

## Dangerous foe or tiny protector? Understanding microglia

**M**icroglia are unique immune cells; they actually live in the brain. For some time, researchers have studied how these cells welcome the immune attack on the brain and spinal cord of people with MS, and even spur it on. But microglia might have another face to show—one that actually **protects** nerve cells. National MS Society grantees are teasing out the roles of these two-faced cells.

Researchers investigating these paradoxical powerhouses are already finding the potential for novel strategies to treat people with MS.

### Keeping the home fires burning

In a healthy immune system, microglia help to keep the brain and spinal cord safe from infectious agents. The immune system proteins that protect the rest of the body are too large to cross the blood-brain barrier (BBB, the lining of cells that protects the brain) so it is microglia that must recognize invaders and initiate the immune defense. They have to move quickly, so they are structured to detect even the smallest sign of danger.

Unfortunately, many immune system defenders switch to the offense in the immune attack

in MS. In MS lab models, it is believed that microglia get involved early, acting as “antigen-presenting cells”—the cells that serve up triggering molecules to immune T cells and spur on the attack. In fact, Eugene D. Ponomarev, PhD, and colleagues (Blood Center of Wisconsin, Milwaukee) showed that microglia were activated even before disease symptoms appeared in mice with the MS-like disease EAE. **The Journal of Neuroscience Research** 2005;81(3):374–89

The role of microglia becomes further clarified when they are deactivated. Frank Heppner, MD (University Hospital Zurich) and colleagues including National MS Society Harry Weaver Neuroscience Scholar Burkard Becher, PhD, designed a mouse model in which they could paralyze microglia to determine their impact on EAE. When microglia were unable to act, symptoms improved and inflammation was reduced in the brain and spinal cord. **Nature Medicine** 2005;11(2):146–52

Some researchers are investigating how microglia might be drawn into the destructive process in MS by focusing on blood proteins that leak into the brain when the BBB breaks down. Katerina Akassoglou, PhD (University of California, San Diego),

and colleagues have uncovered evidence that one such molecule called fibrinogen, known as a blood clotting factor, directly activates microglia. They have developed a method of inhibiting fibrinogen in mice without compromising its clotting capabilities.

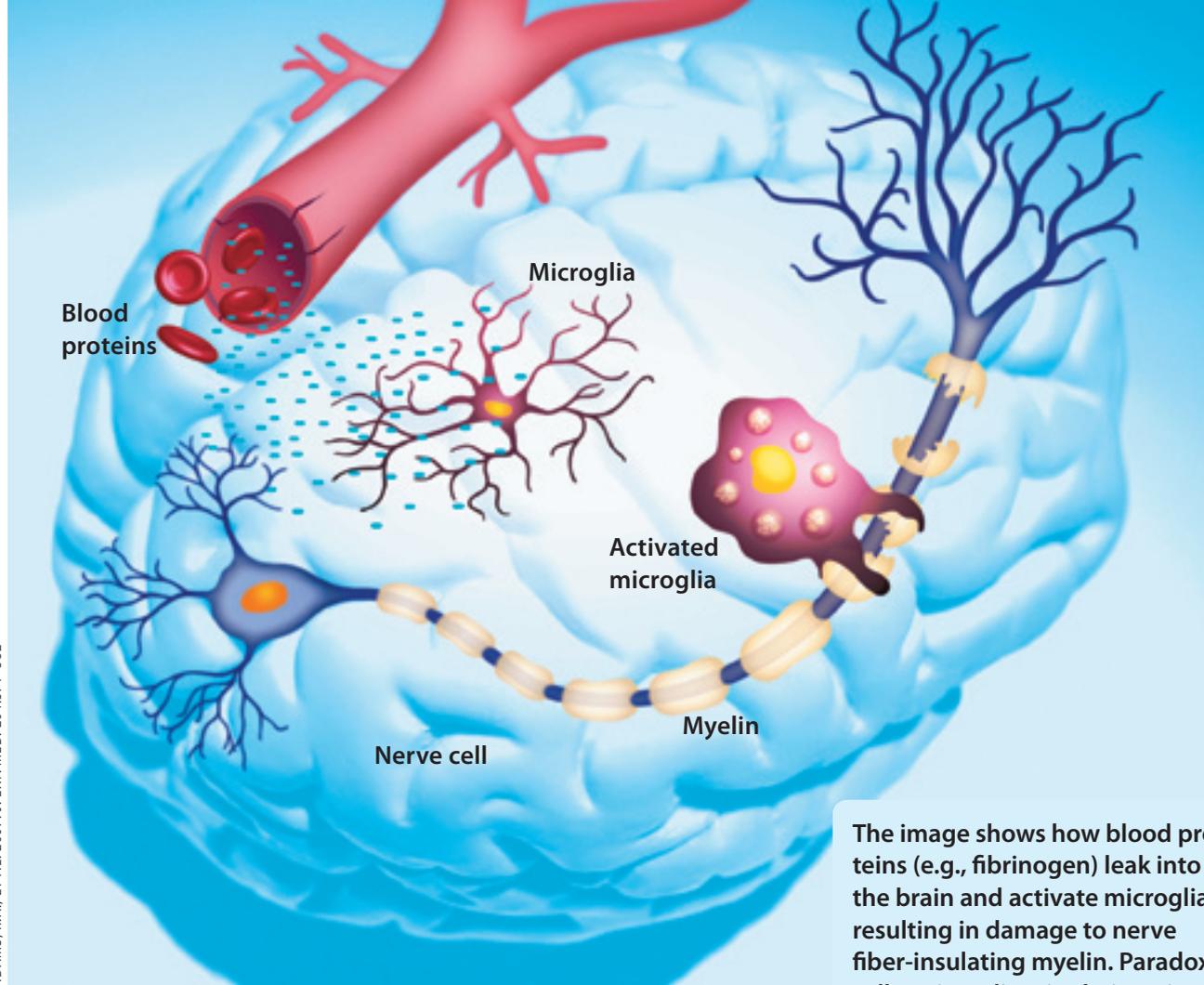
By inhibiting fibrinogen in mice with EAE after the first attack, they were able to decrease the activation of microglia, and subsequent damage to nerve fiber-ensheathing myelin (a main target of the MS attack) diminished dramatically. The treated mice recovered faster as well, and didn't experience further relapses. Further study is necessary to translate these findings into a potential treatment strategy for people with MS.

