Medical Xpress

Unusual alliances enable movement

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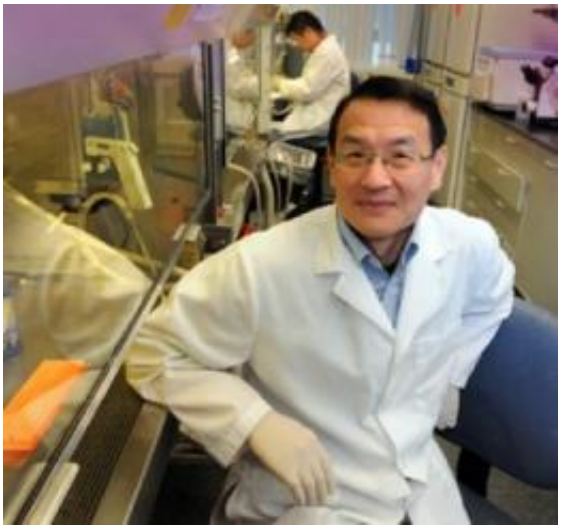

Some unusual alliances are necessary for you to wiggle your fingers, researchers report. Understanding those relationships should enable better treatment of neuromuscular diseases, such as myasthenia gravis, which prevent muscles from taking orders from your brain, said Dr. Lin Mei, director of the Institute of Molecular Medicine and Genetics at Georgia Health Sciences University. Credit: Phil Jones, GHSU Photographer

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Understanding those relationships should enable better treatment of neuromuscular diseases, such as myasthenia gravis, which prevent muscles from taking orders from your brain, said Dr. Lin Mei, Director of the Institute of Molecular Medicine and Genetics at Georgia Health

Sciences University.

During development, neurons in the spinal cord reach out to muscle fibers to form a direct line of communication called the neuromuscular junction. Once complete, motor neurons send chemical messengers, called acetylcholine, via that junction so you can text, walk or breathe.

As a first step in laying down the junction, motor neurons release the protein agrin, which reaches out to LRP4, a protein on the muscle cell surface. This activates MuSK, an enzyme that supports the clustering of receptors on the muscle cell surface that will enable communication between the brain and muscle. The precise alignment between the neuron and muscle cell that occurs during development ensures there is no confusion about what the brain is telling the muscle to do.

A missing piece was how agrin and LRP4 get together.

A study published in the journal *Genes & Development* shows that in the space between the neuron and its muscle cell, agrin and LRP4 first form two diverse work teams: each team has one agrin and one LRP4. The two teams then merge to form a four-molecule complex essential to MuSK activation and to the clustering of receptors that will receive the chemical messenger acetylcholine on the muscle cell.

It was expected that the two agrins would get together first then prompt the LRP4s to merge. "This is very novel," said Mei, and an important finding in efforts to intervene in diseases that attack the neuromuscular junction.

Mei and Dr. Rongsheng Jin, neuroscientist and structural biologist in the Del E. Webb Neuroscience, Aging and Stem Cell Research Center at Sanford-Burnham Medical Research Institute in La Jolla, Calif., are co-corresponding authors of the study.

Myasthenia gravis, which paralyzes previously healthy individuals, targets these protein workers. The condition, which can run in families, likely results from a process called mimicry in which the immune system starts making antibodies to the workers, which it confuses with a previous viral or bacterial infection. The majority of patients have antibodies to acetylcholine receptors and a smaller percentage have antibodies to MuSK. Most recently, GHSU researchers also helped identify LRP4 as an antibody target.

The scientists already are looking at the impact of the antibodies on the LRP4 complex. Understanding its unique structure is essential to designing drugs that could one day block such attacks. "Prior to this we had no idea how they interacted," Mei said.

In addition to providing new information on muscle diseases, this study might also have a far-reaching ripple effect in the field of neuroscience.

"This is just the beginning," says Jin. "Now that we know more about how signals are transferred during the formation of neuromuscular junctions, we can start looking at how a similar system might work in brain synapses and how it malfunctions in neurodegenerative conditions like Alzheimer's and Parkinson's diseases. If we can figure out how to trigger the formation of new brain synapses, maintain old synapses, or simply slow their disappearance, we'd be much better equipped to prevent or treat these diseases."

To reveal the novel mechanism, researchers used a technique known as X-ray crystallography, which produces 3-D "pictures" of protein at the atomic level using powerful X-ray beams.

Provided by Georgia Health Sciences University