Stanford study first to show antibodies involved in nerve repair in injuries

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Antibodies -- warrior proteins the immune system makes to defend the body against invading pathogens such as viruses and bacteria — have a gentler side nobody knew about until now: They function not only as soldiers but also as nurses. And researchers at the Stanford University School of Medicine now think antibodies' absence in the central nervous system (the brain and spinal cord) may be a key part of the reason why nerve damage there doesn't get naturally repaired in humans. That insight could someday lead to new treatments for stroke and spinal-cord trauma.

In a new study conducted in mice, to be published online June 14 in Proceedings of the National Academy of Sciences, the Stanford scientists show for the first time that antibodies are critical to the repair of nerve damage to the peripheral nervous system — nervous tissue that extends outside the brain and spinal cord, such as the sciatic nerve, where circulating antibodies have access. The study also shows that some, but not all, antibodies get the job done. Harnessing those proteins' unanticipated nurturing qualities may lead to new ways of repairing damage from stroke or spinal-cord injury, as well.

"Nobody has known why, but nerve cells in the central nervous system fail to regenerate after injury whereas those in the peripheral nervous system regenerate robustly," said senior study author Ben Barres, MD, PhD, professor and chair of neurobiology. So his group was intrigued by one major difference between the two nervous systems: Antibodies, which are large bulky proteins, have limited access to the brain and

spinal cord (these organs are surrounded by an interface called the blood-brain barrier or, in the spinal cord, the blood-spinal cord barrier), while they have ready access to the peripheral nervous system.

Nerve cells convey electrochemical impulses over long distances by means of long, tubular projections called axons. These axons are typically wrapped in an insulating layer of a fatty substance called myelin.

"After nerve injury, the degenerating myelin downstream from the injury is rapidly cleared in the peripheral, but not the central, nervous system," said Barres. "In fact in an injured human brain or spinal cord, the degenerating myelin just sits there for the rest of the person's lifetime. But after injury to, say, the sciatic nerve, the degenerating myelin is cleared within a week or less."

The two first authors, Mauricio Vargas, MD, PhD, a former student in Barres' lab, and Junryo Watanabe, PhD, a postdoctoral researcher in the lab, wondered whether antibodies to components of degenerating myelin might play a role in that clearance. The researchers obtained mutant laboratory mice that can't make antibodies, and demonstrated that, in those mice, repair of injury to the sciatic nerve is substantially impeded, as is the removal of degenerating myelin downstream from the injury site. Simply injecting the injured mutant mice with antibodies from healthy, uninjured ones restored both myelin removal and sciatic-nerve repair capability in the mice.

While antibodies have been found to play a role in the disposal of aging red blood cells, this is the first time they've been implicated in injury repair, said Vargas, now in his internship at White Memorial Medical Center in Los Angeles pending the start of his residency in ophthalmology at UCLA.

What's more, the investigators threw light on the way in which this happens. "We showed that antibodies grab onto degenerating myelin downstream from the site of the nerve injury, coating the myelin and tagging it for clearance by voracious immune cells called macrophages," Vargas said.

The word macrophage roughly translates from Greek as "big eater." These roving gourmands are especially prone to gobble up antibody-tagged bacteria and diseased cells. "It's analogous to spreading cream cheese on a bagel," said Vargas.

Using various standard laboratory tools, including special staining techniques, the study's authors observed that macrophages do indeed chew up antibody-tagged degenerating myelin downstream from the nerve-injury site. Myelin clearance in the antibody-lacking mice was substantially enhanced when antibodies from healthy mice were provided.

Surprisingly, it made no difference whether the antibodies came from normal mice that had suffered similar injuries or mice that had suffered none. This suggests that the antibodies binding to degenerating myelin and flagging it for demolition by squads of macrophages are already present in uninjured mice, rather than summoned into service only after injury. These "off-the-shelf" natural antibodies save the week or two that it would have taken the body to generate the more sophisticated, precisely shaped antibodies that are produced in response to a particular viral or bacterial infection.

In an additional experiment, the Barres team injected the injured mice with a dose of an antibody that specifically targets a protein known to occur only on myelin. Doing so restored nerve-injury repair, whereas administering antibodies that bind to targets not associated with myelin didn't help. This proved that not just any antibodies, but rather

antibodies that associate with degenerating myelin, are the ones that expedite nerve repair in the peripheral nervous system.

It wouldn't be helpful if naturally occurring antibodies were unable to distinguish between working and worthless myelin — this could result in debilitating autoimmune disease. But, Barres said, degenerating myelin has structural features on its surface that are quite different from those exposed to the immune system on the surface of functioning myelin.

Although these findings all involve the peripheral nervous system, they offer a tantalizing hint as to a possible way to instigate repair to damaged nerve cells in the central nervous system after, say, a stroke or spinal cord injury. "One idea," said Barres, "would be to bypass the blood-brain barrier by delivering anti-degenerating-myelin proteins directly into the spinal fluid. We're hoping that these antibodies might then coat the myelin, signaling to microglia — macrophages' counterparts in the central nervous system — to clear the degenerating myelin." That might, in turn, jump-start the regeneration of damaged nervous tissue, he added.

"This is really important, elegant work," said Zhigang He, PhD, associate professor of neurology at Harvard Medical School whose lab focuses on the intrinsic regenerative ability of nervous tissue and who did not participate in the study but is familiar with it. "Everybody's trying to understand what accounts for the difference between the capacities for repair in the peripheral versus the central nervous system. Now we have a possible mechanism, so we can start to think about some kind of strategy to speed up myelin clearance in the brain."

Provided by Stanford University Medical Center

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