The toxic relationship between ALS and frontotemporal dementia

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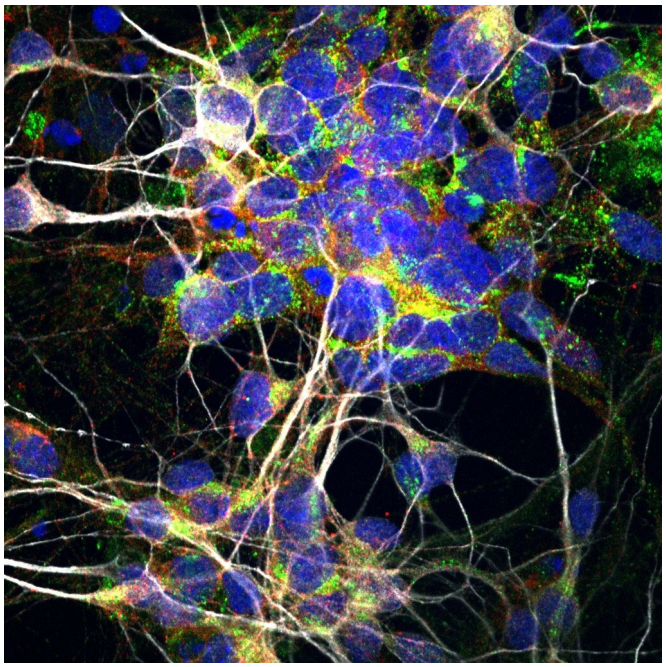

Motor nerve cells. Credit: the Justin Ichida Lab/USC Stem Cell

ALS and frontotemporal dementia (FTD) are two neurodegenerative diseases with a toxic relationship, according to a new USC Stem Cell study published in *Nature Medicine*.

In the study, Yingxiao TK Shi and Shaoyu Sebastian Lin in the laboratory of Justin Ichida describe how a mutation in a gene, called C9ORF72, leads to toxicity in nerve cells—causing 10 percent of all cases of ALS, and an additional 10 percent of FTD.

To understand how this happens, the researchers extracted blood from ALS patients carrying the C9ORF72 mutation, and reprogrammed these blood cells into the motor nerve cells that degenerate and die in the disease.

They also extracted blood from healthy patients, reprogrammed these blood cells into motor nerve cells, and used gene editing to delete the C9ORF72 gene.

Whether patient-derived or gene-edited, all motor nerve cells with the mutation had reduced amounts of the protein normally made by the C9ORF72 gene. Furthermore, by adding supplemental C9ORF72 protein, the researchers could stop the motor nerve cells from degenerating.

Through a series of experiments, the researchers revealed that the motor nerve cells use C9ORF72 protein to build lysosomes—which are cellular compartments used to engulf and break down toxic proteins and other garbage.

Without enough lysosomes, the cells accumulate two key types of garbage. The first type is a large, toxic protein produced by the mutated C9ORF72 gene itself. The second type is an excessive number of receptors, or molecules that receive signals from a neurotransmitter known as glutamate. These receptors respond to glutamate by causing the motor nerve cell to activate. Too much activation can kill a motor nerve cell—a phenomenon known as "excitotoxicity."

Guided by these discoveries, the Ichida Lab is now using patient-derived motor nerve cells to test thousands of potential drugs—with a focus on those that affect lysosomes.

"By understanding the role of lysosomes in ALS and FTD, we can better target our search for new drugs or therapies to treat these devastating diseases," said Ichida, an assistant professor of stem cell biology and regenerative medicine at USC, and a New York Stem Cell Foundation-Robertson Investigator.

More information: Haploinsufficiency leads to neurodegeneration in C9ORF72 ALS/FTD human

induced motor neurons, *Nature Medicine* (2018).
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