

Glia: The Brain's Other Cells

No longer dismissed as just the glue that holds the brain's neurons together, glial cells now appear to nourish, protect, and listen to neurons. They may even talk back

In 1980, Adrienne Salm, then a fledgling neuroscience graduate student at Michigan State University, attended her first Society for Neuroscience meeting. Participants by the thousands were rushing through the corridors to attend crowded lectures on the mysteries of the neuron. But not every session was packed to capacity, recalls Salm, who now has her own lab at West Virginia University in Morgantown. In fact, one slate of talks attracted only herself and a handful of others. The unpopular topic? The brain's other major cell type, the glia, which were then cast in a bit supporting role to the far more glamorous neurons.

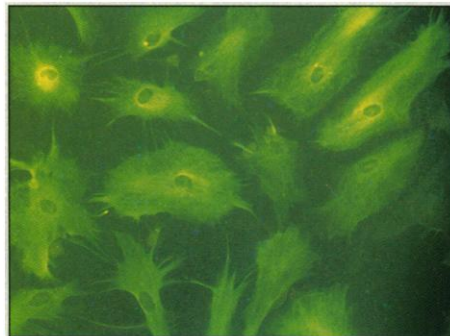
Even the name glia, derived from the Greek word for glue, suggests why these cells were held in such low repute. Despite the fact that they outnumber neurons 9 to 1 and take up more than half the volume of the brain, glia were thought to be little more than the glue that holds the brain together while the neurons do the real work of transmitting and processing information. Now, say Salm and other glia researchers, these forgotten cells are finally gaining their fair share of attention. "The field has exploded, truly exploded," says Edward Lieberman of East Carolina University, who's been studying glia in vertebrates for more than two decades. "It's really been an avalanche," adds University of Illinois neuroscientist William Greenough, who organized a glia workshop at last year's neuroscience meeting.

The "avalanche" of results Greenough refers to may have barely scratched the surface of glial cell function, but it is enough to show that glia do far more than fill the cracks between neurons. "The glia are not simply passive bystanders. They are active participants in the physiology of the brain," says Ira Black of Robert Wood Johnson Medical School in New Jersey, a former president of the Society for Neuroscience.

Those active roles are played by a variety of types of glial cells. In the developing embryo, glia direct migrating neurons to the right targets and help determine what type of neuron each fledgling brain cell becomes. In mature organisms, two types of glia, Schwann cells in the peripheral nervous system and oligodendrocytes in the brain and spinal cord, produce coatings of myelin that insulate neurons and allow their electrical impulses to propagate quickly; another type of glia, the microglia, serve as the brain's immune cells.

But what has really surprised and energized the glia field within the past decade has been a better understanding of star-shaped cells known as astrocytes. These cells now appear to be intimate partners with neighboring neurons, providing nutrients crucial to the neurons' health and aiding in transmission of neuronal signals by mopping up ions and neurotransmitters. And dramatic results reported in the past year suggest that astrocytes may add their own voices to the neuronal chatter, increasing speculation that they play a role in learning and memory.

For the moment, this avalanche of research is important largely for its insights into how the brain works. Ultimately it could



Stars of the show. Astrocytes, such as these, may be neuronal partners in many ways.

be useful in the clinic. In recent years, researchers have been exploring whether transplants of myelinating oligodendrocytes and Schwann cells or of nurturing astrocytes can help rewire damaged spinal cords or repair the ravages of chronic neurodegenerative diseases like Parkinson's, Alzheimer's, and multiple sclerosis. Others are interested in glia because uncontrolled proliferation of these cells causes almost all brain tumors. "If we learn the biology of the glial cell, it will have therapeutic applications. There's no question," says Greenough.

Neuronal care-givers

One aspect of glia that is already attracting a great deal of academic and commercial interest is their talent for producing neurotrophic factors, proteins necessary for the health and survival of surrounding neurons. At this week's neuroscience meeting, for example, Black and his colleagues will present evidence that oligodendrocytes, in addition to their apparent primary task of myelination, express a num-

ber of well-known neurotrophic factors. Among these are nerve growth factor (NGF), the first neurotrophic factor identified, which is now under consideration for clinical trials in patients with Alzheimer's or spinal cord injuries, and neurotrophin-3, which might help peripheral neurons damaged by AIDS or cancer chemotherapy. Production of these factors by oligodendrocytes is "a function that none of us suspected heretofore," says Black.

This talent isn't limited to the oligodendrocytes; astrocytes produce their own repertoire of neurotrophic factors, including NGF, brain-derived growth factor, and glial-derived growth factor (GDNF), which was discovered last year at the biotechnology company Synergen Inc. by a team led by Frank Collins, who has since moved to Amgen. GDNF enhances the survival of the brain neurons that deteriorate in Parkinson's disease, and Synergen is exploring the possibility of using the factor therapeutically. The company expects to announce at the neuroscience meeting results from early animal trials that a Synergen spokesperson describes as "promising."