**The Journal of Experimental Medicine** 2007;204(3):571–82

### Keeping an eye on neurons too?

As is typical for our intricate immune system, microglia may not be all bad. Recent studies showed that microglia actually protected nerve cells after stroke in mice. Bruce Trapp, PhD (Cleveland Clinic Foundation) and colleagues, including Society-funded postdoctoral fellow Wadid Jalabi, PhD, observed that when stimulated by an immune response, microglia in mice become activated and physically surrounded the nerve cell body. **Glia** 2007;55(4):360–8

Dr. Trapp's team has since reported evidence of nerve cell regeneration in chronic lesions



The image shows how blood proteins (e.g., fibrinogen) leak into the brain and activate microglia, resulting in damage to nerve fiber-insulating myelin. Paradoxically, microglia—in their activated form, in which they surround nerve cells—may somehow **protect** these cells.

(areas of tissue damage) in brain tissue samples from people with MS. In 15 chronic lesions, nerve cells were increased by 72% compared with neighboring brain regions. Interestingly, one of the things that was different about these chronic lesions was evidence of an increase in activated microglia. **Brain** 2008;131(Pt 9):2366–75

So what does this mean for MS treatment? How can we stop microglia from over-reacting in terms of their immune system function, without causing them to under-react in terms of protecting nerve cells?

Radmilla Filipovic, PhD, and Nada Zecevic, MD, PhD (University of Connecticut

Health Center, Farmington) were funded to look at a unique approach to this question. The antibiotic minocycline has been shown to inhibit the activation of microglia and yet protect nerve cells from loss in animal models of MS. Small clinical trials in people with relapsing-remitting MS suggested decreased tissue damage, but the data were limited on the effects of minocycline on human nerve cells.

Drs. Filipovic and Zecevic studied whether minocycline would protect human nerve cells grown in lab dishes. They reported that the drug inhibited the activation and proliferation of microglia, but spared nerve cells. In particular, these neuro-

protective effects were noted when a specific enzyme—ERK 1/2—was blocked from signaling. Further studies are needed to confirm these findings, and to determine if they hold true in the current, larger-scale clinical trial of minocycline in people with MS. **Experimental Neurology** 2008 May;211(1):41–51

The two faces of microglia might seem confusing, but researchers investigating these paradoxical powerhouses are already finding the potential for novel strategies to treat people with MS.