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For more information, please contact Sara Harris at (619) 525-6325 or sharris@sfn.org

IMMUNE SYSTEM RESEARCH PROMISES TO HELP TREAT AILMENTS RANGING FROM ALZHEIMER'S AND STROKE TO MENTAL DISORDERS

SAN DIEGO, November 4, 2007 - Recent discoveries in the field of neuroimmunology, which studies the interaction between the immune and nervous systems, are offering promising new leads for the treatment of many devastating neurological disorders, from Alzheimer's disease to stroke.

New research suggests that reducing the expression of an immune system protein in the brain may help repair neurons damaged by spinal cord injury and other trauma. Other research has uncovered the important role that immune molecules perform in the prenatal development of such diseases as autism and schizophrenia. Additional findings reveal that an innovative type of immunotherapy assists with the recovery of memory after stroke.

"The discovery that immune molecules play a crucial role in shaping neuronal connections and are even expressed on nerve cells important in learning and memory is opening up a whole range of potential new treatment targets for diseases in which these connections have gone awry, such as Alzheimer's and other dementias, autism, amyotrophic lateral sclerosis (ALS), Parkinson's disease, schizophrenia, and in nerve injury," says Esther Sternberg, MD, of the National Institutes of Health. "Understanding these neural immune connections at a molecular and cellular level will shed light on the reasons these diseases develop and will help provide new ways to prevent or treat them."

Several years ago, researchers at Harvard Medical School made the unexpected discovery that neurons have major histocompatibility complex (MHC) class I molecules on their cell surface. MHC class I molecules play a central role in a healthy, functioning immune system by helping the body recognize and destroy disease-infected cells.

"We were amazed by this finding," says Carla Shatz, PhD, now at Stanford University. "Previously it had been thought that neurons were the only cells in the body that didn't express these molecules."

When Shatz and her colleagues studied mouse models that lack MHC class I, they found another surprise: greater-than-normal strengthening of the synapses between neurons. This observation suggests that MHC class I acts as a kind of "molecular brake" on synaptic plasticity, the ability of brain cells to rewire themselves. Such plasticity is essential to learning and memory.

In mice, the "brake" for the gene encoding MHC class I appears to be released twice: during early development and again in old age. Interestingly, late in life, the gene's neural expression occurs primarily in the hippocampus and other areas of the brain involved in learning and memory.

"MHC class I neurons may also play a role in age-related neurodegenerative diseases, such as Alzheimer's and Parkinson's," says Shatz. "It may mistakenly signal the immune system to attack brain cells, just as it triggers a similar attack on the joints in cases of rheumatoid arthritis."

More recently, Shatz and her team have reported that neurons also express an immune system protein called paired-immunoglobulin-like receptor-B (PirB), which, over time, gradually inhibits brain plasticity. Mice that lack PirB exhibit greater synaptic plasticity as they age -- a finding that suggests that reducing PirB might help reestablish the connections among neurons damaged by spinal cord injury, stroke, or other trauma.

Together, these studies indicate that immune molecules perform important functions in the brain, including how much or how quickly our brain changes in response to new experiences.

Researchers at the Karolinska Institute in Stockholm, Sweden, have found that removal of synapses from damaged neurons after a motor nerve injury, a process known as "synaptic stripping," is much stronger in mice who lack functioning MHC class I molecules. They also found that such mice are less likely to experience a regeneration of their motor neurons and that their glial cells react differently to the damaged neurons than do those of mice with functioning MHC class I molecules.

"These results provide a surprising link between neuroscience and immunology," says Staffan Cullheim, MD, PhD. They also mark the first time a family of molecules has been linked directly to how the cell body of a neuron reacts after its axon -- the long projection that conducts electrical signals away from the cell's body -- has been injured.

In earlier studies, Cullheim and other scientists had reported that MHC class I molecules can be found in particularly high levels among motor neurons in the brain stem and the spinal cord, especially after the neurons have been damaged. In his most recent study, Cullheim found that the presence of MHC class I helps retain certain inhibitory synapses on the surface of injured motor neurons, thus reducing the likelihood that the neurons will fire a nerve impulse, or action potential, to neighboring cells.

