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### Investigating Localization and Activity-Dependent Translation of Astrocyte mRNA

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# INVESTIGATING LOCALIZATION AND ACTIVITY-DEPENDENT TRANSLATION OF ASTROCYTE mRNA

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While it is well understood that synaptically-activated, rapid, local translation of new proteins in neurons mediates changes at the synapse, it is unclear whether astrocytes also exhibit subcellular translation. Astrocytes are highly polarized cells in the central nervous system, and their hallmark functions include processing and responding to changes at tripartite synapses. I hypothesized that astrocytes utilize local protein synthesis as a response to synaptic changes. This function may compensate for their elaborate somatic arbor, in which one process may contact many thousands of synapses. The lab's preliminary data supports this hypothesis by showing that ribosomes and ribosome-bound mRNAs exist in peripheral astrocyte processes (PAPs). I first focused on validating the presence of PAP-enriched mRNAs, identified via a novel biochemical translome profiling method coined "PAP TRAP" (translating ribosome affinity purification). To localize and validate the presence of mRNAs in PAPs, *in vivo*, I performed fluorescent *in situ* hybridization (FISH) and used confocal microscopy to visualize the mRNAs. Through these experiments, I observed clear subcellular localization of multiple astrocyte-specific mRNAs at PAPs.

Having demonstrated that PAP-enriched mRNAs are truly localized peripherally, I hypothesized, based on astrocyte functional roles in the CNS, that synaptic activity regulates local translation of these mRNAs. I carried out experiments to visualize and measure protein translation in peripheral processes via puromycylation and quantification of puromycin immunofluorescence. I treated acute mouse brain slices with known modulators of synaptic activity and demonstrated that astrocytes do indeed up- and down-regulate peripheral translation in response to treatment-induced changes at tripartite synapses. Overall, this novel work proposes a mechanism of how astrocyte dysregulation and dysfunction could contribute to the pathogenesis of diseases of synaptic connectivity (i.e., schizophrenia, Alzheimer's, autism spectrum disorders).