally synthesized during long-term presynaptic plasticity come from recent profiles of the adult presynaptic transcriptome and axonal translatome (69, 149). Besides mRNAs encoding RPs and mitochondrial proteins, the mRNAs encoding some active zone and cytoskeletal matrix components are enriched in presynapses. Indeed, inhibition of axonal translation for two of these, β-catenin and *Snap25*, reduces the release probability of synaptic vesicles (8, 163). However, mRNAs encoding proteins integral to synaptic vesicles themselves (e.g., synaptotagmins, synapsins, synaptophysins) are uniformly de-enriched from presynaptic terminals (69). Accordingly, integration of these proteins into premature vesicles requires passage through the Golgi complex and *trans*-Golgi network, cellular structures that are dramatically enriched in the soma (143). Furthermore, these proteins are present in over 20,000 copies in a single presynaptic terminal, at least two orders of magnitude more than active zone proteins, for example (177), and thus, sustaining such high demand by local means might be untenable. Indeed, the somatic generation and axonal transport of synaptic vesicles occur at a remarkable scale, in which a single neuron produces millions of vesicles every day and continuously transports them along axons at highly processive and efficient speeds (66). Thus, similar to AMPAR in the postsynapse, the currency of presynaptic activity—vesicles—is mostly produced in somata while the machinery modulating its activity relies on local synthesis.

Pavlovian conditioning: a type of learning where a biologically potent stimulus (the unconditioned stimulus) is paired with an initially neutral stimulus (conditioned stimulus)

CONCLUSION

The goal of neuroscience is to understand the whole brain, but the relatively reduced challenge of understanding a single neuron is formidable. These postmitotic, extremely polarized cells encompass a large and complex repertoire of gene products, which are selectively used in both spatial and temporal domains, allowing the generation of tailored responses to diverse stimuli. More system-wide approaches will be needed to understand the operational principles and describe the regulatory mechanisms and protein functions responsible for the diverse operations of neurons. It is clear from the information described here, though, that extensive regulation of translation in neurons is used to achieve high spatial and temporal resolution of protein functions. Generally, such regulation allows the replenishment of essential local proteins in distal processes and the generation of a protein of interest at the time and place needed. For other local functions, however, local translation is not required or maybe not even suitable, and other forms of regulation are preferred instead. Going forward, it will be important to understand the communication and interconnection of local translation with other regulatory mechanisms. Proteomic studies on local protein degradation are especially needed to understand the other side of the proteostasis coin.

Here, we have discussed our general understanding of the functions of local translation, which is mostly derived from excitatory neurons of the forebrain. Thanks to advancements in scRNA-seq and spatial transcriptomics, it is now clear that the brain contains thousands of molecularly diverse cell types (186), raising the question of how representative our current understanding of neuronal local translation is. Recently, two studies characterizing the subcellular transcriptome of single neurons observed less diversity among dendrites than somata, detecting only a few hundred mRNAs differentially localized according to cell type (132, 172). However, it is possible that

increases in both the number of cells and cell types analyzed will reveal additional subcellular variability among cell types. Additionally, many local functions are currently described within the broad dendritic and axonal compartments. However, several subcompartments within processes have been described (43), and patterns of mRNA localization recently observed by spatial transcriptomics suggest more might exist (1, 172). Thus, our appreciation of the local specificity of translation and its functional contributions is likely just beginning.

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LITERATURE CITED

1. Alon S, Goodwin DR, Sinha A, Wassie AT, Chen F, et al. 2021. Expansion sequencing: spatially precise in situ transcriptomics in intact biological systems. *Science* 371(6528):eaax2656
