Zebrafish discovery could speed testing of motor neuron disease and dementia treatments

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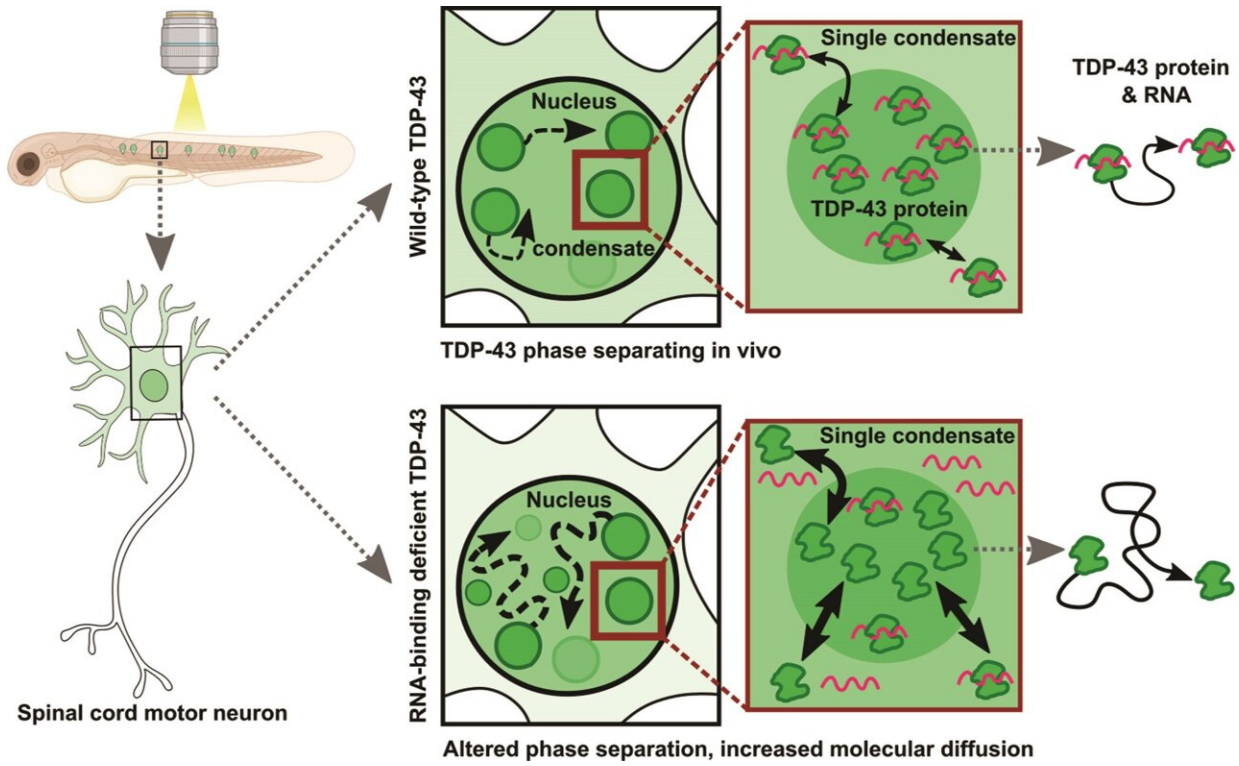

Credit: *Nucleic Acids Research* (2024). DOI: 10.1093/nar/gkae112

Tiny, transparent fish have made it possible for Macquarie University neuroscientists to observe damaging protein clusters forming in real time, opening the way for testing potential early interventions for motor

neuron disease (MND) and dementia.

In a new paper published in *Nucleic Acids Research*, a team of researchers from the Motor Neuron Disease Research Center at Macquarie University described for the first time TDP-43 changing its structure and forming specialized droplets in the spinal neurons of living zebrafish.

TDP-43 is a protein produced in the nucleus of cells in the human brain and central nervous system, including the motor neurons that control movement.

Under normal conditions, it is vital to the healthy functioning of these cells, but when it becomes pathogenic, it leaves the nucleus and begins to form solid clumps in the surrounding cell body, or cytoplasm, clogging it and preventing the cell from functioning properly.

These solid clumps are present in 97% of cases of MND (with amyotrophic lateral sclerosis or ALS being the most prominent form of MND), and in some types of dementia.

Breaking them down, and preventing them from forming in the first place, is the subject of research worldwide.

The paper's senior author, Associate Professor Marco Morsch, says the team harnessed a process known as phase separation to observe the way the protein shifted between different states, and moved from the cell nucleus into the cytoplasm.

Associate Professor Marco Morsch, pictured above, says their breakthrough could speed the development of treatments for MND and dementia. Credit: Macquarie University

"TDP-43 is a dynamic protein that is dispersed throughout the nucleus when it is doing its work, but forms into droplets when it is not," he says.

"An easy way to think of it is as a sort of vinaigrette: shake the vinaigrette and the oil mixes with the vinegar to form an emulsion, but stop shaking and the oil settles back into droplets after a while.

"Normal TDP-43 shifts back and forth between droplet and liquid, but pathogenic TDP-43 droplets may not shift back the same way. For example, when they lose their ability to bind to RNA in the nucleus, they may be more prone to form hardened clumps in the cytoplasm."

The team is now seeking funding to use this information to develop ways of keeping TDP-43 in its liquid-like state.

Once they understand these principles better, they hope to look at modifying certain regions of the protein, or even developing anti-clumping instructions.

Zebrafish and their importance in neurodegenerative disease research

The Macquarie researchers introduced normal and pathogenic human proteins into the spinal cords of zebrafish in order to observe the proteins' behavior.

Previous studies have been able to recreate TDP-43 clumping in vitro, but this is the first time that this dynamic process has been characterized in such detail in a living vertebrate.

Also known as danios, zebrafish are a popular choice for aquarium owners. They have been instrumental in neurodegenerative disease research for many years because they have a very similar genome to humans, sharing 86% or more of our disease-causing genes.

We also share similar cell machinery and basic biological components. In humans, motor neurons control the muscles in our arms and legs, while in zebrafish, they drive the constant movement of their fins.

As adults, zebrafish can grow up to 4 or 5 centimeters, but three days after hatching, they are just a few millimeters long, and breathe by absorbing oxygen molecules from the water through their skin.

Importantly, the tiny hatchlings are also transparent, giving

neuroscientists a literal window into an operating central nervous system that is extremely difficult to achieve with other vertebrates.

The team was able to observe the juvenile zebrafish under the microscope using a gel that kept them still while allowing them to breathe.

Associate Professor Morsch says their discoveries will be important for researchers worldwide, as it will improve testing of new drugs.

"There is an enormous amount of work underway on developing potential treatments that could prevent TDP-43 from clumping, or break down aggregates that have already formed," he says.

"We have developed a platform that researchers can use to test these treatments by introducing them to the water, so the fish absorb them through their skin.

"It will be possible to see in real time whether something is working, which will make pre-clinical testing quicker and easier.

"We hope this could speed the development of treatments for diseases like MND and dementia, and help bring them to human trials more quickly."

More information: Natalie M Scherer et al, RNA-binding properties orchestrate TDP-43 homeostasis through condensate formation in vivo, *Nucleic Acids Research* (2024). DOI: 10.1093/nar/gkae112

Lighthouse.

Provided by Macquarie University