The Neurobiology of Brain Injury

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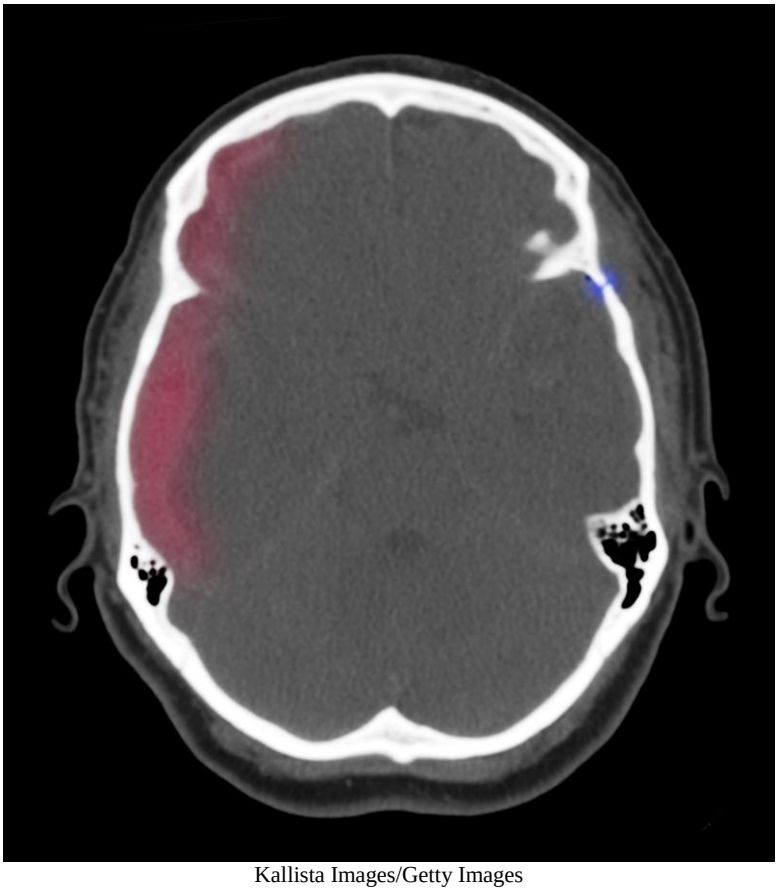

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Editor's note: In a complementary article, Dr. Mark J. Ashley discusses frontline rehabilitation methods that can improve brain injury recovery outcomes. Here, Marcela Pekna and Milos Pekny explain what happens within the brain after injury and how scientists' growing awareness of the brain's capacity for repair could lead to better treatment options.

Article available online at http://dana.org/news/cerebrum/detail.aspx?id=39280

A complementary article, "Repairing the Injured Brain:
Why Proper Rehabilitation Is Essential to Recovering Function" is available online at
http://dana.org/news/cerebrum/detail.aspx?id=39258

Brain injury caused by head trauma or stroke affects all brain cells, including neurons; glial cells such as astrocytes, microglia, and oligodendrocytes; blood vessel cells; and cells that produce and recycle cerebrospinal fluid (CSF), which line the brain's ventricles. In addition to causing direct cell damage and cell loss, brain injuries disrupt blood flow and the blood-brain barrier (a barrier that allows only selective molecules to pass from the bloodstream and come in contact with neurons and astroglial cells). Brain injuries also interfere with the production, distribution, and reabsorption of CSF and cause changes in the metabolism and function of cells not only in close proximity to the dying tissue but also in more remote brain regions functionally and anatomically connected with the injured area.

Brain Injury at the Cellular Level

Neurons continuously receive, process, and integrate information from the whole body, including the brain, and send out signals to other neurons and cells in the periphery. Neurons do not work in isolation; they form intricate circuitry, the function of which is directly or indirectly influenced by all other cellular components of the brain tissue. Brain injury affects neuronal circuitry by causing the death of neurons and glial cells and destroying connections between them. This includes the cellular extensions (dendrites and axons) through which neurons receive and emit signals by means of molecules called neurotransmitters. Brain injury often leads to excessive accumulation of neurotransmitters in the brain tissue, in particular glutamate, which can overstimulate neurons and cause neuronal death.

A limited number of neurons responsible for specific tasks perform the brain's many functions. A specific region in the brain controls the muscles moving the hand, for example, while another group of neurons controls the muscles involved in talking, and yet another region processes the information from our auditory system so we can understand spoken language. This very specific localization of functions within the brain is the reason injuries to different brain regions lead to varied symptoms.