2. Alvarez-Castelao B, tom Dieck S, Fusco CM, Donlin-Asp P, Perez JD, Schuman EM. 2020. The switch-like expression of heme-regulated kinase 1 mediates neuronal proteostasis following proteasome inhibition. *eLife* 9:e52714
3. An H, Harper JW. 2019. Ribosome abundance control via the ubiquitin-proteasome system and autophagy. *J. Mol. Biol.* 432(1):170–84
4. Arrigoni E, Greene RW. 2004. Schaffer collateral and perforant path inputs activate different subtypes of NMDA receptors on the same CA1 pyramidal cell. *Br. J. Pharmacol.* 142(2):317–22
5. Asano S, Fukuda Y, Beck F, Aufderheide A, Förster F, et al. 2015. A molecular census of 26S proteasomes in intact neurons. *Science* 347(6220):439–42
6. Bae B, Miura P. 2020. Emerging roles for 3′ UTRs in neurons. *Int. J. Mol. Sci.* 21(10):3413
7. Baleriola J, Walker CA, Jean YY, Crary JF, Troy CM, et al. 2014. Axonally synthesized ATF4 transmits a neurodegenerative signal across brain regions. *Cell* 158(5):1159–72
8. Batista AFR, Martínez JC, Hengst U. 2017. Intra-axonal synthesis of SNAP25 is required for the formation of presynaptic terminals. *Cell Rep.* 20(13):3085–98
9. Bayer KU, Schulman H. 2019. CaM kinase: still inspiring at 40. *Neuron* 103(3):380–94
10. Ben-Yaakov K, Dagan SY, Segal-Ruder Y, Shalem O, Vuppalanchi D, et al. 2012. Axonal transcription factors signal retrogradely in lesioned peripheral nerve. *EMBO J.* 31(6):1350–63
11. Biederer T, Kaeser PS, Blanpied TA. 2017. Transcellular nanoalignment of synaptic function. *Neuron* 96(3):680–96
12. Biever A, Glock C, Tushev G, Ciirdaeva E, Dalmay T, et al. 2020. Monosomes actively translate synaptic mRNAs in neuronal processes. *Science* 367(6477):eaay4991
13. Bingol B, Schuman EM. 2006. Activity-dependent dynamics and sequestration of proteasomes in dendritic spines. *Nature* 441(7097):1144–48
14. Bingol B, Wang C-F, Arnott D, Cheng D, Peng J, Sheng M. 2010. Autophosphorylated CaMKIIα acts as a scaffold to recruit proteasomes to dendritic spines. *Cell* 140(4):567–78
15. Bohnsack KE, Bohnsack MT. 2019. Uncovering the assembly pathway of human ribosomes and its emerging links to disease. *EMBO J.* 38(13):e100278

16. Brigidi GS, Hayes MGB, Delos Santos NP, Hartzell AL, Texari L, et al. 2019. Genomic decoding of neuronal depolarization by stimulus-specific NPAS4 heterodimers. *Cell* 179(2):373–391.E27
17. Briz V, Zhu G, Wang Y, Liu Y, Avetisyan M, et al. 2015. Activity-dependent rapid local RhoA synthesis is required for hippocampal synaptic plasticity. *J. Neurosci.* 35(5):2269–82
18. Brüning F, Noya SB, Bange T, Koutsouli S, Rudolph JD, et al. 2019. Sleep-wake cycles drive daily dynamics of synaptic phosphorylation. *Science* 366(6462):eaav3617
19. Buccitelli C, Selbach M. 2020. mRNAs, proteins and the emerging principles of gene expression control. *Nat. Rev. Genet.* 21(10):630–44
20. Buffington SA, Huang W, Costa-Mattioli M. 2014. Translational control in synaptic plasticity and cognitive dysfunction. *Annu. Rev. Neurosci.* 37:17–38
21. Burgin KE, Waxham MN, Rickling S, Westgate SA, Mobley WC, Kelly PT. 1990. *In situ* hybridization histochemistry of Ca^{2+}/calmodulin-dependent protein kinase in developing rat brain. *J. Neurosci.* 10(6):1788–98
22. Cajigas IJ, Tushev G, Will TJ, tom Dieck S, Fuerst N, Schuman EM. 2012. The local transcriptome in the synaptic neuropil revealed by deep sequencing and high-resolution imaging. *Neuron* 74(3):453–66
23. Campbell DS, Holt CE. 2001. Chemotropic responses of retinal growth cones mediated by rapid local protein synthesis and degradation. *Neuron* 32(6):1013–26
24. Campbell RR, Wood MA. 2019. How the epigenome integrates information and reshapes the synapse. *Nat. Rev. Neurosci.* 20(3):133–47
25. Chen X, Wu X, Wu H, Zhang M. 2020. Phase separation at the synapse. *Nat. Neurosci.* 23(3):301–10
26. Chirillo MA, Waters MS, Lindsey LF, Bourne JN, Harris KM. 2019. Local resources of polyribosomes and SER promote synapse enlargement and spine clustering after long-term potentiation in adult rat hippocampus. *Sci. Rep.* 9:3861
27. Chiu CQ, Barberis A, Higley MJ. 2019. Preserving the balance: diverse forms of long-term GABAergic synaptic plasticity. *Nat. Rev. Neurosci.* 20(5):272–81
28. Ciolli Mattioli C, Rom A, Franke V, Imami K, Arrey G, et al. 2019. Alternative 3′UTRs direct localization of functionally diverse protein isoforms in neuronal compartments. *Nucleic Acids Res.* 47(5):2560–73
29. Cioni J-M, Lin JQ, Holtermann AV, Koppers M, Jakobs MAH, et al. 2019. Late endosomes act as mRNA translation platforms and sustain mitochondria in axons. *Cell* 176(1–2):56–72.e15
30. Citri A, Malenka RC. 2008. Synaptic plasticity: multiple forms, functions, and mechanisms. *Neuropsychopharmacology* 33(1):18–41
