Research Update

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HELP OR HINDRANCE?

Do motor neurons die in ALS because the immune system is attacking them? With some cellular detective work, Dr. Charles Krieger and Dr. Fabio Rossi hope to finally answer the question.

It's an idea that began to slowly emerge over a decade ago and is now rapidly gaining ground: ALS is, at least in part, an autoimmune disease. Canadian researchers have contributed to this theory's development, and now a brain researcher and a stem cell expert are collaborating in British Columbia to put the idea directly to test.

In the nervous system, immune cells called microglia can perform one of two functions when a neuron is sick or dying: they can go to the affected site and help the neuron, or they can kill the neuron to limit damage and prevent the spread of illness. In ALS, there are changes to both neurons and microglia. Over recent years, evidence has gathered to suggest that in ALS, the microglial cells might kill an initial neuron, and that they don't stop there. Rather, it seems, they turn their attention to neighbouring neurons, killing them also, and the damage spreads progressively.

By fluorescent-labelling the immune cells that become microglia and injecting them into ALS mice, Dr. Charles Krieger, a neurologist at Simon Fraser University, and Dr. Fabio Rossi, stem cell expert at the University of British Columbia, are hoping to track the suspect microglia to the scene of the crime - the site of neuronal death.

"I'm very excited by this collaboration, says Krieger. "My interest is in ALS and Dr. Rossi's is in cell transplants, so I really couldn't do this without him."

"Nobody really knows if the microglia are good players or bad players," says Rossi. "We think we have the genetic tools now to directly show if that is the case or not. If we find out they aren't the bad guys, we will try to hijack the microglia to deliver neurotrophic factors to that area specifically, since they are very good at getting into the disease area." Neurotrophic factors are known to support neurons and to help keep them alive.

The transgenic mice, called so because they carry a human gene known to cause a heritable form of ALS, are injected with the fluorescent immune cells, which at this stage are called monocytes.

"The monocytes turn into microglia to pass from the blood into the nervous system," says Krieger, describing the transformation: "They may have to alter their properties to go from an environment (the bloodstream) where they are primarily this fluid-borne rounded cell, to one (the nervous system), where they have to kind of crawl their way through a dense jungle of neurons and glial cells that do not have a fluid-filled environment. It requires a change of outfit."

The researchers will watch to see if the fluorescent monocytes will circulate in the blood stream and then go to the affected site in the nervous system of the ALS mice. "What we are interested in knowing is why they are triggered to come in, and whether the act of their entry is a good thing or a bad thing," says Krieger.

The involvement of the immune system has been, in part, the rationale for using medications such as minocycline to treat ALS.

Minocycline has anti-inflammatory effects which may act specifically on microglia. The pair hope this new research will shed more light on the immune involvement and how to control it. "If the microglia are not helpful, we have to ask how we can keep them out," says Krieger. "I think it would at least allow us to pursue a novel and more specific type of immune therapy."

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