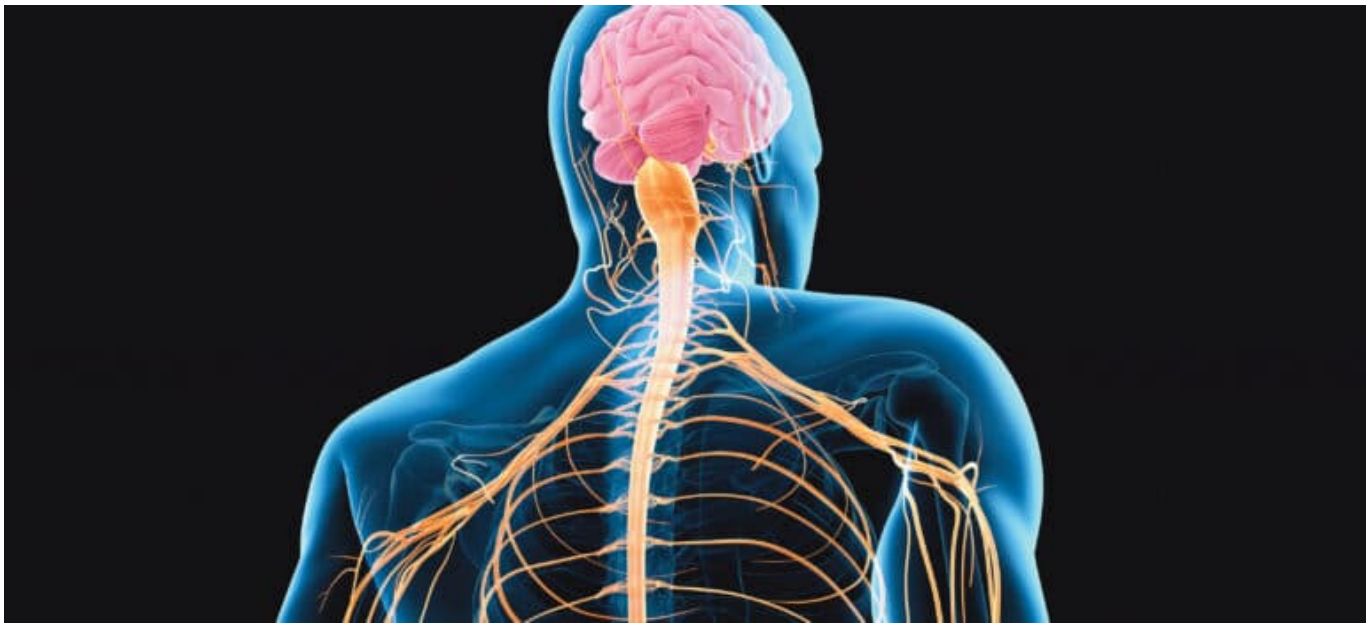
Halting nerve damage



Study focuses on nerve cells.

by Mary E. King, PhD

A new study has provided more insight into the damage to nerve cells that causes many symptoms of multiple sclerosis and has developed ways to identify therapies that could potentially halt the damage.

Katerina Akassoglou, PhD, and her team, Jae Kyu Ryu, PhD (left), and Andrew Mendiola, PhD, are working to find therapies that could halt the damage to nerve cells that cause MS symptoms.

One of the hallmarks of MS progression is damage to nerve cells in the brain and spinal cord. Nerve cell injury causes a variety of symptoms such as numbness, tingling, difficulties walking, cognitive changes and other issues that affect overall quality of life as well as regular daily activities. While some nerve damage is caused by abnormal immune response that causes inflammation, with critical roles played by T and B immune cells, additional factors have also been implicated, particularly in progressive MS.

Katerina Akassoglou, PhD, senior investigator at Gladstone Institutes and professor of neurology at the University of California, San Francisco, and her team recently provided a better understanding of the type of cells and the cellular activities that cause this damage. The team developed a way to identify drugs that could limit or block it.

