MedicalXpress

What helps form long-term memory also drives the development of neurodegenerative disease

May 22 2018

Scientists have just discovered that a small region of a cellular protein that helps long-term memories form also drives the neurodegeneration seen in Amyotrophic Lateral Sclerosis (ALS). This small part of the Ataxin-2 protein thus works for good and for bad. When a version of the protein lacking this region was substituted for the normal form in fruit flies (model organisms), the animals could not form long-term memories—but, surprisingly, the same flies showed a remarkable resistance to neurodegeneration.

The popular "ice bucket challenge" highlighted the social significance of ALS, as well as the need to better understand and treat neurodegenerative conditions. This new research identifies a very specific basic mechanism that facilitates progression of neuronal loss in an animal model of ALS, and, by shedding light on a potential way to protect against cell death in ALS, it should inform strategies for the development of therapeutics to treat or manage these devastating conditions, which are currently incurable.

The Science Foundation Ireland-funded research, involving scientists from the Trinity College Institute of Neuroscience, NCBS Bangalore and HMMI, University of Colorado, Boulder, has just been published in the leading international journal *Neuron*.

Professor of Neurogenetics at Trinity College Dublin, Mani

Ramaswami, said: "This work, by collaborating young researchers based in Irish, Indian and American laboratories, provides a great example of the ability of fundamental research in model organisms to produce biologically and clinically interesting information."

A common feature of neurodegenerative diseases is the presence of specific protein aggregates in nerve cells, which accumulate and clump together—usually as protein fibres called amyloid filaments. Such aggregates are believed to trigger processes that cause the neuronal death associated with these debilitating diseases. For example, amyloid-beta (Aβ) aggregates are associated with Alzheimer's disease, while TDP-43, FUS and Ataxin-2 proteins are commonly found in ALS patients.

The scientists behind the current study set out to test this "amyloid hypothesis" to see whether it may explain how ALS develops. The scientists genetically engineered fruit flies with mutations designed to reduce Ataxin-2 protein assembly into aggregates without affecting other functions of the protein.

Arnas Petrauskas, Trinity, said: "The flies with this altered, non-aggregating version of the protein showed a striking resistance to neurodegeneration. This suggests the normal Ataxin-2 protein and its ability to form aggregates is required for the progression of at least some forms of ALS, which means these results provide support for the amyloid hypothesis."

"What really surprised us though was that this same protein region seems to be required for the flies to develop long-term memory, as those with the altered version of Ataxin-2 showed normal short-term but defective long-term memories."

Fruit flies normally respond strongly to new odorants, but weakly to familiar odorants through a process called habituation. This memory of

the familiar can be of the short-term kind—to an odorant encountered for half-an-hour, or of the long-term kind, to odorants encountered for days (think of it as remembering a phone number of a new acquaintance versus remembering your own phone number). Flies lacking this small domain of Ataxin-2 showed greatly reduced long-term memory.

So how is long-term memory formation and disease progression connected? It turns out that proteins like the TDP-43, FUS and Ataxin-2 found in ALS are also involved in the natural control and management of protein expression in the cell. The very same region of Ataxin-2 is needed to form RNP granules that store RNAs (essentially blueprints, or recipes for specific proteins) in a silent form until they are unpackaged by a signal and used to produce molecules when they are required. This local control of RNAs is required for long-term changes at neuronal synapses that underlie long-term memory.

The new discovery shows that Ataxin-2 concentrates several RNA-binding proteins used in the process of memory storing, but in doing so, it creates a biological environment that can help these proteins aggregate into disease-causing amyloids. A "trade-off" therefore exists in nature where the Ataxin-2 gene increases the danger of neurodegeneration, but helps our cells control RNA and form long-term memories. In a commentary on the research published in the same issue of the journal Neuron, Aaron Gitler, Professor of Genetics in the Stanford Neuroscience Institute, an independent expert in MND research said: "This data suggest that manipulating RNP granule formation by genetically manipulating ataxin-2's IDRs, or by other means could be therapeutic in ALS. Beyond ataxin-2, the race is now on to discover additional proteins that help build RNP granules."

Provided by Trinity College Dublin