31. Collins GA, Goldberg AL. 2017. The logic of the 26S proteasome. *Cell* 169(5):792–806
32. Costa RO, Martins H, Martins LF, Cwetsch AW, Mele M, et al. 2019. Synaptogenesis stimulates a proteasome-mediated ribosome reduction in axons. *Cell Rep.* 28(4):864–76.e6
33. Cox LJ, Hengst U, Gurskaya NG, Lukyanov KA, Jaffrey SR. 2008. Intra-axonal translation and retrograde trafficking of CREB promotes neuronal survival. *Nat. Cell Biol.* 10(2):149–59
34. Cserép C, Pósfai B, Schwarcz AD, Dénes Á. 2018. Mitochondrial ultrastructure is coupled to synaptic performance at axonal release sites. *eNeuro* 5(1):ENEURO.0390-17.2018
35. Dalla Costa I, Buchanan CN, Zdradzinski MD, Sahoo PK, Smith TP, et al. 2021. The functional organization of axonal mRNA transport and translation. *Nat. Rev. Neurosci.* 22(2):77–91
36. Delgado T, Petralia RS, Freeman DW, Sedlacek M, Wang Y-X, et al. 2019. Comparing 3D ultrastructure of presynaptic and postsynaptic mitochondria. *Biol. Open* 8(8):bio044834
37. Dermit M, Dodel M, Lee FCY, Azman MS, Schwenzer H, et al. 2020. Subcellular mRNA localization regulates ribosome biogenesis in migrating cells. *Dev. Cell* 55(3):298–313.e10
38. Desch K, Langer JD, Schuman EM. 2021. Dynamic bi-directional phosphorylation events associated with the reciprocal regulation of synapses during homeostatic up- and down-scaling. bioRxiv 2021.03.26.437166. **https://doi.org/10.1101/2021.03.26.437166**
39. Diering GH, Huganir RL. 2018. The AMPA receptor code of synaptic plasticity. *Neuron* 100(2):314–29
40. Dieterich DC, Karpova A, Mikhaylova M, Zdobnova I, König I, et al. 2008. Caldendrin–Jacob: a protein liaison that couples NMDA receptor signalling to the nucleus. *PLOS Biol.* 6(2):e34. Erratum. 2009. *PLOS Biol.* 7:e1000022
41. Dinamarca MC, Guzzetti F, Karpova A, Lim D, Mitro N, et al. 2016. Ring finger protein 10 is a novel synaptonuclear messenger encoding activation of NMDA receptors in hippocampus. *eLife* 5:e12430

42. Djakovic SN, Schwarz LA, Barylko B, DeMartino GN, Patrick GN. 2009. Regulation of the proteasome by neuronal activity and calcium/calmodulin-dependent protein kinase II. *J. Biol. Chem.* 284(39):26655–65
43. Donato A, Kagias K, Zhang Y, Hilliard MA. 2019. Neuronal sub-compartmentalization: a strategy to optimize neuronal function. *Biol. Rev.* 94(3):1023–37
44. Dörrbaum AR, Alvarez-Castelao B, Nassim-Assir B, Langer JD, Schuman EM. 2020. Proteome dynamics during homeostatic scaling in cultured neurons. *eLife* 9:e52939
45. Dörrbaum AR, Kochen L, Langer JD, Schuman EM. 2018. Local and global influences on protein turnover in neurons and glia. *eLife* 7:e34202
46. Elamri I, Heumüller M, Herzig L-M, Stirnal E, Wachtveitl J, et al. 2018. A new photocaged puromycin for an efficient labeling of newly translated proteins in living neurons. *ChemBioChem* 19(23):2458–64
47. Emmott E, Jovanovic M, Slavov N. 2018. Ribosome stoichiometry: from form to function. *Trends Biochem. Sci.* 44(2):95–109
48. Engholm-Keller K, Waardenberg AJ, Müller JA, Wark JR, Fernando RN, et al. 2019. The temporal profile of activity-dependent presynaptic phospho-signalling reveals long-lasting patterns of poststimulus regulation. *PLOS Biol.* 17(3):e3000170
49. Farris S, Ward JM, Carstens KE, Samadi M, Wang Y, Dudek SM. 2019. Hippocampal subregions express distinct dendritic transcriptomes that reveal differences in mitochondrial function in CA2. *Cell Rep.* 29(2):522–39.e6
50. Ferretti MB, Ghalei H, Ward EA, Potts EL, Karbstein K. 2017. Rps26 directs mRNA-specific translation by recognition of Kozak sequence elements. *Nat. Struct. Mol. Biol.* 24(9):700–7
51. Foley AG, Hartz BP, Gallagher HC, Rønn LCB, Berezin V, et al. 2000. A synthetic peptide ligand of neural cell adhesion molecule (NCAM) IgI domain prevents NCAM internalization and disrupts passive avoidance learning. *J. Neurochem.* 74(6):2607–13
52. Fonkeu Y, Kraynyukova N, Hafner A-S, Kochen L, Sartori F, et al. 2019. How mRNA localization and protein synthesis sites influence dendritic protein distribution and dynamics. *Neuron* 103(6):1109–22.E7
53. Fonseca R, Vabulas RM, Hartl FU, Bonhoeffer T, Nägerl UV. 2006. A balance of protein synthesis and proteasome-dependent degradation determines the maintenance of LTP. *Neuron* 52(2):239–45
54. Formicola N, Vijayakumar J, Besse F. 2019. Neuronal ribonucleoprotein granules: dynamic sensors of localized signals. *Traffic* 20(9):639–49
55. Fornasiero EF, Mandad S, Wildhagen H, Alevra M, Rammner B, et al. 2018. Precisely measured protein lifetimes in the mouse brain reveal differences across tissues and subcellular fractions. *Nat. Comm.* 9(1):4230