Another reason for the excitement about glial cells' capacity to make GDNF is that new work on that factor shows its effects aren't limited just to the neurons that degenerate in Parkinson's. On page 1062, an international team of researchers led by Vassilis Koliatsos of Johns Hopkins University School of Medicine and Arnon Rosenthal of Genentech report that it is also a potent trophic factor for motor neurons, which control the muscles. Consequently GDNF offers a potential avenue for treating other devastating conditions, such as amyotrophic lateral sclerosis (Lou Gehrig's disease), that are caused by motor neuron degeneration.

Cleaning up the house

In addition to their general nursing of neurons, glia appear to "keep house" in the brain by cleaning up the neuronal environment and helping maintain nerve cells' signaling capacity. This housekeeping is particularly important for maintaining the synapses, the specialized structures through which neurons transmit signals to other neurons by releasing chemical neurotransmitters. If neurotransmitters and other substances released into synapses, such as potassium ions, are not removed quickly, they can interfere with subsequent neuronal activity. Says Greenough: "One of the purposes [of

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glia] is to serve synapses.”

One form that service takes is removing glutamate, an excitatory neurotransmitter, whose presence in the synaptic environment at high concentration can be toxic to brain cells. The job of removing glutamate falls to the astrocytes, says Bruce Ransom of Yale University School of Medicine, co-editor-in-chief of *Glia*, a research journal founded just 5 years ago. The astrocytes, he explains, pick up glutamate from the synapse, convert it to a compound called glutamine, and return the glutamine to the neurons. Neurons then use it to make more glutamate as needed.

Though this recycling pathway has been known for many years, says Ransom, most neuroscientists were not convinced that it is crucial, arguing that the neuron could function for some time before needing to be resupplied with glutamine by the glia. That view has now been challenged by David Keyser and Terry Pellmar of the Armed Forces Radiobiology Research Institute in Bethesda, Maryland. In research published earlier this year in *Glia*, they demonstrate that a chemical that disrupts the function of cultured glial cells can, within minutes, interrupt the synaptic transmission of surrounding neurons. The authors suggest that the chemical weakens the glial cells, which are unable to replenish neuronal stores of glutamine. Ransom calls the unexpected result “remarkable” because it suggests the neurons are much more dependent on glia than was previously recognized, and it hints that subtle variations in glial efficiency might modulate neuron activity.

Communication skills

Important as they are, these nurturing activities are not the only—or perhaps even the main—reason many researchers are now excited about glial cells. Another is the growing recognition that the glia may have communication skills that complement those of the neurons themselves—a possibility that’s only begun to be taken seriously within the past few years. The hesitance of the neuroscience community stemmed from the fact that glia seemed to lack all the communication equipment that neurons possess. Glial cells don’t send out the long projections called axons that terminate in synapses on neurons or other cells. Nor do glial cells respond to stimuli by producing action potentials, the rapidly traveling electrical impulses that trigger neurotransmitter release.

But about 10 years ago, neuroscientists got their first clues that glial cells might be

communicative after all. The turning point came in the 1980s, when neuroscientists combined their talents at growing glia in lab cultures with the newfound tools of molecular biology, such as antibodies that could be used to identify cell surface molecules.

One of their first discoveries was that astrocytes sport surface receptors that should allow them to understand the chemical language of the neuron. “There are all kinds of neurotransmitter receptors on the glial cell,” explains East Carolina University’s Lieberman. Among them are receptors for glutamate, GABA (gamma aminobutyric acid), which transmits inhibitory signals, and epinephrine, a hormone that also serves as a neurotransmitter for some neurons.

In the last 5 years, researchers have documented that astrocytes can not only make the proteins needed to receive signals but may also have their own methods for sending them. Although astrocytes don’t have long axons, they do send out shorter, branchlike projections, some of which envelop the synapses while others contact other astrocytes, allowing the glial cells to form large interconnecting networks much as neurons do.

An indication that the interconnecting cells are capable of communicating comes from the discovery that the points of contact between them are equipped with gap junctions, sites where an array of proteins forms a tube linking the cells. Molecules flowing through these portals may be used to transfer signals. When stimulated by an electrode, for instance, astrocytes undergo oscillations in their intracellular concentration of calcium ions. More important, researchers can clearly document increased calcium concentrations in neighboring astrocytes, as if a wave of calcium ions were propagating through them.

