

Worms' nervous system shown to alert immune system in Stanford studies

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The nervous system and the immune system have something in common. Each has evolved to react quickly to environmental cues. Because the nervous system is able to detect some of these cues - say, a characteristic odor signaling a pathogen's presence - at a distance, it sometimes can sense trouble earlier than the immune system, which has to wait until the pathogen invades the organism.

So it makes sense that the two systems might talk to one another. Stanford University School of Medicine geneticists have shown that, indeed, they do.

In a study to be published online Oct. 14 by the journal *Nature Immunology*, Man-Wah Tan, PhD, assistant professor of genetics and of microbiology and immunology, and postdoctoral scholar Trupti Kawli have shown that a change in the secretion patterns of nerve cells in the minuscule soil-dwelling worm, *Caenorhabditis elegans*, induces a change in the worm's susceptibility to a bacterial pathogen, *Pseudomonas aeruginosa*. In humans, *P. aeruginosa* is an important pathogen among cystic fibrosis patients and can cause pneumonia.

Importantly, the Stanford investigators have nailed down the connection between the two systems. They identified a particular molecule that, secreted by nerve cells, binds to receptors in the worm's gut cells. When the levels of the secreted molecule fall, this sets off a complicated chain reaction that activates the powerful immune defense against bacterial infection. Since bacteria are what *C. elegans* mainly eats, this is a handy

defense to have.

The notion of crosstalk between our nervous and immune systems is hardly surprising, said Tan. "A person who is undergoing prolonged psychological stress - say, because they're taking care of someone who is sick - is more likely to have reactivation of a latent infection or become more susceptible to new ones," he said. "That stressful situation cannot be changed. But by identifying the pathways through which the nervous system alters immune function in this simple creature *C. elegans*, we can perhaps start to think about how we can intervene in humans."

The very complexity of the nervous and immune systems would make any interactions between them exceedingly tough to tease out in humans. So Kawli and Tan used *C. elegans*, because both its nervous and immune systems have been entirely mapped out. This enabled the researchers to manipulate the former, then watch what happened to the latter.

C. elegans has nerve cells that ordinarily secrete bioactive molecules contained within tiny membrane-wrapped bundles, called dense-core vesicles. The rate at which these molecules are secreted is governed by the activity of the nervous system. One of those secreted bioactive molecules is called ins-7. The Stanford team obtained or generated various *C. elegans* mutants that lacked the ability either to produce or to secrete ins-7, or secreted it excessively.

By using these and other advanced laboratory tools to manipulate the worm's ability to secrete ins-7, the researchers were able to correspondingly alter the readiness of the minuscule creature's innate immune system: a primitive but potent piece of the immune system shared by *C. elegans* and higher organisms including humans.

People often associate "immune response" with antibodies and roving T-cells dispatched to combat a particular viral or bacterial infection - the so-

called adaptive immune response. But that response takes a week or two to develop, said Tan. In contrast, all of our cells have receptors that can recognize molecular patterns common to whole classes of pathogens (for example, characteristic viral DNA snippets, or bacterial cell-wall constituents), immediately triggering cascades of intracellular reactions, such as the activation of batteries of genes that code for antimicrobial proteins.

Both the innate and adaptive branches of the immune system have to function optimally in order for us to leave a healthy life. "The innate immune system is our first line of defense," said Tan. "If not for the innate immune system, we'd be dead by the time the adaptive immune system raises antibodies to a pathogenic invader we have not encountered before."

It is still a matter of speculation as to how crosstalk between the nervous and immune systems of humans regulates innate immune responses. But now that a clear pathway has been identified in the worm, it will be easier to conduct focused research on higher organisms to see if the phenomenon is universal, Tan said.

Tan acknowledged that it has not yet been proven that the signaling of the nervous system to the immune system of *C. elegans*, as shown in this experiment, occurs in nature. But there's very good reason to believe it does.

In a separate paper set to be published online on Oct. 17 by another journal, PLoS-Pathogens, Tan and other Stanford associates demonstrate that *P. aeruginosa* - which is often isolated from the same soil samples in which *C. elegans* is found and, presumably, co-evolved with *C. elegans* - has a way of subverting this defense against it. The pathogen induces excess production of ins-7 by the worm to dull its immune responsiveness. In contrast, other human bacterial pathogens such as

Salmonella typhimurium and Enterococcus fecalis have no such capability. Nor do abiotic stresses, such as heat or heavy metals.

This suggests to Tan that the fine-tuning of the innate immune response by the nervous system is effective enough in the natural state that some pathogens with which *C. elegans* coexists have evolved strategies to subvert this system.

An inducible immune response makes more sense - in worms and people - than a state of constantly hyper-elevated immune vigilance. People with hyperactive immune systems suffer from autoimmune and inflammatory conditions. Although worms with downregulated secretion from dense-core vesicles are better at combating infection, they don't move well, which would probably prove lethal in the wild. One of the *ins-7*-deficient *C. elegans* mutants used in the Nature Immunology study is called *unc*, said Kawli, the paper's first author. "That stands for 'uncoordinated,'" she said.

Source: Stanford University

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