Scientists Probe Immune System's Role in Brain Function and Neurological Disease

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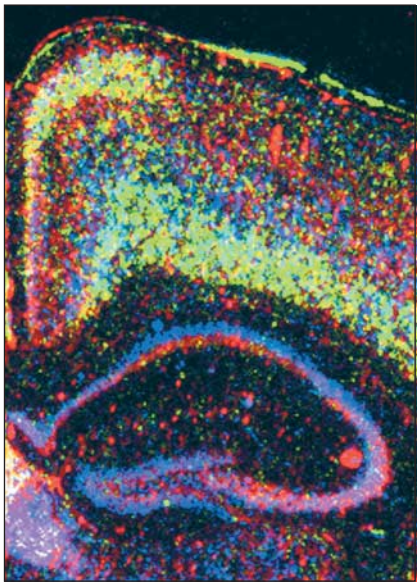
EMERGING EVIDENCE SUGGESTS that proteins associated with the immune system may play additional roles in normal brain development and in the healthy adult brain. Studies also suggest that perturbations of these roles may underlie some neurological diseases.

Contrary to dogma that the blood-brain barrier protects the brain from the immune system by acting as a barricade to its components, scientists have found that certain key immune system proteins are, in fact, expressed and active in healthy brains. For instance, a growing body of evidence highlighted at the annual meeting of the Society for Neuroscience in November suggests that proteins of the major histocompatibility complex class 1 (MHC 1), a large family of immune system proteins that mediate the identification and rejection of transplanted organs, help maintain appropriate connections in the developing and adult brain. And a study published in December suggests that the classic complement cascade, the immune system component charged with tagging foreign entities for destruction by phagocytes, plays a crucial role in pruning synapses in the developing brains of mice.

These findings not only offer new avenues for understanding the development and molecular machinery of the central nervous system, they also may ultimately help scientists unravel the hitherto elusive etiologies of some developmental and neurodegenerative diseases.

OVERLOOKED

The role of various immune system components in the healthy developing and adult central nervous system has long escaped notice in part because scientists believed these molecules were not present, explained Lisa M. Boulanger, PhD, of the University of California-San Diego in an interview.



Gene S. Huh, PhD, and Carla J. Shatz, PhD

Key immune system proteins are active in the brain, as illustrated by this cross section of a mouse brain showing expression of 3 such proteins (shown in red, blue, and green).

The brain is functionally immune privileged, meaning that it is invisible to some forms of immune surveillance, Boulanger said. It was long thought that this was because many cell types in the brain did not synthesize key immune molecules, particularly members of MHC 1, unless the blood-brain barrier was compromised by injury or disease. This hypothesis was strengthened when traditional methods failed to detect significant levels of MHC 1 proteins in the normal healthy brain. However, these methods had important technical limitations, Boulanger said: some tested for traditional immune functions that are now known to be suppressed in the brain, while others used chemical reagents that work differently in the brain than in other tissues.

More recently, however, neuroscientists using newer technologies such as gene chip screenings, have found key immune system proteins being expressed in the brain, including the MHC 1 family. And now they are probing the roles these proteins play in the central nervous system and whether disruption of these roles might contribute to disease processes.

SERENDIPITY

When an unbiased gene screening looking for genes regulated by neuronal signaling in the visual system led Carla Shatz, PhD, and colleagues to conclude that the MHC 1 family of molecules was expressed in the brain, many scientists were skeptical (Corriveau RA et al. *Neuron*. 1998;21[3]:505-520). Shatz, who recently moved her laboratory from Harvard University in Boston to Stanford University in Palo Alto, Calif, and colleagues were surprised as well. They had happened upon the immune system protein as they were studying the process of brain connection pruning that occurs early in brain development. This process is crucial to learning and normal development.

Subsequent work by Shatz's group demonstrated that neural connections between the eye and brain did not de-

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velop properly in mice that lacked functional MHC 1 proteins (Huh GS et al. *Science*. 2000;290[5499]:2155-2159). Since then, a growing body of evidence has suggested that MHC 1 molecules may act as a brake on synaptic plasticity, helping to prune unnecessary connections during development and preventing inappropriate synapses from forming and interrupting brain function in mature brains (Boulanger LM and Shatz CJ. *Nat Rev Neurosci*. 2004;5[7]:521-531; Goddard CA et al. *Proc Natl Acad Sci U S A*. 2007; 104[16]:6828-6833).

