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# Sid knocks them out

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## Abstract

A putative transmembrane protein is required for systemic RNAi in *Caenorhabditis elegans*

# Significance and context

Although diminutive in size, the nematode *Caenorhabditis elegans* has been a giant in the laboratory for many years, holding its own with *Saccharomyces*, *Arabidopsis*, *Drosophila*, *Mus* and *Rattus* as a key model species. The importance of *C. elegans* was further inflated in the late 1990s, when its genome was fully characterized and it was also discovered that injection of gene-specific double-stranded RNA (dsRNA) into one tissue can lead to the silencing of that gene in many other tissues and in the worm's progeny. This process was termed double-stranded RNA-mediated interference (RNAi). Incredibly, this strange phenomenon can also be achieved by soaking the worms in dsRNA or feeding them bacteria expressing dsRNA of the gene to be silenced. Further experimentation with the RNAi process showed that it could be induced at the local (autonomous) or systemic level. In this paper, Winston *et al.* report the discovery, isolation and initial characterization of a gene (*sid-1*) that seems to be required for systemic RNAi to occur.

# Key results

In a genetic screen, three major complementation groups with systemic RNAi-defective (SID) phenotypes were identified. One of these was further characterized by a variety of methods. The cDNA sequence of the responsible gene (*sid-1*) was isolated, where and when the gene is expressed was determined, and the overall protein structure predicted from its sequence. The *sid-1* gene is initially expressed in late-stage embryos and continually thereafter in nearly all non-neural cell types, with the highest levels expressed in cells and tissues exposed to the environment. At the subcellular level, significant enrichment of *sid-1*was seen at the cell periphery, a location consistent with the presence of predicted transmembrane regions in the protein.

# Methodological innovations

The authors constructed a transgenic strain (HC57) of *C. elegans* that allows simultaneous monitoring of localized RNAi (*myo-2::GFP*, in the pharyngeal muscles) and systemic RNAi (*myo-3::GFP*, in the body wall muscles) through the expression of green fluorescent protein (GFP). RNAi was initiated through a third transgene (*myo-2::GFP* dsRNA) under control of the pharynx-specific *myo-2* promoter. Mutants resistant to systemic RNAi were identified by screening for those that were resistant to systemic RNAi of *myo-3*, but sensitive to the local RNAi of *myo-2*.

# Links

Supplementary data to *Science* **295:**2456-2459 include figures and details of experimental procedures and are available at free of charge. The homepage of Craig Hunter's laboratory contains a link to a full copy of the paper.

# Conclusions

The authors suggest that, on the basis of the proposed protein structure, SID-1 may act as a channel through which dsRNA can pass between cells. In addition, SID-1 has strong similarity to predicted human and mouse proteins, suggesting the possibility that RNAi may be systemic in mammals, and that the mechanism may share some components found in *C. elegans*.

# Reporter's comments

In this classic piece of genetic work, Winston *et al.*demonstrated considerable skill and persistence in teasing out the *sid-1* story. This is an important advance in our understanding when placed in perspective: knockout technology generally is one of the most powerful tools available for genetic studies, with the capacity to inform on the function(s) of specific genes during growth and development and to tell us how the absence of a particular gene can affect the response of an organism to a particular stimulus. However, suppressing specific gene expression by RNAi in most model organisms is not as simple as in *C. elegans*. Indeed, it has not been achieved in several important species, notably the rat. An increased understanding of the mechanism(s) underlying RNAi may lead to new methods being developed for suppressing gene expression - methods that are more efficient and easier to carry out than is currently the case. Winston *et al.*have elucidated at least part of the mechanism involved in RNAi and perhaps brought nearer the day when knockouts of single and multiple genes will be as routine as PCR.

# Table of links

*Science*

Supplementary data to *Science* **295:**2456-2459

Craig Hunter's laboratory

# References

1. Winston WM, Molodowitch C, Hunter CP: Systemic RNAi in *C. elegans* requires the putative transmembrane protein SID-1. Science. 2002, 395: 2456-2459. 0036-8075