56. Frey U, Krug M, Reymann KG, Matthies H. 1988. Anisomycin, an inhibitor of protein synthesis, blocks late phases of LTP phenomena in the hippocampal CA1 region in vitro. *Brain Res.* 452(1–2):57–65
57. Fusco CM, Desch K, Dörrbaum AR, Wang M, Staab A, et al. 2021. Neuronal ribosomes dynamically exchange ribosomal proteins in a context-dependent manner. bioRxiv 2021.03.25.437026. **https://doi.org/10.1101/2021.03.25.437026**
58. Gale JR, Aschrafi A, Gioio AE, Kaplan BB. 2018. Nuclear-encoded mitochondrial mRNAs: a powerful force in axonal growth and development. *Neuroscientist* 24(2):142–55
59. Giorgi C, Yeo GW, Stone ME, Katz DB, Burge C, et al. 2007. The EJC factor eIF4AIII modulates synaptic strength and neuronal protein expression. *Cell* 130(1):179–91
60. Glancy B, Kim Y, Katti P, Willingham TB. 2020. The functional impact of mitochondrial structure across subcellular scales. *Front. Physiol.* 11:541040
61. Glock C, Biever A, Tushev G, Bartnik I, Nassim-Assir B, et al. 2020. The mRNA translation landscape in the synaptic neuropil. bioRxiv 2020.06.09.141960. **https://doi.org/10.1101/2020.06.09.141960**
62. Glock C, Heumüller M, Schuman EM. 2017. MRNA transport & local translation in neurons. *Curr. Opin. Neurobiol.* 45:169–77
63. Goard M, Aakalu G, Fedoryak OD, Quinonez C, St. Julien J, et al. 2005. Light-mediated inhibition of protein synthesis. *Chem. Biol.* 12(6):685–93
64. Goncalves J, Bartol TM, Camus C, Levet F, Menegolla AP, et al. 2020. Nanoscale co-organization and coactivation of AMPAR, NMDAR, and mGluR at excitatory synapses. *PNAS* 117(25):14503–11

65. Granneman S, Tollervey D. 2007. Building ribosomes: even more expensive than expected? *Curr. Biol.* 17(11):R415–17
66. Guedes-Dias P, Holzbaur ELF. 2019. Axonal transport: driving synaptic function. *Science* 366(6462):eaaw9997
67. Gumy LF, Yeo GSH, Tung Y-CL, Zivraj KH, Willis D, et al. 2011. Transcriptome analysis of embryonic and adult sensory axons reveals changes in mRNA repertoire localization. *RNA* 17(1):85–98
68. Guo X, Huang X, Chen MJ. 2017. Reversible phosphorylation of the 26S proteasome. *Protein Cell* 8(4):255–72
69. Hafner A-S, Donlin-Asp PG, Leitch B, Herzog E, Schuman EM. 2019. Local protein synthesis is a ubiquitous feature of neuronal pre- and postsynaptic compartments. *Science* 364(6441):eaau3644
70. Hamilton AM, Oh WC, Vega-Ramirez H, Stein IS, Hell JW, et al. 2012. Activity-dependent growth of new dendritic spines is regulated by the proteasome. *Neuron* 74(6):1023–30
71. Hantak MP, Einstein J, Kearns RB, Shepherd JD. 2021. Intercellular communication in the nervous system goes viral. *Trends Neurosci.* 44(4):248–59
72. Hanus C, Geptin H, Tushev G, Garg S, Alvarez-Castelao B, et al. 2016. Unconventional secretory processing diversifies neuronal ion channel properties. *eLife* 5:e20609
73. Harris JJ, Jolivet R, Attwell D. 2012. Synaptic energy use and supply. *Neuron* 75(5):762–77
74. Hegde AN. 2017. Proteolysis, synaptic plasticity and memory. *Neurobiol. Learn. Mem.* 138:98–110
75. Hegde AN, Goldberg AL, Schwartz JH. 1993. Regulatory subunits of cAMP-dependent protein kinases are degraded after conjugation to ubiquitin: a molecular mechanism underlying long-term synaptic plasticity. *PNAS* 90(16):7436–40
76. Herbst WA, Martin KC. 2017. Regulated transport of signaling proteins from synapse to nucleus. *Curr. Opin. Neurobiol.* 45:78–84
77. Heumüller M, Glock C, Rangaraju V, Biever A, Schuman EM. 2019. A genetically encodable cell-type-specific protein synthesis inhibitor. *Nat. Methods* 16(8):699–702
78. Higgins R, Gendron JM, Rising L, Mak R, Webb K, et al. 2015. The unfolded protein response triggers site-specific regulatory ubiquitylation of 40S ribosomal proteins. *Mol. Cell* 59(1):35–49
79. Holt CE, Martin KC, Schuman EM. 2019. Local translation in neurons: visualization and function. *Nat. Struct. Mol. Biol.* 26(7):557–66
80. Horton AC, Ehlers MD. 2003. Neuronal polarity and trafficking. *Neuron* 40(2):277–95
81. Hsu M-T, Guo C-L, Liou AY, Chang T-Y, Ng M-C, et al. 2015. Stage-dependent axon transport of proteasomes contributes to axon development. *Dev. Cell* 35(4):418–31
82. Huganir RL, Nicoll RA. 2013. AMPARs and synaptic plasticity: the last 25 years. *Neuron* 80(3):704–17
83. Ivanova D, Dirks A, Montenegro-Venegas C, Schöne C, Altrock WD, et al. 2015. Synaptic activity controls localization and function of CtBP1 via binding to Bassoon and Piccolo. *EMBO J.* 34(8):1056–77
84. Jarome TJ, Ferrara NC, Kwapis JL, Helmstetter FJ. 2016. CaMKII regulates proteasome phosphorylation and activity and promotes memory destabilization following retrieval. *Neurobiol. Learn. Mem.* 128(C):103–9
