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A micro-RNA as a key regulator of learning and Alzheimer's disease

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Proteins are the molecular machines of the cell. They transport materials, cleave products or transmit signals – and for a long time, they have been a main focus of attention in molecular biology research. In the last two decades, however, another class of critically important molecules has emerged: small RNA molecules, including micro-RNAs. It is now well established that micro-RNAs play a key role in the regulation of cell function.

"A micro-RNA regulates the production of an estimated 300-400 proteins. This class of molecules can be regarded as a switch that coordinates the transition of cells from one state to another," explains Prof. Dr. André Fischer, scientist at the German Center for Neurodegenerative Diseases (DZNE) and Speaker of the DZNE site Göttingen. He and his team have identified a micro-RNA that regulates the learning processes and probably plays a central role in Alzheimer's disease. The researchers have shown that there is too much of a micro-RNA called "miRNA 34c" in mouse models of Alzheimer's disease, and decreasing the level of miRNA 34c in these mice can restore their learning ability. The scientists have identified a new target molecule that might be important for diagnosis and treatment of Alzheimer's disease. The studies were carried out in collaboration with scientists at the European Neuroscience Institute Göttingen, the Göttingen University, the DZNE site in Munich and researchers from Switzerland, USA and Brazil.

miRNA 34c was identified using a highly complex method called

"massive parallel sequencing". With this technology, Fischer and his colleagues captured the complete RNA composition in the hippocampus – the learning region of the brain – and compared this with the RNA of the entire brain. They showed that miRNA 34c is enriched in the hippocampus, especially in during the time window of a few hours after a learning phase. "We suspect that the function of micro-RNA 34c is to switch off a whole range of gene products that are turned on in the learning process," Fischer said. Too much miRNA 34c would then lead to a blockade of learning – which is exactly what was shown in subsequent experiments. In old mice, which do not learn as easily as their younger counterparts, there was indeed too much miRNA 34c. The miRNA-34c level was also elevated in mice that are used as specific research models of Alzheimer's disease. These mice carry a genetic mutation that can cause Alzheimer's in humans and show disturbances of memory function. Moreover, miRNA 34c seems to not only play a role in mice. Fischer and his colleagues showed these levels are also elevated in the brains of Alzheimer's patients.

In further mouse experiments, the researchers showed that miRNA 34c is actually causally involved in the pathogenesis of Alzheimer's disease and memory disorders. An artificial increase of miRNA-34c level in normal mice results in memory impairment in the animals. Secondly, as Fischer and his colleagues have shown, lowering miRNA-34c levels can restore learning ability in mouse models of Alzheimer's disease and in older mice. "Neurodegenerative diseases like Alzheimer's are associated with many factors. We hope that with the identification of micro-RNA 34c, we have found an important mediator of pathogenesis," says Fischer. "Micro-RNA 34c would then be a good candidate for the development of drugs against Alzheimer's."

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Bahari-Javan, Susanne Burkhardt, Farahnaz Sananbenesi1 & Andre Fischer. Micro-RNA-34C is a novel target to treat dementias. EMBO J advance online publication 23 September 2011; doi:10.1038/emboj.2011.327