On the evolutionary trail of molecules that cause Lou Gehrig's disease

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What became a scientific quest for Dr. Hugo Bellen and his colleagues at Baylor College of Medicine in Houston began with trying to define the function of a protein that plays a role in the nervous system.

That led to work with similar proteins in the nerve cells of worms, fruit flies, and people and culminated in important clues about what goes wrong in the nerves and muscles of people with amyotrophic lateral sclerosis (better known as ALS or Lou Gehrig's disease), said Bellen, a professor molecular and human genetics at BCM.

In a report in the current issue of the journal *Cell*, his team and that of Dr. Michael Miller from the University of Alabama at Birmingham show how a single mutation in the human form of the VAMP-Associated Protein B (VAPB) contributes to the nerve and muscle breakdown in flies and worms, similar to ALS in humans.

The story actually begins around 500 years ago, when a Portuguese immigrant to Brazil brought along an uninvited guest – a mutation in the gene for VAPB. That mutation leads to a rare form of inherited ALS that has so far been identified in about 200 people. ALS is a devastating disease that begins in middle age and affects nerves and muscles, destroying the individual's ability to move, talk, swallow and breathe, eventually killing the person who has it. There are an estimated 30,000 people with ALS in the United States alone. It affects people of all ethnicities worldwide.

Working in Drosophila or fruit flies, Bellen and his colleagues found that when the fly VAPB gene equivalent called VAP33 is lacking, the nerve endings are abnormal, suggesting that in its normal form, the protein associated with VAP33 is important at the junction between nerve and muscle.

Then Dr. Mayana Zatz, a professor at the University of Sao Paolo, found several large Brazilian families with a gene mutation or defect in VAPB that led to ALS. (There are mutations in other genes that cause ALS as well). At that point, a postdoctoral fellow in the Bellen lab, Dr. Hiroshi Tsuda, took over.

One of the domains of VAPB is similar to a protein in C. elegans called the major sperm protein (MSP). MSP plays a major role in readying the hermaphroditic worm to reproduce. In effect, it acts as a hormone. Tsuda dubbed the part of the VAP33 protein that resembled major sperm protein the MSP domain in its honor.

They then found that somehow the MSP domain of VAPB was being secreted and circulated in the blood throughout the human body.

"The protein is cleaved, secreted and functions as a hormone," said Bellen.

In collaboration with Miller's team at UAB, they found that MSP actually binds to ephrin receptors, regulating their role in nerve cells and muscles. (Ephrin receptors affect cell interactions, mediating when cells adhere to or repel one another as well as in clustering specific receptors present on neurons and muscle cells).

The scientists' work indicates that the mutated form of the human VAPB protein accumulates in the cell's cytoplasm. As more and more abnormal protein accumulates, both normal and abnormal protein (mutant VAPB)

becomes trapped in the cell's cytoplasm. This prevents it from secreting the MSP domain, which means that the body no longer has its hormonal action. The accumulation also prevents proper protein folding, which can be toxic to neurons.

Bellen and his colleagues found that the mutant form of the protein has two effects. One, it causes the unfolded protein response that ultimately is harmful to the neurons and may affect motor function. Second, it leads to reduced secretion of MSP and a loss of the signaling mediated by ephrin receptors. They believe that these two problems work together to produce some of the key features of ALS.

Source: Baylor College of Medicine

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