NEWS FROM THE SfN ANNUAL MEETING

New Insights into the Shared Molecular Mechanisms of Immune and Neuronal Connections

By Sue Pondrom

ARTICLE IN BRIEF:

✔ Investigators described findings on how major histocompatibility (MHC) Class I genes affect synaptic plasticity and the role they might play in neurodevelopmental disorders such as autism and schizophrenia.

SAN DIEGO—Although the brain was previously thought to be immune privileged, modern research suggests that immune molecules play a crucial role in shaping neuronal connections and affecting brain activity throughout life.

In a special symposium here at the annual meeting of the Society for Neuroscience in November, investigators highlighted some of the exciting work. Lisa Boulanger, PhD, who led the session, defined the "new neuroimmunology" as an emerging field that is based on new evidence of shared molecular machinery in the immune and nervous systems. She contrasted this definition to the more classical one of neuroimmunology as the study of autoimmunity, or of neuronal regulation of immune function.

"Changes in this machinery could thus affect both systems in parallel, so that a single core deficit could lead to a syndrome with both immune and neurological symptoms," said Dr. Boulanger, assistant professor of biology at the University of California-San Diego.

PirB and MHC Class I Genes

Carla Shatz, PhD, head of Stanford University's Bio-X program, an interdisciplinary program of basic and clinical research, described findings that major histocompatibility (MHC) Class I genes — the human leukocyte antigen (HLA) proteins in humans that allow T cells to recognize and destroy infected or neoplastic cells — as well as a MHC Class I receptor — a paired immunoglobulin-like receptor B (PirB) — act in the healthy brain as a brake to limit synaptic plasticity.

PirB is expressed in neurons throughout the brain, Dr. Shatz showed in earlier research (*Science* 2006; 13(5794):1795-1800). Soluble PirB fusion protein binds to cortical neurons and may function broadly to stabilize neural circuits, Dr. Shatz and colleagues wrote.

The research by Dr. Shatz not only provides a better understanding of brain wiring, but it may also provide clues to disorders such as Alzheimer disease and schizophrenia. In the adult hippocampus, for example, MHC is required for normal long-term potentiation and long-term spreading depression, forms of activity-dependent synaptic plasticity involved in learning and memory.



Dr. Ben Barres: "Perhaps the most interesting idea suggested by her [Carla Shatz's] work is that these immune system molecules not only contribute to normal brain wiring, but may also play critical roles in repair — or failure to repair — brain circuitry after injury. These immune molecules provide promising new drug targets for developing new treatments for stroke and spinal cord injury."

Dr. Shatz recently moved to Stanford after several years at Harvard University, where her lab had surprised the scientific community some years ago with evidence that neurons express MHC Class I molecules on the cell surfaces. Expressed at low levels, these pro-

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Neuroimmunology

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teins regulate synaptic stability and plasticity in the hippocampus. When MHC Class I genes were knocked out in mouse models, synaptic plasticity increased.

"This was amazing to us because normally when you knock out a gene that's involved in a plasticity pathway, the plasticity is gone," Dr. Shatz said. "Yet here, what's happened is that we've removed the function of an MHC1 molecule and the plasticity was enhanced."

Further experiments in mice determined that the specific MHC Class I molecules (including H2-D) were involved in ocular dominance plasticity in the visual cortex. The researchers then hypothesized that one way in which an MHC Class I molecule might work would be through a receptor. An exhaustive screening of receptors identified the PirB receptor, and further tests showed that mice lacking PirB had enhanced synaptic plasticity,

"This suggests that there might be a genetic interaction between PirB and MHC Class I proteins," Dr. Shatz said. "There are two arms to this regulatory pathway — a plasticity-enhancing arm and one that limits plasticity. Both have to work together to regulate the rate, rapidity, and stability of synapse remodeling circuit changes during development and in adults."

"Carla Shatz's new findings are important," said Ben Barres, MD, PhD, professor of neurobiology at Stanford. "It has been dogma for decades that the brain does not express any of these immune system molecules, but her lab has found that many of them are normally present and critical. Perhaps the most interesting idea suggested by her work is that these immune system molecules not only contribute to normal brain wiring, but may also play critical roles in repair — or failure to repair — brain circuitry after injury. These immune molecules provide promising new drug targets for developing new treatments for stroke and spinal cord injury."

