At last, hope for ALS patients?

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U of T researchers have found a missing link that helps to explain how ALS, one of the world's most feared diseases, paralyses and ultimately kills its victims. The breakthrough is helping them trace a path to a treatment or even a cure.

"ALS research has been taking baby steps for decades, but this has recently started changing to giant leaps," said Karim Mekhail, professor in the Faculty of Medicine's Department of Laboratory Medicine and Pathobiology. "The disease is linked to a large number of genes, and previously, every time someone studied one of them, it took them off in a different direction. Nobody could figure out how they were all connected."

Mekhail and his team discovered the function of a crucial gene called PBP1 or ATAXIN2 that's often missing in ALS, also known as Lou Gehrig's Disease. Learning how this gene functions has helped them connect a lot of dots.

"This is an extremely important finding that may help us to better understand and target the pathways involved in neurodegenerative disease," said Lorne Zinman, professor of medicine at U of T and medical director of the ALS/Neuromuscular Clinic at Sunnybrook Health Sciences Centre. "The next step will be to determine if this finding is applicable to patients with ALS."

The key lies in a peculiarity of the human genome. It starts with the DNA, the blueprint that contains all our genetic information. The DNA passes its information to the RNA, which floats off to make proteins that help run our bodies. However, without ATAXIN2, the RNA fails to float away. It becomes glued to the DNA and forms RNA-DNA hybrids, said Mekhail. These hybrids gum up the works and stop other RNA from fully forming. Pieces of half-created RNA debris clutter the cell, and cause more hybrids.

"We think the debris and hybrids are on the same team in a never-ending Olympic relay race," said Mekhail. "Over time there's a vicious cycle building up. If we can find a way to disrupt that cycle, theoretically we can control or reverse the disease."

On that front, Mekhail made a very surprising discovery: reducing calories to the minimum necessary amount stops the hybrids from forming in cells missing ATAXIN2. He and his team are studying whether a simple, non-toxic dietary restriction could be used with ALS patients, especially in the early stages or for those at risk of ALS.

Mekhail discovered the hybrids and missing genes in yeast cells and his results were published as the cover article for the July 28 edition of the journal *Developmental Cell*. Now his team is replicating this research on tissue from ALS patients – with very encouraging preliminary results.

"Within the next decade or two, I think there's going to be a revolution in treatment for ALS and all kinds of brain disease," he said. "These hybrids are going to play a role not just in ALS but in a lot of disease."

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