

Nematode tempo

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Hearts beat, throats swallow and Fallopian tubes squeeze. Many parts of us are pumping, pushing, and expanding at regular intervals all day long. And the regularity of these intervals depends on intricate molecular pathways that we are only beginning to understand. Part of the secret is being unveiled thanks to a minute nematode – *Caenorhabditis elegans* – whose rhythmic movements are easy to follow simply because of its transparency. A protein similar to proteins already discovered in humans, and known as Vav-1, seems to be at the heart of rhythms in the worm, which allow it not only to swallow but also to conceive and – less romantically – to expel waste.

We are made up of many kinds of rhythms, two of which are ultradian and circadian. Circadian rhythms occur once a day; ultradian rhythms occur more than once a day and are best illustrated by the heartbeat, breathing or even *Drosophila*'s courtship song.¹ Circadian rhythms depend mainly on gene regulation and expression, whereas ultradian rhythms depend more on signalling pathways. Vav-1 is part of such a pathway, and triggers off – not the worm's act of swallowing, conceiving or evacuating – but the regularity with which each of these processes occurs.



Caenorhabditis elegans

Courtesy of Ralf Sommer

Caenorhabditis elegans is a choice animal for the study of such processes. And not only because it is transparent. It is a free-living nematode which lives in the soil, feeds off bacteria and is far easier to culture in a laboratory than mice or even fruit flies. In the late 1950s, the molecular biologist Sydney Brenner suggested that *C.elegans* would be a choice organism as a metazoan model for the study of higher organisms. And since then, knowledge in mechanisms as diverse as cell death, fear responses, development and signal transduction has taken a huge leap. *C.elegans* was also the first multicellular organism whose genome was sequenced just before the turn of the millennium. And researchers are now well acquainted with its 959 cells which represent the bare minimum of what is needed to make an animal, i.e. a multicellular organism with skin, muscles, a digestive system, a reproductive system and even a nervous system.

Swallowing, fertilising and discharging are movements which demand rhythm. These three rhythmic movements whose periodicity ranges from sub-seconds to seconds and minutes, respectively, are orchestrated by Vav-1 in *C.elegans*. In Vav-1 mutants, the nematode does not swallow so frequently, and dies of hunger at an early stage. The other end of its intestines also loses its usual tempo and the nematode suffers from constipation. As for the reproductive system, *C.elegans* is hermaphrodite and sends oocytes down to the spermatheca by way of coordinated contractions and dilations. In Vav-1 mutants, coordination is

¹ Read Protein Spotlight issue 6

disturbed and eggs either do not reach the sperm, or get there too early or too late.

Vav-1 must play a key role in a major molecular pathway for it to be the cause of such physiological drawbacks. As far as tissue distribution goes, it is found in the nematode's pharynx, the proximal gonad, the spermatheca, its intestine and in the rectal epithelia. It is a nucleotide exchange factor and is activated upon tyrosine phosphorylation. Once stimulated, it catalyses the swap of GDP for GTP on Rho family GTPases, which in turn regulate the binding of messenger IP3 – inositol 1,4,5-trisphosphate – to its receptor. This results in the downstream activation of calcium channels. As a result, intracellular calcium levels also change in an oscillatory fashion – as is expected in the event of rhythmic movements. Vav-1 does not affect the actual spasms required to swallow, fertilise or excrete but it does interfere with their regularity, causing starvation, infertility and constipation.

Besides establishing a worm's interior tempo, vav-1 could give insight into certain forms of cancer. Studies on nematode vav-1 were financed because of its analogy to proto-

oncogenes in mammals, i.e. genes which – once mutated – can give rise to a given type of cancer. Mutant vav genes can cause cancer-like changes in mammalian cells in vitro. And humans also have vav genes. But it is not known whether they could also be proto-oncogenes.

When immune cells are stimulated by foreign bodies, like bacteria, the vav genes are activated. Intracellular calcium levels are modified as a result, sending off a signal to the immune system to react, and cells to multiply. If vav activation is tampered with and not switched off, for instance, the net result would be the unhindered multiplication of cells, i.e. cancer. If such is the case, a greater knowledge of the nematode vav-1 gene could lead to anti-cancer therapies – because if drugs are designed to hinder the rhythmic movements of *C.elegans* by interfering with vav-1, then these drugs could also be effective anti-cancer drugs. The leap from worms to humans is great, yet there is no reason to doubt that human vav genes are also involved in the same rhythmic movements in humans, since we too swallow, ovulate and defecate.

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Vav-1, *Caenorhabditis elegans* : Q45FX5

References

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