85. Jarome TJ, Kwapis JL, Ruenzel WL, Helmstetter FJ. 2013. CaMKII, but not protein kinase A, regulates Rpt6 phosphorylation and proteasome activity during the formation of long-term memories. *Front. Behav. Neurosci.* 7:115
86. Ji S-J, Jaffrey SR. 2012. Intra-axonal translation of SMAD1/5/8 mediates retrograde regulation of trigeminal ganglia subtype specification. *Neuron* 74(1):95–107
87. Ju W, Morishita W, Tsui J, Gaietta G, Deerinck TJ, et al. 2004. Activity-dependent regulation of dendritic synthesis and trafficking of AMPA receptors. *Nat. Neurosci.* 7(3):244–53
88. Jung Y, Seo J-Y, Ryu HG, Kim D-Y, Lee K-H, Kim K-T. 2020. BDNF-induced local translation of *GluA1* is regulated by HNRNP A2/B1. *Sci. Adv.* 6(47):eabd2163
89. Juszkiewicz S, Hegde RS. 2017. Initiation of quality control during poly(A) translation requires site-specific ribosome ubiquitination. *Mol. Cell* 65(4):743–50.E4
90. Juszkiewicz S, Hegde RS. 2018. Quality control of orphaned proteins. *Mol. Cell* 71(3):443–57
91. Kang H, Schuman EM. 1996. A requirement for local protein synthesis in neurotrophin-induced hippocampal synaptic plasticity. *Science* 273(5280):1402–6

92. Kapur M, Monaghan CE, Ackerman SL. 2017. Regulation of mRNA translation in neurons—a matter of life and death. *Neuron* 96(3):616–37
93. Kelmer Sacramento E, Kirkpatrick JM, Mazzetto M, Baumgart M, Bartolome A, et al. 2020. Reduced proteasome activity in the aging brain results in ribosome stoichiometry loss and aggregation. *Mol. Syst. Biol.* 16(6):e9596
94. Klein ME, Castillo PE, Jordan BA. 2015. Coordination between translation and degradation regulates inducibility of mGluR-LTD. *Cell Rep.* 10(9):1459–66
95. Kock M, Nunes MM, Hemann M, Kube S, Jürgen Dohmen R, et al. 2015. Proteasome assembly from 15S precursors involves major conformational changes and recycling of the Pba1–Pba2 chaperone. *Nat. Comm.* 6:6123
96. von Kügelgen N, Chekulaeva M. 2020. Conservation of a core neurite transcriptome across neuronal types and species. *WIREs RNA* 11:e1590
97. Kulkarni VV, Maday S. 2018. Compartment-specific dynamics and functions of autophagy in neurons. *Dev. Neurobiol.* 78(3):298–310
98. Kuzniewska B, Cysewski D, Wasilewski M, Sakowska P, Milek J, et al. 2020. Mitochondrial protein biogenesis in the synapse is supported by local translation. *EMBO Rep*. 21:e48882
99. Lee S-H, Choi J-H, Lee N, Lee H-R, Kim J-I, et al. 2008. Synaptic protein degradation underlies destabilization of retrieved fear memory. *Science* 319(5867):1253–56
100. Lein ES, Hawrylycz MJ, Ao N, Ayres M, Bensinger A, et al. 2007. Genome-wide atlas of gene expression in the adult mouse brain. *Nature* 445(7124):168–76
101. Levy S, Avni D, Hariharan N, Perry RP, Meyuhas O. 1991. Oligopyrimidine tract at the 5′end of mammalian ribosomal protein mRNAs is required for their translational control. *PNAS* 88(8):3319–23
102. Licznerski P, Park H-A, Rolyan H, Chen R, Mnatsakanyan N, et al. 2020. ATP synthase c-subunit leak causes aberrant cellular metabolism in Fragile X syndrome. *Cell* 182(5):1170–85.e9
103. Lin JQ, van Tartwijk FW, Holt CE. 2021. Axonal mRNA translation in neurological disorders. *RNA Biol.* 18(7):936–61
104. Liu K, Jones S, Minis A, Rodriguez J, Molina H, Steller H. 2019. PI31 is an adaptor protein for proteasome transport in axons and required for synaptic development. *Dev. Cell* 50(4):509–24.e10
105. Lokireddy S, Kukushkin NV, Goldberg AL. 2015. cAMP-induced phosphorylation of 26S proteasomes on Rpn6/PSMD11 enhances their activity and the degradation of misfolded proteins. *PNAS* 112(52):E7176–85
106. Lopez-Salon M, Alonso M, Vianna MRM, Viola H, Mello e Souza T, et al. 2001. The ubiquitin-proteasome cascade is required for mammalian long-term memory formation. *Eur. J. Neurosci.* 14(11):1820–26
107. Lörincz A, Notomi T, Tamás G, Shigemoto R, Nusser Z. 2002. Polarized and compartment-dependent distribution of HCN1 in pyramidal cell dendrites. *Nat. Neurosci.* 5(11):1185–93
108. Mabb AM, Je HS, Wall MJ, Robinson CG, Larsen RS, et al. 2014. Triad3A regulates synaptic strength by ubiquitination of Arc. *Neuron* 82(6):1299–316
109. Majzoub K, Hafirassou ML, Meignin C, Goto A, Marzi S, et al. 2014. RACK1 controls IRES-mediated translation of viruses. *Cell* 159(5):1086–95
110. Mardakheh FK, Paul A, Kümper S, Sadok A, Paterson H, et al. 2015. Global analysis of mRNA, translation, and protein localization: Local translation is a key regulator of cell protrusions. *Dev. Cell* 35(3):344–57
