Workhorse immune molecules lead secret lives in the brain

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Molecules assumed to be in the exclusive employ of the immune system have been caught moonlighting in the brain - with a job description apparently quite distinct from their role in immunity.

Carla Shatz, PhD, professor of neurobiology and of biology, and her colleagues at the Stanford University School of Medicine have shown that members of a large family of proteins critical to immune function (collectively known as HLA molecules in humans and MHC molecules in mice) also play a role in the brain. "We think that this family of molecules has an important role in learning and memory," Shatz said. Surprisingly, the absence of one or another of them in the brain can trigger improved motor learning, although perhaps at the expense of other learning ability.

The study will be published online on March 30 in the journal Proceedings of the National Academy of Sciences.

The proteins in question sit like jewel cases on the outer surfaces of most cells in the body, displaying fragments of the cell's innards, called peptides, to best advantage for window-shopping by roving inspectors called T-cells. When a T-cell "sees" a peptide with an aberrant chemical sequence - a sign of possible infection or cancer - it can attack the aberrant cell directly or alert the immune system, which responds with a vengeance.

It was long thought that MHC molecules are found on the surfaces of

brain cells only when the brain suffers injury or infection. But that picture was altered several years ago when a group led by Shatz compared gene expression in normally reared mice and another group that had been deprived of visual stimuli. In particular, they looked at a region of the brain that processes visual input. "Completely unexpectedly, we found that one of the genes needing input from the eye in order to be expressed encodes an MHC molecule," said Shatz.

She and her colleagues then showed that knocking out the expression of most MHC molecules in a brain region that processes visual stimuli caused developmental abnormalities in the circuitry of the mouse's visual system. "That implied indirectly that at least some MHC molecules were needed" for normal tuning up of brain circuits needed for vision, Shatz said, "but which ones?" There are about 60 in the mouse genome - and even more in the human genome.

The researchers found that two of those molecules in particular - called "K" and "D" - were expressed in the cerebellum, a brain structure critical to motor learning. It's believed that by detecting and reporting differences between intended and executed acts, cerebellar circuitry guides the body toward ever better piano recitals or tennis games. Practice makes perfect.

A key element in these circuits is a particular cell type called the Purkinje cell. Motor skills are perfected via the strengthening and weakening of connections, called synapses, between Purkinje cells and other cells supplying inputs to them.

In the new study, the Shatz laboratory looked at mice's ability to learn how to keep from falling off a rotating rod called a rotarod. "It's like a circus trick," said Shatz. First author Mike McConnell, a postdoctoral researcher now at the Salk Institute in La Jolla, Calif., put two batches of mice - normal ones, and bioengineered mice that lacked the "K" and "D"

proteins - through their paces on the rotarod without knowing which batch was which. He noticed that one batch was consistently superior at learning the task. A week later he retested them, with the same results. After another three-month rest, the early winners continued to excel while the slower group had to relearn the rotarod routine pretty much from scratch.

When the identity of the two mouse groups was revealed, it turned out that the good learners were the mutant mice. Looking closely at the mice's cerebellar circuitry, the researchers also discovered that contacts between Purkinje cells and the cells feeding them inputs were altered more easily in the K- and D-deficient mice than in the normal ones.

"This proves that changes in levels of these two MHC molecules is enough to account for both changes in motor learning and the ease of strengthening or weakening connections in the cerebellum," Shatz said. "It implies that, normally, these molecules are putting a brake on the nervous system's ability to alter its circuitry in response to changing experiences. When you take the MHC molecules away, you remove the brake."

In the wild state, motor performance - running from predators, chasing down meat - is a nice thing to have. If the K- and D-deficient mice learn and retain motor skills better, why doesn't evolution select for the deficient mice? Said Schatz: "Several other forms of learning besides motor learning - cognitive learning, spatial learning, recognition - don't take place in the cerebellum. There may be tradeoffs between one kind of learning and another - you're better able to escape but don't know exactly what to do in the next environment you encounter after running away - as well as between learning ability and circuit stability. More-easily altered circuitry might also be more prone to epilepsy."

The Stanford researchers have found other MHC molecules expressed in

other types of neurons in other parts of the brain. "These molecules keep showing themselves to be important in limiting how much circuits can change by strengthening or weakening connections between nerve cells. We think they're going to figure as important players in many neurological disorders," Shatz said, noting a tantalizing if still controversial link between immune function and developmental brain disorders such as autism and schizophrenia.

"Traditionally, there's been a kind of provincialism about molecules," she said. "You know, 'Some molecules are used only by the immune system, other ones only by neurons.' But I think the assumption that the immune system would have sole ownership over these molecules is pretty naive.

"We could have ignored this finding. We could have said, 'Well, MHC isn't supposed to be there, so it must be an artifact.' And we would have missed one of the most exciting aspects of doing research, which is the unexpected."

Source: Stanford University Medical Center (news : web)