

 GENE EXPRESSION

## Argonaute on the move

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...NRDE-3 is responsible for silencing nuclear-localized RNAs...”

Argonaute proteins function in small interfering RNA (siRNA)-mediated cytoplasmic RNA interference (RNAi). But Guang *et al.* now describe a function for the *Caenorhabditis elegans* Argonaute protein NRDE-3 in the nuclear import of siRNAs and in nuclear RNAi.

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A genetic screen identified mutations in *nrde-3* that resulted in animals that were defective in nuclear RNAi; however, cytoplasmic RNAi was unaffected in *nrde-3*-mutant worms. The mutant phenotype could be rescued by a fusion protein of wild-type NRDE-3 with green fluorescent protein. Whereas wild-type NRDE-3 localized to the nucleus, mutation of the siRNA-binding PAZ domain of NRDE-3 caused the redistribution of the protein to the cytoplasm. Animals that were defective for endogenous

(endo)-siRNA production also had cytoplasmic NRDE-3, which indicates that binding of endo-siRNA to NRDE-3 is essential for its nuclear localization.

The authors also showed that NRDE-3 is responsible for silencing nuclear-localized RNAs, including pre-mRNAs, although the mechanisms of nuclear silencing remain unknown. The absence of the conserved catalytic residues that are essential for endonuclease activity further supports the notion that NRDE-3 is likely to be unimportant for cytoplasmic RNAi. In addition, the 5' ends of endo-siRNAs in association with NRDE-3 suggest that these siRNAs have been generated by RNA-dependent RNA polymerases. This implies that NRDE-3-mediated nuclear RNAi is probably a downstream function of primary RNAi events in the cytoplasm.

So, is nuclear silencing dependent on the nuclear localization of NRDE-3? Mutant NRDE-3 that lacked its nuclear localization signal failed to rescue the *nrde-3*-mutant phenotype. Therefore, NRDE-3 must localize to the nucleus to trigger nuclear RNAi. It is possible that NRDE-3 is required only for nuclear import and that a second Argonaute protein mediates nuclear RNAi. It would also be interesting to test whether other types of small RNAs that are known to function in the nucleus, such as Piwi-interacting RNAs, are imported into the nucleus by similar mechanisms.

Arianne Heinrichs

**ORIGINAL RESEARCH PAPER** Guang, S. *et al.* An Argonaute transports siRNAs from the cytoplasm to the nucleus. *Science* **321**, 537–541 (2008)

**FURTHER READING** Hutvagner, G. & Simard, M.J. Argonaute proteins: key players in RNA silencing. *Nature Rev. Mol. Cell Biol.* **9**, 22–32 (2008)



BANANASTOCK