CELL BIOLOGY OF THE NEURON

The power of 3′ UTRs

> “Neuropil-enriched isoforms exhibited much longer 3′ UTRs than did soma-enriched isoforms”

Neurons comprise several different compartments — for example, dendrites and soma — and mRNA transcripts can be targeted to various neuronal compartments to facilitate efficient local translation. Information encoded in the 3′ untranslated region (3′ UTR) of mRNA transcripts may affect such mRNA localization, as well as transcript stability and translation. In a new study, Tushev et al. examine the 3′ UTRs of mRNA transcripts in different neuronal compartments and report new insights about the importance of these sequences in localization, translation, stability and plasticity.

The authors microdissected the somatic and neuropil layers of the hippocampal CA1 region, and used 3′ end sequencing to characterize all of the 3′ UTR isoforms of each expressed mRNA transcript — identifying a total of 35,393 3′ UTR isoforms corresponding to 14,102 gene loci. Using similarly prepared 3′ UTR isoform data sets from neuron-enriched and glial-cell-enriched cultures (together comprising a total of 21,603 3′ UTR isoforms from 11,301 gene loci), the authors established which of the isoforms expressed in the hippocampus were likely to be expressed in neurons or glia. More than 70% of neuron-enriched transcripts were expressed as two or more different 3′ UTR isoforms, suggesting that 3′ UTR diversity is particularly high in neurons.

The authors assessed the lengths of the isoforms expressed in the hippocampus. Neuropil-enriched isoforms exhibited much longer 3′ UTRs than did soma-enriched isoforms. Moreover, neuron-enriched transcripts tended to have longer 3′ UTRs than glial-cell-enriched transcripts, with cell-type-enriched transcripts being generally longer than transcripts that were not enriched in either cell type. Interestingly, long, neuropil-enriched 3′ UTR isoforms were enriched for transcripts encoding synaptic proteins. Short and long isoforms of the same transcript family tended to be enriched within the same compartment, although in some instances — particularly in the case of certain synapse-related and dendritic spine-related transcripts — different isoforms were differentially localized to different compartments, with longer isoforms more often localized in the neuropil than shorter ones.

Next, the authors examined how different 3′ UTR isoforms might contribute to transcript stability and regulation. Measures of GC content and predicted secondary structure suggested that soma-enriched and neuropil-enriched isoforms were less and more stable, respectively, than non-localized transcripts. In addition, 22% of all microRNAs expressed in the CA1 region had binding sequences in isoforms that were enriched in one compartment or the other. Furthermore, neuropil-enriched isoforms were, on average, longer-lived than shorter isoforms, and the authors found that binding sites for different microRNAs in the 3′ UTRs were associated with shorter or longer half-lives. Together, these findings suggest that different 3′ UTRs may be associated with differences in the stability, longevity and regulation of transcripts.

To determine the effects of neuronal activity on 3′ UTR expression, the authors measured changes in the levels of soma-enriched and neuropil-enriched transcripts in hippocampal slices that had been treated with the GABA type A receptor antagonist bicuculline for 4 hours. In total, 783 isoforms were upregulated or downregulated by the treatment, with some isoforms showing coordinate regulation in both the somatic and neuropil layers and others showing differential regulation in the two compartments. Of these activity-dependent changes in isoform levels, about three-quarters were blocked by treatment with transcription inhibitors and were therefore due to altered transcription. Interestingly, however, some other activity-dependent changes were associated with differential trafficking or remodelling (lengthening or shortening) of localized isoforms. Thus, neuronal activity greatly affects the levels of different 3′ UTR isoforms in various ways.

Together, these data paint a complex picture of the association of diverse 3′ UTRs with differences in the localization, stability and activity-dependent changes in the expression of neuronal transcripts.

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Credit: Louis Fox/DigitalVision

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