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SMALL RNAS

piRNA surveillance in the *C. elegans* germline

PIWI-interacting RNAs (piRNAs) are small RNAs that are key to the regulation of germline development and in the maintenance of germline genome integrity, but the targets and functional mechanism of piRNAs in *Caenorhabditis elegans* have remained elusive. Four related studies have now elucidated a role for *C. elegans* piRNAs in genome-wide surveillance of germline transcripts, leading to long-term silencing of transcripts recognized as 'non-self'.

Bagijn, Miska and colleagues and Lee, Mello and colleagues took a transgene approach, in which they generated *C. elegans* strains (that is, piRNA sensor strains) carrying a GFP–histone H2B fusion into which they had inserted a sequence known to be complementary to an endogenous piRNA. This non-self transgene was silenced in the germline but not in the PIWI protein mutant *prg-1* (PRG-1 is essential in piRNA biogenesis).

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Both groups showed that the silencing was independent of the slicer activity of PRG-1. However, they found that PRG-1 is essential for the production of the RNA-dependent RNA polymerase (RdRP)-generated RNAs, known as 22G-RNAs, that interact with a group of worm Argonaute (WAGO) proteins. These 22G-RNAs negatively regulate a specific subset of endogenous genes. Thus, both groups present evidence that piRNA silencing proceeds by means of the production of 22G-RNAs. Surveys by both groups of potential targets of piRNAs in the *C. elegans* genome suggest that piRNAs use relaxed pairing criteria to perform surveillance of the genome for 'harmful' transcripts, most notably for transposable elements.

In separate studies, Ashe, Miska and colleagues and Shirayama, Mello and colleagues show that after a transgene has been silenced by piRNAs, it remains silent permanently and can act dominantly to silence other homologous transgenes permanently. Shirayama, Mello and colleagues term this phenomenon RNA-induced epigenetic silencing (RNAe). By crossing silenced lines with *prg-1* mutants, both groups showed that the initial piRNA trigger is not required to maintain the memory.

So how does this system distinguish self from non-self? Shirayama, Mello and colleagues present evidence supporting the idea of this distinction being made through memory of RNA expression. For example, transgene regions composed of germline-expressed sequences seem to be protected from piRNA-induced silencing and in some cases an active transgene triggered reactivation of a silent copy of that transgene. The Argonaute CSR-1 may be involved in the transcriptional memory.

In addition, both groups show that downstream factors required for silencing memory are shared between the RNAi and piRNA pathways. The components include a germline-specific nuclear WAGO protein, WAGO-9 (also known as HRDE-1) and histone-modifying enzymes. Indeed, Shirayama, Mello and colleagues show increased histone H3K9me3 at a piRNA-silenced transgene.

Together, these studies reveal a novel role for piRNAs; it will be interesting to explore whether similar roles exist in other animals.

Hannah Stower

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