111. Martínez JC, Randolph LK, Iascone DM, Pernice HF, Polleux F, Hengst U. 2019. Pum2 shapes the transcriptome in developing axons through retention of target mRNAs in the cell body. *Neuron* 104(5):931–46.e5
112. Mazaré N, Oudart M, Moulard J, Cheung G, Tortuyaux R, et al. 2020. Local translation in perisynaptic astrocytic processes is specific and changes after fear conditioning. *Cell Rep.* 32(8):108076
113. Merkin J, Russell C, Chen P, Burge CB. 2012. Evolutionary dynamics of gene and isoform regulation in mammalian tissues. *Science* 338(6114):1593–99
114. Miller CA, Gavin CF, White JA, Parrish RR, Honasoge A, et al. 2010. Cortical DNA methylation maintains remote memory. *Nat. Neurosci.* 13(6):664–66

115. Miller S, Yasuda M, Coats JK, Jones Y, Martone ME, Mayford M. 2002. Disruption of dendritic translation of CaMKIIα impairs stabilization of synaptic plasticity and memory consolidation. *Neuron* 36(3):507–19
116. Misgeld T, Schwarz TL. 2017. Mitostasis in neurons: maintaining mitochondria in an extended cellular architecture. *Neuron* 96(3):651–66
117. Monday HR, Bourdenx M, Jordan BA, Castillo PE. 2020. CB_1-receptor-mediated inhibitory LTD triggers presynaptic remodeling via protein synthesis and ubiquitination. *eLife* 9:e54812
118. Monday HR, Younts TJ, Castillo PE. 2018. Long-term plasticity of neurotransmitter release: emerging mechanisms and contributions to brain function and disease. *Annu. Rev. Neurosci.* 41:299–322
119. Moor AE, Golan M, Massasa EE, Lemze D, Weizman T, et al. 2017. Global mRNA polarization regulates translation efficiency in the intestinal epithelium. *Science* 357(6357):1299–303
120. Moritz CP, Mühlhaus T, Tenzer S, Schulenborg T, Friauf E. 2019. Poor transcript-protein correlation in the brain: Negatively correlating gene products reveal neuronal polarity as a potential cause. *J. Neurochem.* 149(5):582–604
121. Motosugi R, Murata S. 2019. Dynamic regulation of proteasome expression. *Front. Mol. Biosci.* 6:30
122. Murata S, Yashiroda H, Tanaka K. 2009. Molecular mechanisms of proteasome assembly. *Nat. Rev. Mol. Cell Biol.* 10(2):104–15
123. Nader K, Schafe GE, Le Doux JE. 2000. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature* 406(6797):722–26
124. Nagano S, Jinno J, Abdelhamid RF, Jin Y, Shibata M, et al. 2020. TDP-43 transports ribosomal protein mRNA to regulate axonal local translation in neuronal axons. *Acta Neuropathol.* 140:695–713
125. Nelson AD, Jenkins PM. 2017. Axonal membranes and their domains: assembly and function of the axon initial segment and node of Ranvier. *Front. Cell Neurosci.* 11:136
126. Nishiyama J, Yasuda R. 2015. Biochemical computation for spine structural plasticity. *Neuron* 87(1):63–75
127. Noya SB, Colameo D, Brüning F, Spinnler A, Mircsof D, et al. 2019. The forebrain synaptic transcriptome is organized by clocks but its proteome is driven by sleep. *Science* 366(6462):eaav2642
128. Okuno H, Akashi K, Ishii Y, Yagishita-Kyo N, Suzuki K, et al. 2012. Inverse synaptic tagging of inactive synapses via dynamic interaction of Arc/Arg3.1 with CaMKIIβ. *Cell* 149(4):886–98
129. Ostroff LE, Santini E, Sears R, Deane Z, Kanadia RN, et al. 2019. Axon TRAP reveals learning-associated alterations in cortical axonal mRNAs in the lateral amygdala. *eLife* 8:e51607
130. Parvin S, Takeda R, Sugiura Y, Neyazaki M, Nogi T, Sasaki Y. 2019. Fragile X mental retardation protein regulates accumulation of the active zone protein Munc18-1 in presynapses via local translation in axons during synaptogenesis. *Neurosci. Res.* 146:36–47
131. Patrick GN, Bingol B, Weld HA, Schuman EM. 2003. Ubiquitin-mediated proteasome activity is required for agonist-induced endocytosis of GluRs. *Curr. Biol.* 13(23):2073–81
132. Perez JD, tom Dieck S, Alvarez-Castelao B, Tushev G, Chan IC, Schuman EM. 2021. Subcellular sequencing of single neurons reveals the dendritic transcriptome of GABAergic interneurons. *eLife* 10:e63092
133. Perlson E, Hanz S, Ben-Yaakov K, Segal-Ruder Y, Seger R, Fainzilber M. 2005. Vimentin-dependent spatial translocation of an activated MAP kinase in injured nerve. *Neuron* 45(5):715–26
134. Perry RB-T, Doron-Mandel E, Iavnilovitch E, Rishal I, Dagan SY, et al. 2012. Subcellular knockout of importin β1 perturbs axonal retrograde signaling. *Neuron* 75(2):294–305
135. Popov V, Medvedev NI, Davies HA, Stewart MG. 2005. Mitochondria form a filamentous reticular network in hippocampal dendrites but are present as discrete bodies in axons: a three-dimensional ultrastructural study. *J. Comp. Neurol.* 492(1):50–65
136. Poulopoulos A, Murphy AJ, Ozkan A, Davis P, Hatch J, et al. 2019. Subcellular transcriptomes and proteomes of developing axon projections in the cerebral cortex. *Nature* 565(7739):356–60