Akassoglou, Andrew S. Mendiola, PhD, a National Multiple Sclerosis Society Postdoctoral Fellow in Akassoglou's laboratory, and colleagues described how specific immune cells that typically reside in the brain are activated to release reactive oxygen species (ROS), toxic substances that damage nerve cells and myelin in a process called oxidative injury. The researchers refer to these cells as "toxic immune cells." The researchers created a directory of the toxic immune cells in the spinal cord that contribute to killing nerve cells, Akassoglou says. Then they developed laboratory procedures to help them identify known therapeutic agents that might stop or slow the process. They found that one of those agents stops immune cells from producing toxic substances and prevents nerve damage in an animal model of MS.

Like much of today's medical research, this project involved a large number of collaborators; in this instance from the Gladstone Institutes, the UCSF Weill Institute for Neurosciences and the Small Molecule Discovery Center (SMDC) at UCSF and Baylor College of Medicine. Mendiola and Jae Kyu Ryu, PhD, assistant adjunct professor of neurology at UCSF and also a former MS Society postdoctoral fellow in Akassoglou's laboratory, are co-lead authors of the April 2020 paper in Nature Immunology that details the procedures and results.

Mendiola explains that the researchers started with developing a new specialized technology to identify toxic immune cells that release the substances that damage nerve cells and analyze their genetic codes. They were able to determine which of the cells' genes are "on" or "off" during this process. They hoped this process would help them identify treatments that could target these specific genes and, in this way, slow or stop the damage to nerve cells in MS.

"Surprisingly," Mendiola emphasizes, "we discovered that only one small group of cells — one subtype of a commonly occurring brain cell called microglia — are the 'toxic cells' responsible for most of this damage." The work was done initially in mouse models of MS called EAE, and it was confirmed in human brain tissue from autopsies of individuals with progressive MS.

The next step was to use a screening procedure in microglia cells in the laboratory. They

checked 1,907 chemicals that researchers identified as potentially able to block the genes they think are involved in producing the harmful substances. Further testing narrowed the list to 128 promising chemicals. They honed in on one particular agent, acivicin, to test in animal models of MS. The screen was funded by a Society FastForward grant to Akassoglou and Michelle Arkin at UCSF SMDC.

“Acivicin is a drug that has been used in cancer but not MS,” Mendiola explains. “One way it may help stop the nerve damage is by interrupting the normal breakdown of the natural antioxidant glutathione that is made in the brain.” The antioxidant has chemical properties that may allow it to destroy the harmful substances released by toxic immune cells before nerve cell damage can occur.

Ryu and his colleagues tested acivicin and were excited to discover that it prevented the development of MS-like symptoms in two different EAE mouse models. First, acivicin blocked the development of EAE in genetically predisposed mice that had not yet developed symptoms of the disease. Secondly, it also prevented relapse in anothegroup of mice that had a chronic, longer-term form of EAE. In this experiment, the control mice, which did not get acivicin, got sicker, but the mice receiving acivicin did not.

Acivicin itself may not be a promising therapy in MS because of its known severe side effects when used as a cancer treatment. However, the work has demonstrated an exciting new target for the development of new safe therapies to preserve glutathione and block oxidative injury in MS. The team also discovered other small molecules targeting pathways relevant to MS to test in future studies. Their study also introduced a novel approach to identify agents that can protect nerve cells and could slow or stop the progression of MS.

Both scientists are excited about the possibilities of future research, including finding ways to selectively eliminate toxic immune cells from the brain and identifying safer compounds that block oxidative damage to nerve cells. Akassoglou also stresses that all of the data for genes and drugs from the recent study are available in an open-source format so that the research community as a whole can use these novel approaches to target this type of nerve damage not just in MS but in other neurodegenerative diseases as well.

Says Mendiola of their work: “I’m very passionate about this line of research. We are trying to look at this aspect of MS, the development of nerve damage in progressive disease, in a new light.”

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