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Restoring protein homeostasis improves memory deficits in Down syndrome model

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Down syndrome is the most common genetic cause of intellectual disability, and currently there is no effective treatment. Memory deficits are a hallmark of this condition and a study published today in the

journal *Science* reports that the defects in a conserved stress pathway dubbed the 'integrated stress response,' or ISR, could explain the cognitive deficits in a mouse model of Down syndrome.

The authors found that ISR is activated in the brains of a mouse model that recapitulates the cognitive deficits of the human syndrome and also in postmortem human brain samples from patients. More importantly, inhibition of the ISR, either by genetic or pharmacological means, reversed memory deficits in the mice. The findings support conducting future studies to explore the possibility that modulating the ISR might help treat Down syndrome and other disorders resulting from disruption of this network.

"In the current study, we investigated the role protein homeostasis networks play in Down syndrome," said corresponding author Dr. Mauro Costa-Mattioli, professor of neuroscience and Cullen Foundation Endowed Chair at Baylor College of Medicine. "A decline in protein homeostasis networks is strongly linked to several neurological conditions, from aging to neurodegenerative disorders, but little was known about its role in Down syndrome."

The researchers first discovered that the rates of protein synthesis were reduced in the brains of Down syndrome mice and in human cells isolated from individual with the syndrome. They also found that activation of the ISR, an evolutionarily network that regulates protein homeostasis by regulating protein synthesis, could explain the protein synthesis deficits associated with Down syndrome.

Motivated by these encouraging findings, Costa-Mattioli and his colleagues investigated whether the activation of the ISR mediated the long-term memory deficits in Down syndrome mice. To answer this question, they used four independent genetic and pharmacological manipulations to correct the ISR in the Down syndrome mouse model.

"Down syndrome mice exhibit problems with long-term memory," said first author Dr. Ping Jun Zhu, assistant professor of neuroscience and senior investigator in the Costa-Mattioli group. "In one set of experiments we trained Down syndrome and control mice in a new task. Down syndrome mice did not learn the task as well as control mice. However, when we genetically or pharmacologically inhibited the ISR, the animals were able to learn almost as well as control mice."

The researchers also measured the strength of the synaptic connections in the Down syndrome mice and found that the connections were not as strong as those in control mice. But inhibiting the ISR in Down syndrome mice was able to reverse the deficits in synaptic function.

At the cellular level, synaptic plasticity—the ability to form neural connections—is believed to be a central mechanism that could explain how memories are formed, therefore these findings support the researchers' hypothesis that the activation of the ISR network mediates the memory deficits associated with Down syndrome.

"In the last 10 years, we and others have shown the ISR is a molecular switch for normal long-term memory formation. In this study, we found that the switch is off in Down syndrome. More importantly, turning the switch back on in these mice reverses their memory deficits," Costa-Mattioli said. "These very encouraging results suggest that tuning the ISR may emerge as a promising avenue to alleviate a wide range of cognitive disorders with a disruption in protein homeostasis."

More information: P.J. Zhu el al., "Activation of the ISR mediates the behavioral and neurophysiological abnormalities in Down syndrome," *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aaw5185

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