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Remodeling mRNA can be presented like an 'endless' conveyor belt of sushi

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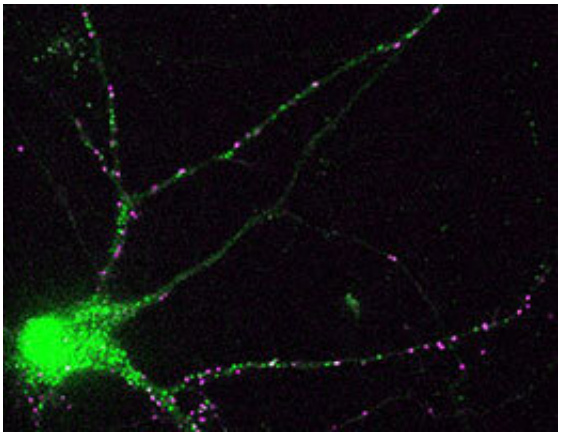

Fluorescence micrograph of a hippocampal neuron growing in culture medium, showing the cell body (lower left) and dendrites. Synapses are imaged in violet and mRNA in green. Source: K. E. Bauer and M. A. Kiebler. Credit: LMU

Synapses between nerve cells in the brain undergo constant remodeling, which is the basis of learning. An LMU team has now traced the molecules that direct remodeling and shown that they circulate in the living cell like running sushi.

The human brain is like a long-term construction site—there's always something else to be done. This is certainly true of synapses, the functional links between nerve cells, which are constantly being strengthened, attenuated or demolished. Indeed, this process termed synaptic plasticity is the basis of our ability to store and recall

information—in other words, to learn. The instructions for the synthesis of necessary components, which are encoded in molecules known as messenger RNAs (mRNAs), are delivered to the specific synapses that need them by a specialized transport system. But how the blueprints reach their destinations is poorly understood. In order to learn more about the underlying mechanisms, cell biologist Professor Michael Kiebler and his group at the LMU Biomedical Center have now followed the transport of individual mRNAs to specific synapses. Their analysis shows that the same mRNA can be presented to potential addresses several times—a system which the researchers compare to running sushi, the use of an 'endless' conveyor belt to enable patrons to pick and choose from the delicacies on offer.

In order to serve the extensive network of synapses on a typically elongated process termed dendrite, the mRNAs must be transported from the nucleus in the cell body to the terminal branches at the end of the process. To monitor this process, the LMU team used cell cultures derived from neurons isolated from the hippocampus of the rat, which serves as a model for the human hippocampus. "We labelled specific mRNAs in living cells with a fluorescent dye, which enabled us to track their progress in real time," Kiebler explains. "This approach permitted us to determine, for the first time, whether or not a given molecule is delivered directly to a particular synapse, and whether different mRNAs are handled differently in this respect. In one case, we were able to follow how an mRNA entered one of the spine-like processes extended by a dendrite," he says. "Dendrites act as antennas that receive inputs from synapses on other cells." The observations revealed that one and the same mRNA may repeatedly circulate back and forth between the cell body and the nerve processes—like sushi wending its way between the tables in a restaurant—until it finds a synapse that needs it.

Certain recognition sequences located in the segment of the mRNA that follows the stop codon (which marks the end of the protein-coding

blueprint) serve as both the postage stamp and the address to direct the molecule to ensure that the molecule reaches the right region of the cell. "We have also demonstrated that, if the postage stamp is left intact, transport from the cell body to the neural processes is more effective and the mRNA is brought closer to the synapse than when it has been removed," says Kiebler. In addition, RNA-binding proteins such as Staufen2 play an important role in the regulation of mRNA transport by this cellular sorting system. Earlier studies had previously shown that Staufen2 is capable of binding several different mRNAs—so that the same mechanism can distribute distinct mRNAs. In addition, the new report confirms early results which had suggested that uptake of the mRNA by the synapse depends on both the nature of the binding protein and the level of activity of the synapse. Taken together, the new data provide further details on the mechanisms underlying the delivery of proteins to synapses, and will have an impact on future efforts to understand the molecular basis of synaptic plasticity in mammals.

More information: Karl E. Bauer et al. Live cell imaging reveals 3′-UTR dependent mRNA sorting to synapses, *Nature Communications* (2019). DOI: 10.1038/s41467-019-11123-x

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