Importantly, the brain can limit the spread of damage by forming a glial scar that seals off the damaged region.[1-4] Glial cells (astrocytes, oligodendrocytes, and microglia) are particularly important in this process. Astrocytes produce glucose and other nutrients,

as well as support the viability of the surviving cells. Researchers studying brain injury have reduced the injury-triggered activation of astrocytes in experimental mouse models[5-7] and found that the ensuing damage was greater than damage in animals with fully responding astrocytes, implying that astrocytes are protective in brain injuries.[8, 9]

Researchers are giving astrocytes, once considered just the glue filling the space between neurons, ever increasing attention. They have long known the importance of astrocytes in maintaining brain environment stability (homeostasis), providing nutrition for neurons, and recycling neurotransmitters. More recently, researchers showed that astrocytes also control many functional aspects of the brain in health and disease. These include control of blood flow,[10] induction and functional control of neuronal synapses,[11, 12] and plasticity and regeneration processes.[2, 4] To learn more, see box one on page 5.

Neuroplasticity and Repair

In contrast to other organs that can replace even large numbers of cells lost to injury or disease (such as the skin and liver), brain tissue's capacity to regenerate is extremely limited. However, nervous tissue has a remarkable ability to adapt its function rather than to regenerate its structure in response to a changing environment; this ability constitutes the basis for learning. In neurobiological terms, this ability to adapt to and learn from experiences is called neural plasticity. At the structural level, neural plasticity could be defined by the number and complexity of dendrites and axons, the density of synapses (connections between neurons, through which information is transmitted from one neuron to another), and in some brain regions also by the number of neurons. Brain injury leads to increased neural plasticity in the spared regions. This allows the neurons in these regions to take over the sensory or motor functions that had been performed by the damaged areas. This remapping of function (indeed similar to drawing a new map) is critical in the recovery of function.

Astrocytes are important regulators, controlling the number of neurotransmitter molecules present in the space between neuronal and astroglial cells. A large change in the size of this space leads to the development of brain swelling. Recent findings show that the capacity of astrocytes to take up the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) is reduced in the zone surrounding brain cells killed by

stroke.[13] The inhibition of neurons by excessive amounts of GABA counteracts neural plasticity and impairs functional recovery. Importantly, a drug that blocks the binding of GABA to some of its receptors can reduce this GABA-mediated inhibition. Such a treatment, if provided at the right time after stroke, results in a faster recovery of function in mouse models.[13] However, when administered too early, the drug can increase the amount of brain tissue damaged by stroke. These findings, together with many other reports, demonstrate that the response of brain tissue to injury is complex, that many cellular and biochemical events take place in an orchestrated cascade, and that each phase of the healing process has a specific purpose. Therefore, the timing of any therapeutic intervention is critically important to the outcome.

Neural plasticity peaks within one to three months after injury; this creates a unique window of opportunity. During this window, neurorehabilitation—physical therapy, for example—is most effective. However, significant improvements can occur even at later stages, especially when rehabilitation combines task-specific training with therapies that activate neural plasticity.[14]

The Role of the Immune System

Research findings during the past decade show that the immune system in the brain itself and immune cells and molecules from the blood play an important role in the normal development of nervous tissue as well as the brain and spinal cord's response to injuries.[15-17] For a more detailed explanation, see box two on page 6. Reactive astroglial cells in the glial scar produce molecules that inhibit the growth of neuronal processes and thus limit recovery. At a later stage (weeks and months after injury), when the activity of the astroglial cells is no longer needed for limiting the spreading of tissue damage, the immune system signals to the astroglial cells in the scar to reduce their activation. The down-regulation of astroglial cell activity is necessary for effective repair and functional recovery, however, the signals from the immune system that downregulate astroglial cells' activity may come too late or may not be sufficient to achieve the maximum desired effect on their own. This opens an opportunity for therapeutic interventions.

Immune activity in the brain changes with time after injury and needs to be tightly controlled, as its malfunction can aggravate the damage. Astrocytes contribute to immune

regulation through their role in resealing the blood-brain barrier as well as via secretion of factors that directly regulate immune-cell activity. The degree and timing of such cross-talk between the immune and glial cells can be suboptimal, which opens a possibility for designing pharmacological interventions that would reduce the astrocytes' reactive response and modulate the immune cell activity.

The cells and molecules of the immune system also exert direct effects on brain cells, including neurons, astrocytes, and neural stem cells, and in this way stimulate neural plasticity and promote recovery of brain function. Immune system activity declines as we age, and the resulting imbalance could be one reason for poorer recovery from brain injury in older people and for the age-related decline of perception, motor behavior, cognition, and memory function.

In summary, brain injury affects both neural and nonneural cell populations in the brain and causes cell death as well as cellular dysfunction, the latter not only in the areas directly affected by the primary injury but also in more remote brain regions. Although the brain's repair capacity is limited, the injury-induced increase in neural plasticity is important in the recovery of function. The right timing of any intervention, aligned with the neurobiological processes that take place in the injured brain, is critical to the outcome. Astroglial cells and the cells of the brain's and body's immune system emerge as novel and important targets for future therapeutic interventions in situations such as neurotrauma or stroke.