137. Ramachandran KV, Fu JM, Schaffer TB, Na CH, Delannoy M, Margolis SS. 2018. Activity-dependent degradation of the nascentome by the neuronal membrane proteasome. *Mol. Cell* 71(1):169–177.E6
138. Ramachandran KV, Margolis SS. 2017. A mammalian nervous-system-specific plasma membrane proteasome complex that modulates neuronal function. *Nat. Struct. Mol. Biol.* 24(4):419–30

139. Ramsköld D, Wang ET, Burge CB, Sandberg R. 2009. An abundance of ubiquitously expressed genes revealed by tissue transcriptome sequence data. *PLOS Comput. Biol.* 5(12):e1000598
140. Rangaraju V, Lauterbach M, Schuman EM. 2019. Spatially stable mitochondrial compartments fuel local translation during plasticity. *Cell* 176(1–2):73–84.e15
141. Rangaraju V, Lewis TL, Hirabayashi Y, Bergami M, Motori E, et al. 2019. Pleiotropic mitochondria: the influence of mitochondria on neuronal development and disease. *J. Neurosci.* 39(42):8200–8
142. Rishal I, Fainzilber M. 2014. Axon–soma communication in neuronal injury. *Nat. Rev. Neurosci.* 15(1):32–42
143. Rizalar FS, Roosen DA, Haucke V. 2021. A presynaptic perspective on transport and assembly mechanisms for synapse formation. *Neuron* 109(1):27–41
144. Rousseau A, Bertolotti A. 2018. Regulation of proteasome assembly and activity in health and disease. *Nat. Rev. Mol. Cell Biol.* 19:697–712
145. Sakers K, Lake AM, Khazanchi R, Ouwenga R, Vasek MJ, et al. 2017. Astrocytes locally translate transcripts in their peripheral processes. *PNAS* 114(19):E3830–38
146. Scarnati MS, Kataria R, Biswas M, Paradiso KG. 2018. Active presynaptic ribosomes in the mammalian brain, and altered transmitter release after protein synthesis inhibition. *eLife* 7:e36697
147. Schmidt-Hieber C, Nolan MF. 2017. Synaptic integrative mechanisms for spatial cognition. *Nat. Neurosci.* 20(11):1483–92
148. Schratt GM, Tuebing F, Nigh EA, Kane CG, Sabatini ME, et al. 2006. A brain-specific microRNA regulates dendritic spine development. *Nature* 439(7074):283–89
149. Shigeoka T, Jung H, Jung J, Turner-Bridger B, Ohk J, et al. 2016. Dynamic axonal translation in developing and mature visual circuits. *Cell* 166(1):181–92
150. Shigeoka T, Koppers M, Wong HH-W, Lin JQ, Cagnetta R, et al. 2019. On-site ribosome remodeling by locally synthesized ribosomal proteins in axons. *Cell Rep.* 29(11):3605–19.e10
151. Shrestha P, Ayata P, Herrero-Vidal P, Longo F, Gastone A, et al. 2020. Cell-type-specific drug-inducible protein synthesis inhibition demonstrates that memory consolidation requires rapid neuronal translation. *Nat. Neurosci.* 23(2):281–92
152. Silva AJ, Stevens CF, Tonegawa S, Wang Y. 1992. Deficient hippocampal long-term potentiation in alpha-calcium-calmodulin kinase II mutant mice. *Science* 257(5067):201–6
153. Sjöstedt E, Zhong W, Fagerberg L, Karlsson M, Mitsios N, et al. 2020. An atlas of the protein-coding genes in the human, pig, and mouse brain. *Science* 367(6482):eaay5947
154. Spillane M, Ketschek A, Merianda TT, Twiss JL, Gallo G. 2013. Mitochondria coordinate sites of axon branching through localized intra-axonal protein synthesis. *Cell Rep.* 5(6):1564–75
155. Steward O, Farris S, Pirbhoy PS, Darnell J, Van Driesche SJ. 2014. Localization and local translation of *Arc/Arg3.1* mRNA at synapses: some observations and paradoxes. *Front. Mol. Neurosci.* 7:101
156. Steward O, Wallace CS, Lyford GL, Worley PF. 1998. Synaptic activation causes the mRNA for the IEG *Arc* to localize selectively near activated postsynaptic sites on dendrites. *Neuron* 21(4):741–51
157. Sun C, Nold A, Tchumatchenko T, Heilemann M, Schuman EM. 2020. The spatial scale of synaptic protein allocation during homeostatic plasticity. bioRxiv 2020.04.29.068833. **https://doi.org/10.1101/2020.04.29.068833**
158. Sutton MA, Ito HT, Cressy P, Kempf C, Woo JC, Schuman EM. 2006. Miniature neurotransmission stabilizes synaptic function via tonic suppression of local dendritic protein synthesis. *Cell* 125(4):785–99
159. Tai H-C, Schuman EM. 2008. Ubiquitin, the proteasome and protein degradation in neuronal function and dysfunction. *Nat. Rev. Neurosci.* 9(11):826–38
160. Takabatake M, Goshima Y, Sasaki Y. 2020. Semaphorin-3A promotes degradation of Fragile X mental retardation protein in growth cones *via* the ubiquitin-proteasome pathway. *Front. Neural Circuits* 14:5
161. Tasic B, Yao Z, Graybuck LT, Smith KA, Nguyen TN, et al. 2018. Shared and distinct transcriptomic cell types across neocortical areas. *Nature* 563(7729):72–78
162. Taylor AM, Berchtold NC, Perreau VM, Tu CH, Jeon NL, Cotman CW. 2009. Axonal mRNA in uninjured and regenerating cortical mammalian axons. *J. Neurosci.* 29(15):4697–707