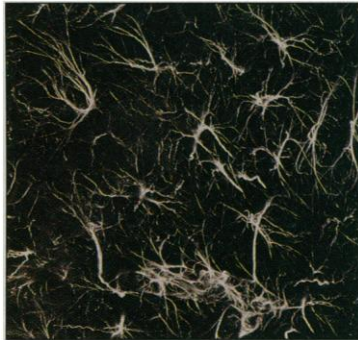
These calcium waves may be functionally analogous to the action potentials neurons use to communicate, says Stephen Smith, a Stanford University neuroscientist. In 1990, Smith, then at Yale University, and his colleagues showed that glutamate, when added to astrocytes in culture, ignites a calcium wave that moves slowly through dozens of other astrocytes. To Smith, this suggested a role for the glutamate receptors found on glia: When stimulated, the receptors prompt the intracellular release of calcium, which may in turn signal glial cells to perform some activity, such as quickening the cleanup of potassium and glutamate.

If the apparent ability of astrocytes to listen to neurons and to talk to one another

weren’t surprising enough, research published earlier this year closed the circle—and in so doing rocked many in the field. Two groups independently showed that astrocytes can send signals back to neurons, at least in the petri dish. In the 25 March issue of *Science*, Maiken Nedergaard of Cornell University Medical College in New York City reported that a calcium wave initiated in a single astrocyte prompted nearby neurons to respond by increasing their own levels of intracellular calcium. And in the 20 June issue of *Nature*, a group at Iowa State University led by Philip Haydon announced similar findings.

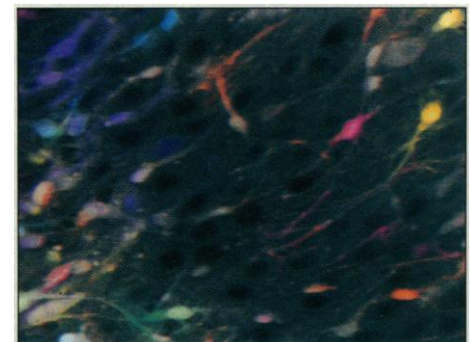
These findings are preliminary, as they were obtained using cultured cells. If similar communication between astrocytes and neurons actually occurs in the brain, the implications could be far-reaching. Some neuroscientists suggest it would be like adding a whole new layer of wiring in the brain. “Astrocytes might participate in memory and information processing. It would change the way you look at the brain,” says Nedergaard.

Additional groups have since confirmed the calcium spikes in neurons, but a major mystery remains as to the mechanism that carries the signal from glia to neuron. Nedergaard, for one, argues that the signal is sent through gap junctions. Haydon and others present a different case. They note that in addition to sporting receptors for neurotransmitters, glial cells have the ability to manufacture many neurotransmitters. And Haydon says his team’s data indicate that calcium waves stimulate astrocytes to release glutamate, which in turns binds to a neuronal receptor that sends a cascade of signals into the brain cell, telling it to release cal-



Together. Branched astrocytes intermingle with neurons (unstained) in the rat hippocampus.

J. W. DANI



Lighting up. The colored cells indicate astrocytes whose internal calcium ion concentrations have increased in response to stimulation.

cium. “Both mechanisms could occur. What I think is crucial is that the signaling is occurring,” he says.

Not out of the shadows yet

In spite of these remarkable findings, glial researchers emphasize that their discipline is still emerging out of the shadows of the neuron. The last decade, they say, has largely been spent cataloging the molecules made

by glial cells in culture and speculating on what the functions of these brain cells could be. "What we are lacking in the field is rigorous hypothesis testing," comments Barbara Barres, a Stanford neuroscientist.

The provocative notion that glia play a role in information processing within the brain, for instance, has no solid evidence to back it up. It rests largely on observations of the cells' behavior in culture, which may be misleading. "A culture reorganizes itself. It can lose its brainlike features," warns University of California, Riverside, neuroscientist Glenn Hatton.

The field is trying to move beyond simple cultures to establish the true roles of glia in the brain. Hatton, for instance, has been study-

ing the hypothalamus, comparing control rats to lactating ones. He's found that in the lactating rats, glia that ensheath and isolate neurons retract their extensions, allowing neurons to move closer and form gap junctions between themselves. It's unclear why this happens, he says, but it may show how glia can play a role in the brain's plasticity, its capacity for rewiring even when mature.

Indeed, there appears to be no end to the proposals being put forth for glia. Some labs are exploring the role of astrocytes in maintaining the blood-brain barrier, while others ponder whether glia help create circadian rhythms. No longer can neuroscientists look only at the brain's neurons and ignore the contributions of glia, Salm and others assert.

"As time goes by," she says, "we'll see a complex and delicate dance that the two cells do together." And in stark contrast to the handful who listened to the presentations about glia in 1980, at this year's neuroscience meeting, hundreds of neuroscientists will join Salm in enjoying that dance.

