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Insects may have complex immunity

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Insects may possess a hitherto unsuspected molecular complexity in their immune system, comparable to the antibody system of mammals, scientists report online this week in *Science*.

"The number of immune receptors might go from a couple of dozen up to thousands in insects. The complexity there might have really been underestimated," senior author Dietmar Schmucker, of Harvard Medical School in Boston, told *The Scientist*.

In 2000, Schmucker and colleagues discovered that the Down syndrome cell adhesion molecule gene (*Dscam*) could, through alternative splicing, generate more than 38,000 proteins in *Drosophila*. The immunoglobulin super family receptor appeared to guide neuronal wiring.

In the current study, the researchers investigated whether *Dscam* played a role in immune response. Using reverse transcriptase polymerase chain reaction (RT-PCR), they found *Dscam* expression in *Drosophila* fat body cells, which secrete antimicrobial peptides, and hemocytes, which are involved in phagocytosis. Using antibodies against extracellular domains of *Dscam*, they also found a soluble Dscam protein secreted in hemolymph serum.

Microarray analysis for alternatively spliced *Dscam* exons suggested that fat body cells and hemocytes could generate more than 18,000 receptor isoforms, Schmucker and colleagues reported. Comparative genomic analysis between insect orders Diptera, Hymenoptera, Coleoptera, and Lepidoptera revealed high conservation of orthologous *Dscam* genes.

The ability to generate extensive diversity of immune receptors was generally thought to be limited to jawed vertebrates. "This diversity of proteins certainly raises the parallel to antibodies in higher mammals," Brenton Graveley at the University of Connecticut Health Center in Farmington, who did not participate in this study, told *The Scientist*. "In mammals, T-cell receptors have recently been found to be expressed in the brain, so this shows another class of molecules that play an important role in both nervous and immune systems."

To investigate what *Dscam's* immune function might be, the researchers challenged wild-type and *Dscam*-deficient hemocytes with heat-killed fluorescent-labelled *E. coli*. Only 55% of *Dscam*-deficient hemocytes ingested bacteria after 10 minutes, compared to 85% to 90% of normal hemocytes.

Schmucker and colleagues subsequently found that isoforms Dscam-7.27.25-Fc and Dscam-7.27.13-Fc could bind to live *E. coli*, while binding of Dscam-1.30.30-Fc was barely detectable. This raises the possibility that different isoforms might bind specifically to distinct epitopes on bacteria.

"A whole series of new studies are needed to address whether these different isoforms really are capable of an adapted, specific response to pathogens," Schmucker said. "We could purify hemocytes out, challenge them with different pathogens and have microarrays look at *Dscam* splicing to see if you do upregulate certain isoforms in a predictable way, if you have a gram-positive infection or a gram-negative one or of yeast." Another open question these findings raise is whether insects possess immunological memory, he added.

In the end, levels of insect and mammalian immune molecular diversity may reflect very different lifestyles, Schmucker noted. "Insects live only a few months, some a few years, so that makes a big impact in how you invest in immunity. Immune receptor diversity may not be as important there when compared with vertebrates, many of which live many years," he explained.

"If this is adaptive immunity in insects, it's probably a case of convergent evolution with mammals," Graveley said. "Both are composed of Ig domains but are very different structurally and involve very different mechanisms of alternative splicing and gene rearrangement. And there is a *Dscam* homolog in mammals that is not alternatively spliced to an appreciable extent."

Given the millions of extant insect species, different spectra of *Dscam* isoforms likely exist, added Larry Zipursky of the University of California, Los Angeles, who did not participate in this study. "That might in some way reflect a difference in their susceptibility to pathogens, and understanding that or even interfering with that may have important implications for issues of agriculture or of insects that act as vectors for human disease, such as with mosquitoes and malaria," he told *The Scientist*.

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