

Restoring Astrocytes' Protective Nature

Scientists are looking for ways to control the course of this sometimes wayward support cell.

THE MOTOR NEURONS THAT CONTROL MUSCLES CAN'T SURVIVE ON THEIR own. They rely on a complicated relationship with another member of the nervous system, cells called astrocytes. ¶ Astrocytes act as sheltering mothers to motor neurons, providing nutrition when needed, keeping their chemical world in balance, protecting them from outside invaders, even physically supporting them. “The motor neurons are very demanding cells,” explains Rafael Radi, an HHMI international research

scholar. “They demand from the astrocytes the right growth factors at the right time. Otherwise, they die.”

Defective astrocytes can turn against the motor neurons, however, and are at the root of the muscle-wasting disease amyotrophic lateral sclerosis (ALS), according to recent findings by Radi and his team at the Universidad de la República in Uruguay. Their work, published April 16, 2008, in the *Journal of Neuroscience*, agrees with findings published in *Nature Neuroscience* last year by a competing research group from Columbia University.

Even more important, Radi's team has identified a drug that might guide astrocytes back to their nurturing role, a move that they hope can slow or stop the disease's progress. ALS—sometimes called Lou Gehrig's disease—has no treatment. “You cannot grow new motor neurons, but you can prevent new ones from dying,” Radi says. “If our

hypothesis is right and we can rescue astrocytes, then they would not kill the motor neurons” and the muscles would be saved.

Chemical Cell Killer

Radi didn't set out to uncover the cellular secrets behind ALS. His lab studies how immune system cells called macrophages fight off bacteria and other pathogens by using the toxic chemical peroxynitrite. But Radi and his colleagues have found that peroxynitrite has a darker side, which emerges when cells malfunction. They have linked the cell-killing chemical to cardiovascular disease,

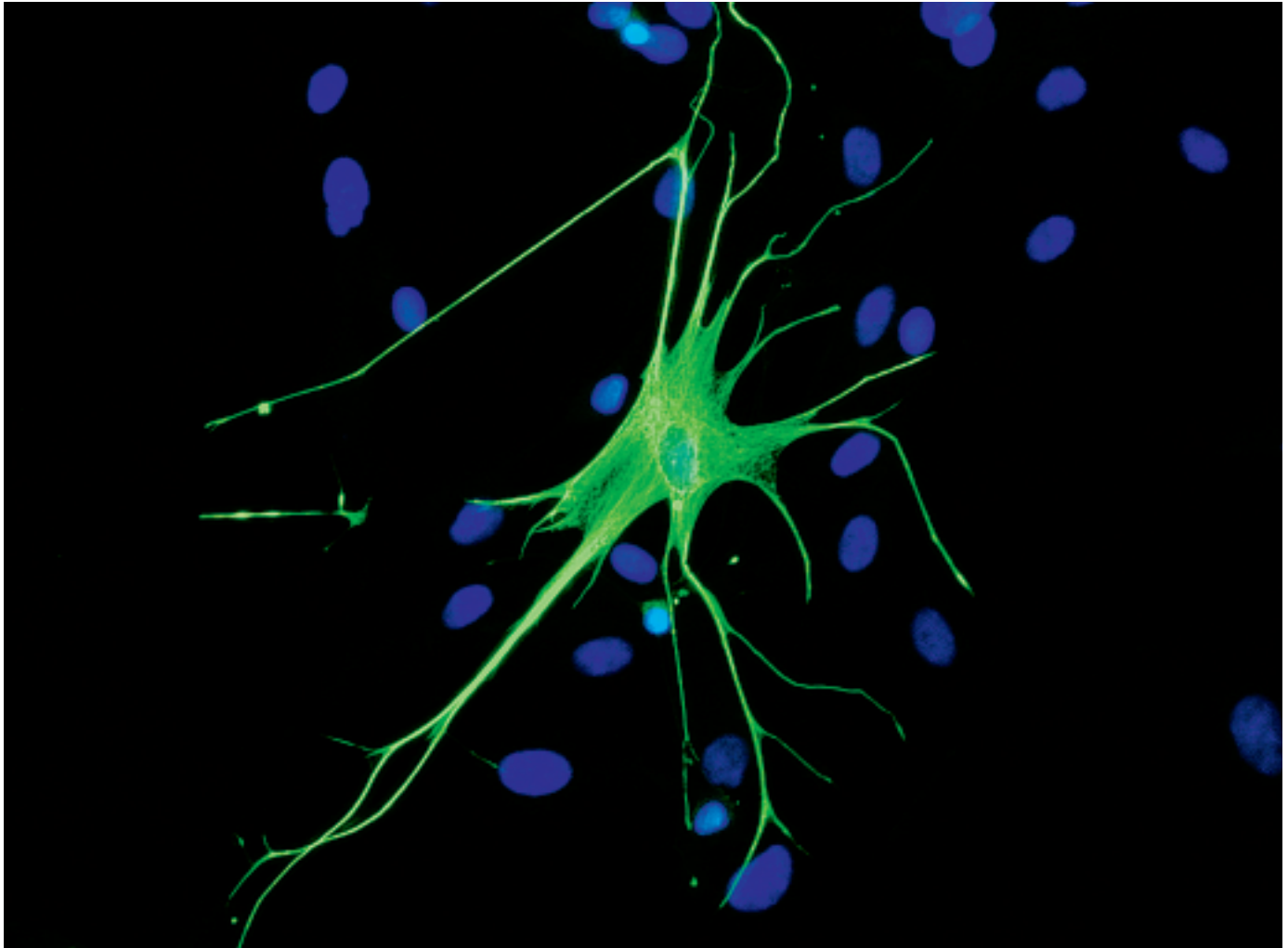
high blood pressure, and neurodegenerative conditions such as Alzheimer's disease. “In infectious diseases, it is a good guy because a macrophage is generated to kill parasites and bacteria,” Radi explains. “But if formed in neurons or astrocytes or vascular endothelial cells, peroxynitrite will harm you. You want to keep this guy under control.”