—John Travis

Additional Reading

B. Ransom and H. Kettenmann, Eds., *Neuroglia* (Oxford University Press, Oxford, U.K., in press).

S. Smith, "Neuromodulatory astrocytes," *Current Biology* 4, 807 (1994).

G. Somjen, "Nervenkitt: Notes on the history of the concept of neuroglia," *Glia* 2, 2 (1988).

HIGH-ENERGY PHYSICS

Making the Stuff of the Early Universe

Recreating the past isn't uncommon—biographers and psychoanalysts do it for a living. But few venture as far back in time as physicists at CERN, Europe's particle physics center at Geneva, are attempting to do. This week researchers will try to create matter that existed only in the first few instants after the Big Bang. "We will be studying the matter of the very early childhood of the universe," says theorist Helmut Satz of CERN.

The CERN physicists hope to be the first to create something called a quark-gluon plasma. Most subatomic particles, including protons and neutrons, are themselves made up of two or three smaller particles called quarks, which are in turn held together by particles called gluons. The theory that describes this interaction, called quantum chromodynamics (QCD), predicts that if protons and neutrons are pressed together with extreme force, they will rupture, spilling and intermingling their constituent quarks and gluons to form a hot, ultradense plasma. This state of matter was thought to exist in the early moments of the universe, but after the first 10 milliseconds it had expanded and cooled sufficiently for the plasma to coalesce into the kind of matter we see today—atoms with their separate nuclei.

Bringing the plasma back will not only yield insights into the Big Bang, physicists hope; it will also allow them to check the only remaining unverified part of QCD. To recreate the quark-gluon stuff in the lab, in the 1980s physicists began accelerating beams of ions to a very high speed and smashing them into stationary targets. The rationale for this strategy was that a heavy

ion (one with a lot of protons and neutrons, together known as nucleons) from the beam would hit an atomic nucleus in the target, and the heat of collision would turn the two nuclei into a plasma fireball. Two years ago, U.S. researchers at the Brookhaven National Laboratory accelerated beams of gold ions with 197 nucleons. Bulk isn't everything, however; the ions also need to carry a high energy. And the Brookhaven accelerator could only boost the ions to an energy of 12 giga-electron volts (GeV) per nucleon, which proved insufficient to create a quark-gluon plasma. "We've had interesting hints, but no conclusive signals yet," says Peter Braun-Munzinger of the State University of New York. "There's certainly a chance they will do it [at CERN] if the equipment is ready."

CERN has spent the past 2 years adapting its accelerators to handle lead ions with 208 nucleons. A new linear accelerator for lead was installed to create the beam, which will be hiked up to higher and higher energies as it passes through three of CERN's accelerator rings. According to CERN's Helmut Haseroth, the final beam will have a peak energy of 177 GeV per nucleon, and the lead ions will be traveling at 99.998% of the speed of light.

Although theory predicts this will be sufficient energy to produce a quark-gluon plasma, detecting it is far from easy. "There is no unambiguous signal," says University of Frankfurt physicist Reinhard Stock. "It is like in a criminal court: You must accumulate evidence." This is why CERN has arrayed seven detectors, each looking for different types of evidence (see table), such as the particular spectrum of photons emitted when the compressed nucleons transform into a plasma.

There is also one wild card in the pack of detectors: A 550-meter mass spectrometer looking for a predicted particle known as a "strangelet." The energy of impact will create a type of quark—dubbed "strange"—that is somewhat heavier than the usual ones. Some theorists believe that such quarks can remain in the plasma as it cools and their electric charge balances the charges on other quark types, making it more favorable for the plasma to condense into a giant, single nuclear particle—a strangelet—rather than separating into smaller nucleons.

Some believe that such strangelets, if they exist, could solve a number of astrophysical mysteries, such as that of the missing mass of the universe—large strangelets left over from the Big Bang may be simply floating around in interstellar space, and one such object the size of a tennis ball would weigh more than a trillion tons. Satz says that he thinks it "extremely unlikely" that they will find strangelets—although the result would be remarkable. But if the CERN researchers can create the never-before-seen plasma, no one will go home disappointed at their recreation of very ancient history.

—Daniel Clery

CERN'S QUARK-GLUON PLASMA DETECTORS

Detector Type	Purpose
Omega spectrometer to detect multiply-strange baryons and anti-baryons	Detect strangeness enhancement in quark-gluon plasma
Array of calorimeters for direct photon detection, plus some hadron detection	Detect formation of quark-gluon plasma
Pion and kaon spectrometer	Measure size of plasma in its final state
Electron spectrometer	Analyze initial state of quark-gluon plasma
Wide-acceptance hadron spectrometer	Analyze final state of quark-gluon plasma
Muon spectrometer	Analyze initial state of quark-gluon plasma
Charged-particle spectrometer	Detection of strange matter particles