Box One: Pros and cons of reactive astrocytes in brain injury

Astrocytes become activated after events such as neurotrauma and stroke. This phenomenon, known as reactive gliosis, is accompanied by an altered expression of many genes and profound changes in the properties and function of astrocytes. The cellular hallmarks of reactive gliosis are the thickening (hypertrophy) of astrocyte processes, proliferation of astrocytes, and increases in the amount of intermediate filaments (also called nanofilaments). Intermediate filaments form a scaffold-like network within the cell cytoplasm, a highly dynamic structure involved in cell signaling, adhesion, and migration that can act as a signaling platform, helping cells and tissues cope with stress in health and injury.

By using mouse models that lack intermediate filament proteins, we and other researchers have demonstrated that intermediate filaments play a key role in astrocyte activation, and that astrocyte activation itself is important for the early- and late-stage responses after neurotrauma.[5, 8] These and other mouse models demonstrated that at an early stage after brain injury, astrocyte activation has a positive effect on the preservation of neuronal synapses,[8] limits the lesion size in stroke[9] and neurotrauma,[6, 7] and promotes wound healing.[5, 6] But these early positive effects come at a price. At a later stage of injury, animal models of attenuated reactive gliosis showed reduced regeneration of neuronal synapses,[8] limited regeneration of neuronal axons,[18] and largely failed integration of neural grafts or neural stem cells.[19, 20] Astrocytes may represent a novel therapeutic target and modulation of reactive gliosis within a defined time window after neurotrauma or stroke might be a new way to improve functional recovery.

Box Two: The immune response in the healthy brain and after brain injury

Traditionally, the central nervous system (CNS), which encompasses the brain, spinal cord, and retina, was viewed as immune-privileged, or sequestered from the immune system. Researchers and medical doctors regarded any immune activity in brain tissue to be harmful. However, increasing evidence shows that normal development of the CNS, along with its maintenance, repair, and renewal, requires both the innate and adaptive immune responses.

The innate immune response is the rapid first line of defense against infection. It lacks specificity and responds in the same manner to a wide range of triggering events. In contrast, the adaptive immune response is inefficient upon a first encounter with an infectious agent (such as a virus or bacteria), but its efficiency increases with time. The adaptive immune response is very specific and has "memory,"—it responds in a much more rapid and efficient manner upon a repeated encounter with the same bacteria or virus. Both the innate and adaptive immune systems rely on many different immune cell types as well as cell-bound soluble immune molecules.

For example, normal neurogenesis in the hippocampus and normal cognitive performance require cells of the adaptive immune response called T lymphocytes; the cells also protect neurons from secondary degeneration after injury. Innate immune

response cells called microglia constantly survey brain tissue for protein aggregates or cell debris, which they efficiently remove. However, their prolonged and excessive activity is associated with release of a range of substances that are toxic to the neurons. Monocytes recruited from the blood are important regulators of the local immune response, including the activity of microglia.[15-17]

The complement system, a group of immune system proteins known for initiating inflammation and eliminating pathogenic bacteria, has multiple roles in the CNS. During normal development, this system is involved in eliminating excessive synapses. The same process in adulthood, however, might be the first step in neurodegeneration.[21] The complement system also functions as a positive regulator of neurogenesis in a healthy brain and after ischemic stroke.[22] Thus, in the diseased or injured brain, the complement system can increase tissue damage—or it can be protective and contribute to repair and recovery.

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lead to the development of new markers of functional recovery and the designing of novel and individualized treatments for stroke patients.

Milos Pekny, M.D., Ph.D., received his M.D. from Charles University in Prague in 1989 and his Ph.D. from Uppsala University in Sweden in 1994. He is a professor in the Department of Clinical Neuroscience and Rehabilitation and the director of the Laboratory of Astrocyte Biology and CNS Regeneration at the Center for Brain Repair and Rehabilitation (CBR), Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Sweden. Pekny's laboratory pursues basic, translational, and clinical research in the field of CNS repair and regeneration. He and his colleagues focus on the modulation of astrocyte function as a basis for the development of new treatment strategies for stroke, neurotrauma, and neurodegenerative diseases. Dr. Pekny coordinates the program *Novel strategies for brain regeneration after stroke—from lab to patient to population,* co-financed by the AFA insurance company. He is also a steering committee member and leader of the Gothenburg University node in the EU-funded Marie Curie Training Network *EduGlia*: *Innovative techniques and models to study glia-neuron interactions in health and disease*, which connects European laboratories of excellence in the field, and he is a partner in the EU-funded collaborating network focusing on stroke *TargetBraIn: Targeting brain inflammation for improved functional recovery in acute neurodegenerative disorders.*

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For more about brain plasticity and its therapeutic modulation, see Pekna, M., Pekny, M., & Nilsson, M. (2012). Neural plasticity as a basis for stroke rehabilitation. L.M. Carey, (Ed.), *Stroke Rehabilitation: Insights from Neuroscience and Imaging* (pp. 24-34). New York, NY: Oxford University Press.

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