MHC class I also has an effect on the action of glial cells, which in turn may influence neurons in various ways. Although microglia, the "immune cells" of the central nervous system, responded more weakly in the absence of MHC class I molecules, other glial cells, known as astrocytes, responded more vigorously. If -- and how -- these different responses are linked with synaptic stripping is not yet known.

"The consequences of the effects of MHC class I is still not clear," says Cullheim, "but it may be linked with the the ability of motor neurons to produce new axons. Mice with peripheral nerve lesions in their hind limbs exhibit less axonal bridging on those lesions when their MCH class I function is impaired."

High levels of MHC class I, on the other hand, may pose a danger to neurons in the same way as is seen for other cell types -- during viral infection, for example. These high levels may even be involved in the development of neurodegenerative diseases. Research has shown that motor neurons involved in ALS and dopaminergic neurons involved in Parkinson's disease express among the largest amounts of MHC class I molecules in the nervous system.

At the University of California, San Diego, Lisa Boulanger, PhD, and her colleagues have found that changes in the levels of specific immune molecules, members of the MHC class I family, are sufficient to cause cellular and behavioral symptoms of autism and schizophrenia in mice.

One set of preliminary studies from Boulanger's laboratory suggests that normal levels of MHC class I are needed for proper neuronal signaling by the neurotransmitter glutamate. The disruption of the glutamate signaling system is a hallmark of schizophrenia. It's also been recently characterized in patients with autism.

In a second line of research, Boulanger has found that changes in MHC class I levels cause a striking disruption of the ability to "tune out" irrelevant sensory information, as measured by a neurological phenomenon known as prepulse inhibition, or PPI. Scientists have long known that PPI is impaired in people with schizophrenia, and recent studies suggest that it's also impaired in people with autism.

"We found in our current study that mice with altered levels of MHC class I share both abnormal glutamate signaling and this deficit in PPI," Boulanger says. "These results are exciting because they may provide clues to understanding the puzzle of why immune abnormalities are frequent among patients with autism and schizophrenia and their close relatives."

Boulanger and her colleagues are currently investigating whether MHC class I molecules are altered in people with autism and schizophrenia. They are also using animal models to determine how immune signaling may affect the earliest events in fetal brain development.

"Human data show that in genetically predisposed individuals, a maternal viral infection during pregnancy increases the chance of the child developing either autism or schizophrenia later in life," says Boulanger. "Recent research in animal models suggests that it's not the infection itself, but rather an unknown, shared feature of the immune response to a variety of infectious agents that disrupts fetal brain development and leads to impairments in PPI."

A leading candidate for this mysterious immune trigger is the release of cellular signals called cytokines, which are produced during infection and injury. Cytokine levels are altered in the fetal brain following a maternal infection -- and in the brains of people with autism. Cytokines can increase the levels of MHC class I molecules in many types of cells, including neurons.

"We're now trying to determine if changes in MHC class I molecules are the necessary link between maternal infections and abnormal fetal brain development," says Boulanger.

An experimental treatment called anti-NOGO-A immunotherapy has been found to improve performance on a test of cognitive ability after stroke in aged rats, according to a new study from a team of researchers led by Gwendolyn Kartje, MD, PhD, at Loyola University and the Edward Hines VA Hospital in Chicago. This finding may one day lead to more effective treatments for the millions of people worldwide who survive a stroke each year and for the millions of others suffering from Alzheimer's disease and other memory disorders.

Anti-NOGO-A immunotherapy blocks the NOGO-A protein, a molecule found in the brain. The precise role of this protein is unknown, but it appears to inhibit aberrant growth. When the brain becomes damaged, however, this inhibitory function turns harmful, preventing injured cells from regenerating and repairing themselves. It also prevents uninjured cells from changing to help with the recovery.

In earlier studies, Kartje and her colleagues showed that anti-NOGO-A immunotherapy led to the recovery of forepaw and arm movement after induced stroke in aged rats. The new study found that the therapy also improved cognitive recovery when testing performance on a spatial memory task.

"This suggests that the NOGO-A protein limits the recovery of memory after stroke and that by blocking the protein, more recovery may occur," Kartje says. Her laboratory next plans to look for structural changes in the brain that underlie the recovery process.