163. Taylor AM, Wu J, Tai H-C, Schuman EM. 2013. Axonal translation of β-catenin regulates synaptic vesicle dynamics. *J. Neurosci.* 33(13):5584–89

164. Trapman J, Retèl J, Planta RJ. 1975. Ribosomal precursor particles from yeast. *Exp. Cell Res.* 90(1):95–104
165. Turrigiano GG, Leslie KR, Desai NS, Rutherford LC, Nelson SB. 1998. Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature* 391(6670):892–96
166. Tushev G, Glock C, Heumüller M, Biever A, Jovanovic M, Schuman EM. 2018. Alternative 3′ UTRs modify the localization, regulatory potential, stability, and plasticity of mRNAs in neuronal compartments. *Neuron* 98(3):495–511.e6
167. Tyssowski KM, DeStefino NR, Cho J-H, Dunn CJ, Poston RG, et al. 2018. Different neuronal activity patterns induce different gene expression programs. *Neuron* 98(3):530–546.e11
168. Uhlén M, Fagerberg L, Hallström BM, Lindskog C, Oksvold P, et al. 2015. Tissue-based map of the human proteome. *Science* 347(6220):1260419
169. van Niekerk EA, Willis DE, Chang JH, Reumann K, Heise T, Twiss JL. 2007. Sumoylation in axons triggers retrograde transport of the RNA-binding protein La. *PNAS* 104(31):12913–18
170. Villarin JM, McCurdy EP, Martínez JC, Hengst U. 2016. Local synthesis of dynein cofactors matches retrograde transport to acutely changing demands. *Nat. Comm.* 7(1):13865
171. Völgyi K, Gulyássy P, Háden K, Kis V, Badics K, et al. 2015. Synaptic mitochondria: a brain mitochondria cluster with a specific proteome. *J. Proteom.* 120:142–57
172. Wang G, Ang C-E, Fan J, Wang A, Moffitt JR, Zhuang X. 2020. Spatial organization of the transcriptome in individual neurons. bioRxiv 2020.12.07.414060. **https://doi.org/10.1101/2020.12.07.414060**
173. Wang X, You X, Langer JD, Hou J, Rupprecht F, et al. 2019. Full-length transcriptome reconstruction reveals a large diversity of RNA and protein isoforms in rat hippocampus. *Nat. Comm.* 10(1):5009
174. Wang Z, Ma J, Miyoshi C, Li Y, Sato M, et al. 2018. Quantitative phosphoproteomic analysis of the molecular substrates of sleep need. *Nature* 558(7710):435–439
175. Warner JR. 1999. The economics of ribosome biosynthesis in yeast. *Trends Biochem. Sci.* 24(11):437–40
176. Waung MW, Pfeiffer BE, Nosyreva ED, Ronesi JA, Huber KM. 2008. Rapid translation of Arc/Arg3.1 selectively mediates mGluR-dependent LTD through persistent increases in AMPAR endocytosis rate. *Neuron* 59(1):84–97
177. Wilhelm BG, Mandad S, Truckenbrodt S, Kröhnert K, Schäfer C, et al. 2014. Composition of isolated synaptic boutons reveals the amounts of vesicle trafficking proteins. *Science* 344(6187):1023–28
178. Willis DE, van Niekerk EA, Sasaki Y, Mesngon M, Merianda TT, et al. 2007. Extracellular stimuli specifically regulate localized levels of individual neuronal mRNAs. *J. Cell Biol.* 178(6):965–80
179. Xue S, Tian S, Fujii K, Kladwang W, Das R, Barna M. 2015. RNA regulons in *Hox* 5′ UTRs confer ribosome specificity to gene regulation. *Nature* 517(7532):33–38
180. Yap E-L, Greenberg ME. 2018. Activity-regulated transcription: bridging the gap between neural activity and behavior. *Neuron* 100(2):330–48
181. Yogev S, Shen K. 2017. Establishing neuronal polarity with environmental and intrinsic mechanisms. *Neuron* 96(3):638–50
182. Yoon YJ, Wu B, Buxbaum AR, Das S, Tsai A, et al. 2016. Glutamate-induced RNA localization and translation in neurons. *PNAS* 113(44):E6877–86
183. Younts TJ, Monday HR, Dudok B, Klein ME, Jordan BA, et al. 2016. Presynaptic protein synthesis is required for long-term plasticity of GABA release. *Neuron* 92(2):479–92
184. Yudin D, Hanz S, Yoo S, Iavnilovitch E, Willis D, et al. 2008. Localized regulation of axonal RanGTPase controls retrograde injury signaling in peripheral nerve. *Neuron* 59(2):241–52
185. Zappulo A, van den Bruck D, Ciolli Mattioli C, Franke V, Imami K, et al. 2017. RNA localization is a key determinant of neurite-enriched proteome. *Nat. Comm.* 8:583
186. Zeisel A, Hochgerner H, Lönnerberg P, Johnsson A, Memic F, et al. 2018. Molecular architecture of the mouse nervous system. *Cell* 174(4):999–1014.E22
187. Zhai S, Ark ED, Parra-Bueno P, Yasuda R. 2013. Long-distance integration of nuclear ERK signaling triggered by activation of a few dendritic spines. *Science* 342(6162):1107–11
188. Zhang Y, Chen K, Sloan SA, Bennett ML, Scholze AR, et al. 2014. An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *J. Neurosci.* 34(36):11929–47
189. Zovkic IB, Paulukaitis BS, Day JJ, Etikala DM, Sweatt JD. 2014. Histone H2A.Z subunit exchange controls consolidation of recent and remote memory. *Nature* 515(7528):582–86