In the mid-1990s, Radi's colleague Joseph Beckman, then at the University of Alabama at Birmingham, postulated that peroxynitrite could kill neurons, which would make it a key player in ALS. But Radi's team knew it wasn't produced only by the motor neurons; damage to motor neurons alone wasn't enough to cause muscle wasting symptoms in rat models of ALS. “Another cell was participating,” Radi says. “The most immediate cell we started looking at was the astrocyte.”



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RAFAEL RADI



Motor neurons rely on astrocytes—like the one shown here in green—for nutrition, protection, insulation, and support. When astrocytes are defective, they can turn against the neurons they’re meant to protect.

Because astrocytes play such a key role in the life of motor neurons, Radi and his colleagues searched for a defect that could cause astrocytes to turn from nurturers into killers. They already knew that oxidative stress—a condition in which highly reactive chemicals overwhelm a cell—could cause astrocytes to change.

Looking closer, the team saw that oxidative stress caused the astrocyte’s internal engines, the mitochondria, to fill up with misfolded proteins, triggering a chemical chain of events within the overwhelmed mitochondria that converts normally harmless nitric oxide into peroxynitrite. “It is possible that this peroxynitrite formation in the astrocytes participates in signaling the death of the adjacent motor neuron,” says Radi.

To investigate whether these dysfunctional mitochondria caused motor neuron death—and ALS—Radi’s team looked for a drug that could restore balance in the astrocyte. “We thought that if we could send specific molecules to the mitochondria to eliminate the oxidative stress, we could reverse this neurotoxicity,” he explains. They gave specially designed antioxidants that target the mitochondria to rats with a form of ALS. It appeared to work: the drug restored mitochondrial function and spinal cord damage was significantly delayed in the animals treated with the mitochondria-targeted antioxidants compared with untreated rats, and peroxynitrite disappeared.

There is much Radi’s team still doesn’t understand about this process, most impor-

tantly how the mitochondria-targeted antioxidants reverse oxidative stress and slow progress of the disease. They also don’t know how the rat models of ALS will respond to long-term trials of the targeted antioxidants—so far, treatment time has been less than a week because the mitochondria-targeted antioxidant is custom-made and hard to get. But their research partners are scaling up production of the drug and they hope to start larger animal trials soon.

Radi expects that, whatever they find, peroxynitrite will play an important role. “I think peroxynitrite is a central mediator of cell death,” he says. “It can kill pathogens, but it can also kill your own cells.” ■

—ANDREA WIDENER