Recently, Shatz and colleagues have identified an immune system receptor that may mediate the role of MHC 1 molecules in the brain (Syken J et al. *Science*. 2006;313[5794]:1795-1800). They found that messenger RNA encoding this receptor, called paired immunoglobulin-like receptor B (PIRB), is highly expressed in many regions of the mouse central nervous system. Subsequently, they found that mice that do not have functioning PIRB receptors have higher than normal levels of synaptic plasticity, which would support a role for MHC 1 working with PIRB to keep such plasticity in check.

The findings may have exciting clinical implications, Shatz explained in an interview. They may help explain how the immune system interacts directly with the nervous system, and why immune system abnormalities or malfunctions may lead to neurological problems.

Boulanger, a former student of Shatz, and colleagues are probing whether perturbations in the neurological roles of the MHC 1 family of proteins might play a role in neurological diseases such as schizophrenia and autism. Epidemiological studies have suggested that in genetically predisposed individuals, maternal infections during the second trimester of pregnancy may increase the risk of the child developing one of these disorders. These data from human studies and recent experiments in animal models (Smith SE et al. *J Neurosci*. 2007;27[40]:10695-10702) suggest that the mother's immune response to the infection somehow interferes with normal brain development. Boulanger and colleagues are using animal models to determine whether the maternal immune response to second trimester infection can change the levels of MHC 1 proteins during brain development, and whether such changes contribute to the development of specific neurodevelopmental disorders. The results of these studies may one day lead to immune-based strategies for diagnosing, treating, or even preventing autism and schizophrenia, Boulanger said.

SHAPING CONNECTIONS

Another team of scientists studying mice has found that the classic complement cascade, a key component of the innate immune system, also appears to play a crucial role in the pruning of weak or inappropriate synapses during normal development. Their findings suggest that inappropriate reactivation of this cascade in adults may contribute to glaucoma in a mouse model of the disorder (Stevens B et al. *Cell*. 2007; 131[6]:1164-1178).

Ben A. Barres, MD, PhD, a member of the team and professor of neurobiology at the Stanford University School of Medicine, explained in an interview that scientists have known for many years that proteins involved in the cascade were present in the brain and that they hypothesized that these proteins might play a role in the brain's response to injury. In fact, scientists had published the finding that the protein that initiates the cascade, the C1q protein, was not expressed in healthy adult brains. But when Barres and colleagues conducted a gene chip experiment designed to determine which neuronal genes were regulated by astrocytes, they were surprised to find that only the gene encoding the C1q protein was strongly controlled by these star-shaped glial cells. They realized the neurons they were studying were from developing brains, and further studies revealed that C1q is expressed at synapses throughout the developing brain.

The fact that C1q was found at the synapses only during the period of development, when selective synapse pruning is shaping the structure of the brain, coupled with C1q's known immune system role in tagging items for elimination, led Barres and colleagues to the hypothesis that C1q helps tag weak or inappropriate synapses for elimination during normal development. Their subsequent studies have supported this hypothesis.

Evidence also points to a role for C1q in neurodegenerative diseases. The protein is elevated in many such diseases; for example, expression of C1q is upregulated 70-fold in Alzheimer disease, Barres said.

As part of their study, Barres and colleagues studied mice with a glaucoma-like disorder and examined the animals' retinal tissue at various developmental stages. They found that synapses in the areas where retinal neurons ultimately die were studded with the protein.

Barres said the findings suggest that improper reactivation of the C1q protein and the resulting cascade may be a common step in various neurodegenerative diseases. "The very exciting idea is that C1q-mediated synapse loss in the adult brain is driving the degenerative process; neurons die only after losing too many synapses," he said.

His group next plans to test whether the neuron degeneration progresses in mice that have this glaucoma-like disorder but lack C1q. If it does not, therapies blocking C1q or other parts of the classic complement cascade may be a way to prevent neuron loss in individuals with neurodegenerative diseases.

Barres and Shatz also are considering collaborating to explore how their findings might dovetail. The fact that synapse connections are abnormal both in mice with mutant C1q proteins and in those with mutant MHC 1 proteins "raises the possibility that we are all studying part of the same pathway," said Shatz. □

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