Team finds genetic link between immune and nerve systems

September 19 2008

DURHAM, N.C. —Duke University Medical Center researchers have discovered genetic links between the nervous system and the immune system in a well-studied worm, and the findings could illuminate new approaches to human therapies.

For some time, researchers have theorized a direct link between the nervous and immune systems, such as stress messages that override the protective effects of antibodies, but the exact connection was unknown.

"This is the first time that a genetic approach has been used to demonstrate that specific neurons in the nervous system are capable of regulating immune response in distant cells," said Alejandro Aballay Ph.D., Assistant Professor in the Duke Department of Molecular Genetics and Microbiology.

They studied a neural circuit in the roundworm *Caenorhabditis elegans*.

"The study of neural-immune communications is quite challenging in mammals," Aballay said. "The simple, well-characterized nervous system of *C. elegans* and its recently discovered innate immune system make it a prime system for research. We can study the mechanisms and biological meaning of the cross-talk between the immune and nervous systems, and our studies should set the stage for a new field of research."

Pamela Marino, Ph.D., who oversees molecular immunology grants at the National Institute of General Medical Sciences of the National

Institutes of Health, said, "Dr. Aballay has made use of the well defined genetics of the roundworm to reveal evidence of cross talk between the nervous system and the innate immune system. Beyond neuronal regulation of immunity, this work opens the door to understanding how neurons may affect other non-neural processes, such as fat storage and longevity."

The study, published in the Sept. 18 issue of *Science,* was funded by grants from the Whitehead Scholars Program and the National Institutes of Health.

The research team used two approaches to show the genetic connection between nerve cells and immune-response cells.

They found that NPR-1, a worm cell receptor linked to proteins that are similar to mammalian neuropeptide Y, functions to suppress the activity of specific neurons that block immune responses. They then studied worms with a mutated npr-1 gene that produced an NPR-1 receptor that didn't function. The scientists showed that when the flawed receptor didn't work, the neurons were able to block the immune response and the worms became more susceptible to infection by pathogens.

The three different neurons found to express the receptor NPR-1 are exposed to the body fluids of the roundworm – the equivalent of the bloodstream in humans. Signals from the neurons can travel and communicate with other tissues, such as intestinal tissue, which often directly contacts microbial pathogens, Aballay said.

They also performed a full-genome analysis on roundworms that had altered nerve-cell function because of a mutation in the npr-1 gene. This analysis showed the animals had poorly regulated expression of genes that encode markers of innate immune responses. In particular, they found that most of the immune marker genes were regulated by a P38

MAPK signaling pathway, which is required for immunity in animals from worms to humans.

"The complexity of the network involved in the communication between the neural system and the immune system expands the number of possible targets for therapeutic interventions," Aballay said. "The nervous system alone provides a large number of targets for novel approaches to boost innate immunity against different pathogens."

Source: Duke University Medical Center