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New control over worm rhythms

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A previously unrecognized *Caenorhabditis elegans* gene is vital for rhythmic muscle movements, according to a study published in last week's *Cell*. When the gene *vav-1* is disabled, nematodes cannot swallow, ovulate, or defecate normally.

"It seems, at least in the worm, that *vav* has a key regulatory function in controlling biological rhythms," said senior author Andres Villu Maricq of the University of Utah in Salt Lake City.

Still, Villu Maricq and his colleagues note that many other animals have *vav* genes whose function may be conserved.

Previous work has shown that oscillations in intracellular calcium trigger *C. elegans* muscle contractions necessary for peristalsis, gonadal contractions, and defecation. Studies in mammalian immune cells have also suggested that members of the Vav protein family may control intracellular calcium signaling.

Maricq and his colleagues identified an open reading frame in the *C. elegans* genome that encodes a protein containing all the characteristic domains of the vertebrate Vav proteins. This protein, which they name VAV-1, is expressed in rhythmically contracting tissues, including the pharynx, intestine, gonads, and rectal epithelia.

When Maricq and his co-workers created a mutant worm with a deletion mutation in *vav-1*, all the worms died early in the larval stage. It was a "huge surprise" that *vav-1* was larval-lethal, Maricq told *The Scientist*, and an equally big surprise that the cause of death was a lack of pharyngeal pumping.

Contractions normally occur every 1 to 2 seconds, but in the mutants, these movements were weak and asynchronyous, as were calcium fluctuations in pharyngeal cells. When the researchers restored expression of VAV-1 protein in the mutants, however, normal pharyngeal function returned and they no longer died prematurely.

To examine other rhythmic movements in *C. elegans*, the researchers restored VAV-1 protein expression exclusively in the pharynx. As adults, the mutants displayed normal locomotion but severely reduced fertility. Fertilization in *C. elegans* hermaphrodites requires a "complex choregraphy," Maricq said, of gonadal sheath-cell contractions, oocyte maturation, and opening of the spermatheca, which houses sperm and receives eggs ready to be fertilized. "That timing has completely gone awry" in *vav-1* mutants, Maricq said.

The rhythmic defecation cycle was also destroyed by the *vav-1* mutation. The extremely regular normal defecation cycle—once every 45 to 50 seconds—became irregular and, on average, much longer in mutants, Maricq said. As in the pharynx, the mutants' intestinal cells also showed highly irregular calcium fluctuations.

The authors did additional genetic experiments to dissect the pathway through which VAV-1 is likely controlling calcium concentrations. In vertebrates, Vav protein phosphorylation leads to activation of

GTPases that then activate channels embedded in organelle membranes called inositol triphosphate (IP_3) receptors; these channels release calcium into the cytoplasm.

Maricq and his colleagues found that gain-of-function mutations in the *C. elegans* IP_3 receptor suppressed the abnormal defecation cycle of vav-1 mutants. They also found that simultaneously disabling two genes encoding GTPases led to a defecation cycle the same as in *vav-1* mutants.

It's surprising that these rhythmic pathways "could be so profoundly disrupted by mutations in *vav-1*," said Leon Avery of the University of Texas-Southwestern. "I would have thought we actually understood most of what was going on in those cells," Avery said. "I didn't really expect that there would be room for something new…to have such a strong effect."

Scientists knew that intracellular calcium oscillations underlie rhythmic behaviors like defecation and that IP_3 receptors control these oscillations, Paola Nix of the University of California, Berkeley, told *The Scientist.* This study provides a more complete picture, she added. "We really didn't know anything upstream of IP_3 receptor function." Neither Nix nor Avery were involved in the study.

What lies upstream of *vav-1* is still a mystery, Maricq said. Evidence from vertebrates suggests that cell-surface receptors activate *vav-1*. Different types of receptors may be coupled to *vav-1*'s control of calcium, Maricq said, "so different tissues may have different upstream signaling pathways."

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