Immune system may target some brain synapses

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A baby's brain has a lot of work to do, growing more neurons and connections. Later, a growing child's brain begins to pare down these connections until it develops into the streamlined brain of an adult.

Now researchers at the Stanford University School of Medicine have discovered the sculptor behind that paring process: the immune system.

The value of this discovery goes beyond understanding how connections are weeded out in a normal, developing brain. The finding could also help explain some neurodegenerative disorders - such as glaucoma, Alzheimer's disease and multiple sclerosis - that result from the loss of too many neuronal connections, which are known as synapses.

The advance, which has implications for drugs that could halt or reverse such conditions, will be published in the Dec. 14 issue of the journal *Cell*.

It was widely known that synapse elimination occurs during normal development of a child's brain, but until now, no one knew how certain synapses were flagged for removal. "We have identified the long-mysterious mechanism by which excess synapses are sculpted away in the developing brain," said the study's senior author, Ben Barres, MD, PhD, professor of neurobiology.

Barres' team found that the brain-sculpting process was controlled by a component of the immune system known as the classical complement

cascade.

The complement cascade is one part of the multipronged attack the immune system launches throughout the body when it detects a foreign invader. Consisting of more than 20 small proteins that normally circulate in the blood in their inactive forms, the complement system is triggered into action by an invading parasite. The first activated protein activates a second one, which in turn activates a third, continuing down the line in a domino effect, ultimately yielding a membrane-attack response that kills cells.

Barres' team produced the first proof that the complement system also plays a role in the brain by showing that complement proteins bind to unwanted synapses, targeting them for elimination. Future studies will determine how the synapses are marked for death.

When children reach the age of 10, synapse elimination normally shuts down. But the researchers found that this elimination process becomes reactivated very early in glaucoma, a neurodegenerative disease that is a major cause of blindness. They found that the earliest known sign in glaucoma was the complement cascade becoming active at synapses, followed by massive synapse loss. Only much later did the neurons die, which is the hallmark of neurodegenerative diseases.

"This is interesting, as these complement proteins are known to be drastically up-regulated in nearly every neurodegenerative disease process that has been examined," said Barres. Up-regulation is the process by which a cell increases the amount of a molecule, such as a protein, in response to a change in its environment. Alzheimer's disease, which involves massive synapse loss, has a hundredfold up-regulation of complement proteins, he said.

First author Beth Stevens, PhD, a postdoctoral scholar in Barres' lab, said

these findings in glaucoma made the team wonder if the same synapse-elimination process is restarted in other neurodegenerative diseases. "It's an exciting thought, as this would be the earliest sign of disease so far," she said.

The Barres laboratory has long been interested in the development and function of glial cells, which constitute around 90 percent of the cells in the human brain. These cells - specifically oligodendrocytes and astrocytes - provide support and protection for neurons, but the main role of the glia is a mystery, said Barres. His lab has been systematically identifying proteins and chemical factors that glial cells produce to modulate the activity of neurons.

The current finding of the complement cascade's involvement in the synapse-paring process was a bit of serendipity, said Stevens. The team knew the process coincided with the appearance of astrocytes in the developing brain, so they decided to run a microarray - the lab tools that can screen thousands of genes at a time - to see which neuronal genes were most active when neurons are exposed to astrocytes.

Unexpectedly, they found that the first protein in the complement cascade, called C1q, was the most up-regulated of all proteins.

"The role of the complement system was known in the rest of the body, but this opened up the question of what was going on in the brain," said Stevens. "It was surprising that C1q was the most changed protein; we didn't even think it was expressed in the brain."

Stevens went on to painstakingly characterize the role of the complement cascade. She ultimately showed that astrocytes make complement proteins that "tag" brain synapses during development. Complement protein C1q, and another one called C3, were required for synapse elimination.

Based on their finding that synapse elimination was reactivated in glaucoma, Stevens and Barres have a number of collaborations under way looking at the complement cascade's role in other neurodegenerative disorders, including Alzheimer's, autism, Lou Gehrig's disease (known as ALS), multiple sclerosis and Parkinson's.

"As synapse loss and C1q up-regulation are prominent features of all these diseases, our findings imply that drugs that blockade the complement cascade may provide a new treatment for many different neurodegenerative diseases," Barres said.

Source: Stanford University