MHC Class I Molecules: Autism and Schizophrenia

In another report, Dr. Boulanger described findings that changes in the cell surface levels of MHC Class I molecules are sufficient to cause cellular and behavioral symptoms of autism and schizophrenia in mice. This raises the possibility that changes in immune signaling could affect brain development by altering the levels of MHC Class I proteins, which play a key role in normal brain development.

"We know that autism and schizophrenia are two disorders where patients often have both immunological and neurological abnormalities," she said. "Our results show that MHC Class I molecules, which are known for their role in the adaptive immune response, are also critical for the establishment of normal functional brain circuitry."



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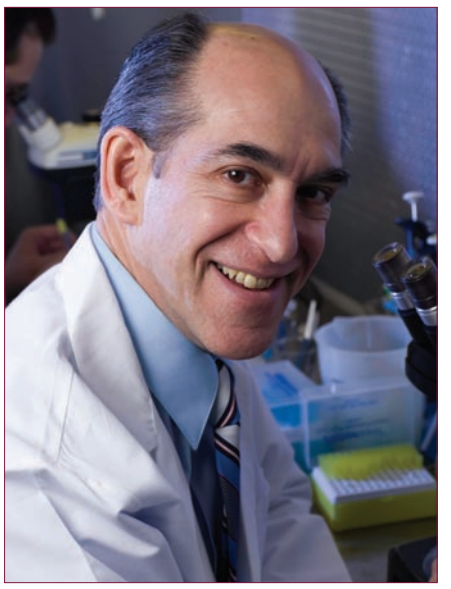
These results are interesting in the context of epidemiology suggesting that maternal viral infection in genetically-predisposed individuals is a risk factor for a child developing either autism or schizophrenia, Dr. Boulanger said. "These are primarily genetic disorders. However, environmental factors can also contribute, since identical twin concordance is less than 100 percent. Maternal viral infection may be an environmental risk factor, and we are beginning to investigate the possibility that this risk is mediated by changes in the MHC I proteins."

'As a cautionary note, there remain many questions about whether immune system responses, in either the child or mother, act through this MHC 1 family of proteins on neurons to cause functional deficits.'

In both autism and schizophrenia, abnormalities are observed in glutamatergic signaling and in prepulse inhibition (PPI), a behavioral test that measures the ability to "tune out" irrelevant sensory information. Dr. Boulanger's team examined the brains of mice with genetically-altered cell surface levels of MHC Class I. In particular, they studied the glutamate signaling system in one experiment, and in another, PPI. Both studies were in mice with altered MHC Class I levels.

"We found in our current study that mice with altered levels of MHC Class I share both abnormal glutamate signaling and a deficit in PPI," she said. "These results demonstrate that changes in particular immune molecules are sufficient to cause neurodevelopmental disruption that reproduces these two core symptoms. Our studies may provide clues to understanding why immune abnormalities are frequent among patients with autism and schizophrenia and their close relatives. Perhaps they are the result of the same core deficit."

Another neuroscientist who was not involved in Dr. Boulanger's work —Emmanuel DiCicco-Bloom, MD, of the University of Medicine and Dentistry New Jersey-Robert Wood Johnson Medical School — said her studies were "exciting because they provide a key to unlock potential relationships between brain development and the immune system, and, in turn, provide insights into how immune challenges, such as maternal infections, may negatively impact the developing brain."



Dr. Emmanuel DiCicco-Bloom said the studies by Dr. Boulanger are "exciting because they provide a key to unlock potential relationships between brain development and the immune system, and, in turn, provide insights into how immune challenges, such as maternal infections, may negatively impact the developing brain."

linking immune proteins to normal brain development and function. "Indeed, it may be over-simplistic to call these 'immune proteins' any more than to call the ubiquitous fibroblast growth factors in the brain 'renal proteins' based on their prominent role in the kidney," he said. ■

The research by Dr. Shatz not only provides a better understanding of brain wiring, but it may also provide clues to disorders such as Alzheimer disease and schizophrenia.

"The changes in glutamate signaling and animal behavior that are observed when MHC Class I proteins is deleted are both features associated with neurodevelopmental disorders, including schizophrenia and autism spectrum disorders," he added.

"However, as a cautionary note," he said, "there remain many questions about whether immune system responses, in either the child or mother, act through this MHC 1 family of proteins on neurons to cause functional deficits."

He believes that these unexpected findings may lead to more discoveries

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