NON-CODING RNAS

PIWI's new assistant

> an integral role for GTSF1 in the Piwi–piRNA pathway

PIWI-interacting RNA (piRNA)-mediated silencing of transposable elements is one of many mechanisms used by animal cells to safeguard genomic integrity, as transposons can disrupt genes and alter the genome. Recent work identifies a protein — originally called Asterix and referred to as gametocyte-specific factor 1 (GTSF1) in two subsequent studies — that is a key cofactor of piRNA-mediated transcriptional silencing in *Drosophila melanogaster*.

piRNAs are non-coding RNAs that associate with PIWI proteins, of which there are three in *D. melanogaster*: the cytoplasmic Aubergine and Argonaute 3, and the nuclear Piwi. Piwi interacts with piRNAs in the cytoplasm, forming a complex that is imported into the nucleus to mediate transcriptional silencing of transposons that are complementary to the piRNAs. However, the underlying mechanism and the precise composition of the nuclear silencing complex are not fully understood.

Photodisc/Getty images

Previous work had shown that GTSF1 is required for transposon silencing in mouse testes. Muerdter *et al.*, Ohtani *et al.* and Dönertas *et al.* knocked down the homologue of GTSF1 in *D. melanogaster* and found that this blocked silencing of piRNA-targeted transposons. Interestingly, the phenotype of *D. melanogaster* lacking GTSF1 was comparable to those of Piwi–piRNA pathway mutants. These findings suggest a key role for GTSF1 in transposon silencing as part of the Piwi–piRNA pathway.

The groups sought to identify which step of the piRNA pathway GTSF1 is involved in. They found that loss of GTSF1 did not affect piRNA levels or Piwi–piRNA localization, indicating that it is not involved in piRNA biogenesis or nuclear import of the complex. Instead, GTSF1 interacts with Piwi *in vitro*, and the two proteins colocalize in the nuclei of *D. melanogaster* ovarian cells *in vivo*. Thus, GTSF1 might act as a cofactor in the silencing process. Notably, Dönertas *et al.* found that GTSF1 does not interact with Piwi through its CHHC zinc-finger motifs (which Ohtani *et al.* show are required for its activity) but through its carboxyl terminus.

Piwi mutants show a significant increase in RNA polymerase II occupancy (a sign of active transcription) and decreased levels of the repressive mark trimethylated histone 3 at Lys 9 (H3K9me3) at transposons. Importantly, Ohtani *et al.* and Dönertas *et al.* observed that knockdown of GTSF1 increased RNA polymerase II occupancy. Moreover, all three groups observed decreased enrichment of H3K9me3 at Piwi-repressed transposons, which, together with the increased RNA polymerase II occupancy, is similar to what has been observed in Piwi mutants.

These studies reveal an integral role for GTSF1 in the Piwi–piRNA pathway, acting during transcriptional silencing of transposons. Further work is now needed to determine the exact role of GTSF1 in the silencing complex.

Rachel David

ORIGINAL RESEARCH PAPERS Muerdter, F. *et al.* A genome-wide RNAi screen draws a genetic framework for transposon control and primary piRNA biogenesis in *Drosophila*. *Mol. Cell* **50**, 736–748 (2013) | Ohtani, H. *et al.* DmGTSF1 is necessary for Piwi–piRISC-mediated transcriptional transposon silencing in the *Drosophila* ovary. *Genes Dev.* **27**, 1656–1661 (2013) | Dönertas, D., Sienski, G. & Brennecke J. *Drosophila* Gtsf1 is an essential component of the Piwi-mediated transcriptional silencing complex. *Genes Dev.* **27**, 1693–1705 (2013)
FURTHER READING Czech, B. *et al.* A transcriptome-wide RNAi screen in the *Drosophila* ovary reveals factors of the germline piRNA pathway. *Mol. Cell* **50**, 749–761 (2013) | Siomi, M. C. *et al.* PIWI-interacting small RNAs: the vanguard of genome defence. *Nature Rev. Mol. Cell Biol.* **12**, 246–258 (2011)