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How worms tackle stress

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When an animal cell encounters a bacterial or chemical toxin, it needs to respond to ensure its survival, but how it does this is still poorly understood. Now, two independent studies clarify the involvement of the c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) signalling pathways in these responses in *Caenorhabditis elegans*.

Both JNK and p38 are well known mediators of stress responses in mammalian cells, and in *C. elegans*, these proteins, other components involved in their signalling pathways, and their involvement in stress responses are conserved. The two new papers, reported in the July 12 issue of Proceedings of the National Academy of Sciences USA, together reveal an evolutionarily interconnected mechanism for responding to bacterial stress.

"MAPKs appear to be one of the most ancient defense pathways known from plants, yeasts, and animals," said Hinrich Schulenburg, from the University of Münster, and who was not involved in the two *PNAS* studies. "These two studies now provide evidence for the role of two different MAPK pathways in the worm's defense against pathogens," Schulenburg told *The Scientist*.

In the first report, Danielle Huffman, Raffi Aroian, and their colleagues analyzed how *C. elegans* responded to Cry5B, a bacterial pore-forming toxin made by *Bacillus thuringiensis* (*Proc Natl Acad Sci USA* 2004, DOI:10.1073/pnas.0404073101). "Twenty-five percent of all known bacterial virulence factors are pore-forming toxins... We asked the question of whether animals cells have evolved a defense mechanism against this kind of an attack," said Aroian, from University of California, San Diego.

To begin tackling this question, Huffman, Aroian, and colleagues fed *C. elegans* bacteria expressing Cry5B and then determined what effect this had on gene expression through the use of microarrays. They found over 1000 genes that changed in response to Cry5B exposure, two of which were members of p38 and JNK pathways, namely the MAPK kinase gene *sek-1* and the JNK-like gene *kgb-1*, respectively.

The elimination of either the *sek-1* or *kgb-1* gene resulted in worms that were highly sensitive to Cry5B. In addition, the authors found that inhibiting the p38 pathway in mammalian baby hamster kidney cells caused hypersensitivity to the bacterial toxin aerolysin. "Therefore, the mechanism is conserved from worms to mammalian cells, and reveals that cells can mount defenses to these toxins," Aroian told *The Scientist*.

In the second report, Dennis Kim, Frederick Ausubel, and their colleagues revealed a link between the *C. elegans* JNK and p38 MAPK pathways with regard to pathogen immunity. They found two components of *C. elegans* KGB-1 JNK-like pathway, namely the MAPK kinase MEK-1 and the MAPK phosphatase VHP-1, were able to modulate resistance to the pathogen *Pseudomonas aeruginosa*by effecting the p38 protein PMK-1.

In fact, in *mek-1* knockout worms, PMK-1 activation was reduced, and this correlated with increased pathogen susceptibility, whereas reduction of VHP-1 levels by RNA interference increased PMK-1 activation and could suppress the pathogen susceptibility of *mek-1* knockout worms. These results reveal

that components of the *C. elegans* JNK pathway are also involved in the p38 pathway and "suggest that cells can integrate their stress-regulated pathways under some circumstances," said Kim.

"Such cross-talk may be pivotal in generating an economic and most efficient response towards environmental offences," said Schulenburg. "Without such fine-tuning, an organism may be forced to mount the complete stress response irrespective of the challenge."

Alejandro Aballay, from Duke University, agreed that the two papers provide an "elegant" look at how interacting and intersecting pathways involved in innate immunity are regulated in *C. elegans*. "I envision more and more works in which dead and live bacteria will be used to address whether a given gene affects innate immunity," he told *The Scientist*.

Schulenburg does add that much is still to be learned about how JNK and p38 pathways act, and interact, to regulate stress responses. Nevertheless, the new results "should be of immense importance in understanding the complexity of signaling pathways, especially MAPK signaling, in living organisms," he said.

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