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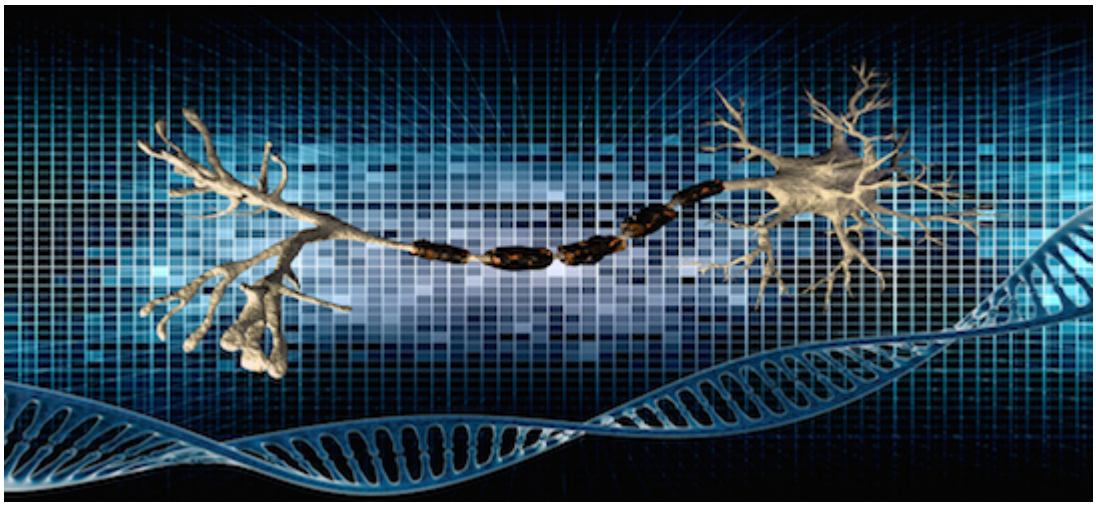
Genetic Discoveries in Spinal Nerve Cells Hold Promise for Treating Some Neurodegenerative Diseases

Researchers at the University of Miami Miller School of Medicine took three big steps that could someday help people with neuromuscular diseases including amyotrophic lateral sclerosis, spinal muscular atrophy, Charcot-Marie-Tooth disease, and hereditary spastic paraplegia.



Armed with the knowledge that motor neurons in the spine – particularly the axons of these cells – dysfunction in certain inherited neuromuscular conditions, Mario Saporta, M.D., Ph.D., MBA, assistant professor of neurology and human genetics and director of the Charcot-Marie-Tooth Association (CMTA) Center of Excellence at the Miller School, and colleagues set out to learn more.

First, Dr. Saporta and colleagues grew motor neurons using induced pluripotent stem cells (iPSCs) derived from three

healthy volunteers. This relatively new technology allowed them to overcome a historical research obstacle – an inability to study nerve cells from a living human.

"The use of human, stem-cell derived motor neurons provides a unique opportunity to investigate this process and its role in health and disease," said Dr. Saporta.

Next, they figured out how these motor neurons orchestrate all their functions under normal conditions. In so doing, they became the first researchers to map the entire "transcriptome," a complete set of genetic instructions in the axons of these cells. This transcriptome helps the motor cell axons with mitochondrial function, microtubule-based transport, and other vital tasks.

The third step, once the researchers gained a clear picture of which gene expressions are essential, was determining what goes awry for people with neuromuscular disorders. Their findings were featured as the cover story in the September 2018 issue of *Experimental Neurology*.

Dr. Saporta, lead author Renata Maciel, Ph.D., MBA, and their colleagues were able to distinguish gene expression among different parts of the neuron, such as the axonal component versus the somatodendritic compartment. This allowed them to appreciate the importance of "local" activity.

They also narrowed down the more than 19,000 genes detected in these two compartments. They identified the 1,000 genes with the highest average expression in each and also discovered the compartments shared 859 of these genes in common. This left the investigators with about 150 distinct genes to assess

further.

The research also confirms the role of messenger RNA (mRNA) in normal axon functioning.

“We demonstrated that approximately 13 percent of total mRNA are enriched in the axonal compartment of human iPSC-derived motor neurons, in accordance with recent studies using rat motor neurons and human glutamatergic cortical neurons,” said Dr. Saporta.

The mRNAs help cells translate the instructions from the genetic transcriptome into proteins that carry out various tasks. At the axons, these mRNAs are essential for axonal outgrowth and regeneration, for example.

Again, the local angle is important.

“The identification of locally expressed mRNA in the axon of motor neurons is extremely important for the better understanding of normal axonal function and its role in neurological diseases,” said Dr. Saporta. “Also, discovery of the transcripts enriched in the axons may create a platform for drug discovery using those genes as therapeutic targets.”

All of these research advances were accomplished at the Miller School, demonstrating the institution’s leading role in neurological disease modeling with iPSC and next-generation RNA sequencing.

The next phase of the research is underway. Dr. Saporta and colleagues are looking at motor neurons derived from patients with inherited neuropathies and comparing their axonal transcriptome to neurons from healthy controls. Additionally,

they are developing high-throughput drug-screening platforms for drug development for genetic neuropathies using human iPSC-derived motor neurons.

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