Advanced nerve cell system could help cure diabetic neuropathy, related diseases

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Multiple sclerosis, diabetic neuropathy, and other conditions caused by a loss of myelin insulation around nerves can be debilitating and even deadly, but adequate treatments do not yet exist. That's in large part because of deficiencies in model research systems. In an upcoming issue of the journal *Biomaterials*, a UCF team addresses this problem with a report on the first lab-grown motor nerves that are insulated and organized the same way they are in the body.

The group's model system, along with further advances now within reach, could dramatically improve understanding of the causes of myelin-related conditions, and enable discovery and testing of new drug therapies.

Nerve malfunctions, or neuropathies, involve a breakdown in the way the brain sends and receives electric signals along nerve cells. In mammals, these signals are able to travel long distances because of breaks in their myelin insulation called nodes of Ranvier, each of which chemically boosts the signal, allowing it to travel to the next node. "They're like power station relays," says James Hickman, a bioengineer at UCF who led the new research, which achieved the first successful nodes of Ranvier formation ever on motor nerves in a lab culture, among other advances.

Multiple sclerosis (MS), diabetic neuropathy, Guillain-Barré syndrome, and other demyelinating conditions are caused when nerve signals can't travel their normal path from node to node due to myelin breakdown.

Within the brain and spinal cord, where the damage from MS occurs, cells called oligodendrocytes surround the nerves and produce this critical myelin. In the peripheral nervous system, where the problems associated with diabetic neuropathy originate, Schwann cells perform this function.

Due to the famous complexity of the nervous system, studying demyelinating neuropathies has proven exceedingly challenging. "People have basically been stuck doing work in animal models, and they don't work very well," says Hickman.

Researchers have long recognized the need for lab-grown motor nerve cells that myelinate and form nodes of Ranvier so that, under controlled laboratory conditions, they can zero in on the causes of and solutions for demyelination. Researchers have achieved Myelination and nodes of Ranvier formation with sensory neurons, but accomplishing the same task with the motor nerves that play more critical roles in some diseases has remained an elusive goal.

Working with Hickman, UCF graduate student John Rumsey was able to accomplish this very feat, though, for the first time. "It was exciting because it was totally unexpected," says Hickman. The key to their surprising successes is one that other researchers in the field may find surprising, and one that makes their new model system better suited to advancing neuropathy research than anything ever before available.

"It was such a long shot I didn't believe the results at first," says James Hickman, leader of the team that developed the new model, "It took two months before I was convinced we had what he had."

Accomplishing the Complex by Keeping It Simple

Nerve cells in the body grow in two strikingly different environments. In

the relatively open peripheral nervous system, cells are exposed to blood and other fluids that contain high protein concentrations and copious other constituents in variable concentrations. In the isolated central nervous system the spinal cord and brain are instead surrounded by cerebrospinal fluid that is nearly sterile, with only a trace of protein.

Especially during initial experiments, researchers typically grow cell cultures in serum isolated from cow or human blood, which effectively promotes growth. But serum also complicates studies by making it difficult to discern the relative impacts of different chemical components. Once growth in serum is accomplished, researchers will often attempt culturing in a serum-free medium, especially for drug discovery work where serum's components make it difficult to isolate the effects of a drug.

Past research aimed at getting Schwann cells to myelinate motor nerves, or motoneurons, had followed this pattern, but the Hickman group began serum-free. They had already developed techniques for growing various nervous system cells in serum-free media, including motoneurons, so they decided to attempt myelination using the growth medium they have spent years tweaking.

Hickman hypothesizes that while serum contains components that promote cell growth it may also contain some that inhibit growth. Therefore, starting with a serum-free medium, rather than ending there, may well have led to the team's success.

What's Next: Drug Discovery Potential

Among numerous goals, the Hickman team plans to use their new model system to explore the origins of diabetic neuropathy, a condition that can cause a range of complications from digestive problems to pain in the limbs.

Currently researchers have incomplete understanding of even the basics of how demyelination occurs. So, one line of experiments will be to treat cultured motoneuron systems with factors found in high concentrations in diabetics, such as fatty acids or cholesterol. This will allow them to identify what causes myelin to degrade, which could in turn help them identify targets for new drug therapies that could also be tested using the model. Other planned experiments will focus on how electrical signals travel through myelinated and unmyelinated nerves to reveal how nerves malfunction.

"Being able to study these fully developed structures means we can really start looking at these things in a way that just wasn't possible before," says Hickman.

Though the myelination work has involved embryonic rat cells, the Hickman team was also the first to culture adult motoneurons and hopes to eventually extend myelination work to those as well. Such an advance would, for instance, offer a more realistic model for spinal cord injury research. Effective treatment of spinal injuries would be dependant on remyelination of adult motoneurons, including nodes of Ranvier formation. If that can be achieved in the lab, it will be a sign of hope that treatments could be developed to accomplish the same in patients.

Another major goal for the Hickman group will be to induce myelination by the oligodendrocytes that insulate the central nervous system motoneurons involved in multiple sclerosis, a goal preliminary experiments suggest may be achievable.

Even without that advance, the Schwann cell myelination model could reveal new drug treatment possibilities for multiple sclerosis based on improved understanding of demyelination. For the roughly 400,000 Americans and countless others around the globe suffering from this and other related diseases with limited treatment options, all these

possibilities are sure to be welcome news.

Source: University of Central Florida (news : web)