The Piwi-piRNA Pathway Provides an Adaptive Defense in the Transposon Arms Race

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Increasingly complex networks of small RNAs act through RNA-interference (RNAi) pathways to regulate gene expression, to mediate antiviral responses, to organize chromosomal domains, and to restrain the spread of selfish genetic elements. Historically, RNAi has been defined as a response to double-stranded RNA. However, some small RNA species may not arise from double-stranded RNA precursors. Yet, like microRNAs and small interfering RNAs, such species guide Argonaute proteins to silencing targets through complementary base-pairing. Silencing can be achieved by corecruitment of accessory factors or through the activity of Argonaute itself, which often has endonucleolytic activity. As a specific and adaptive regulatory system, RNAi is used throughout eukarya, which indicates a long evolutionary history. A likely function of RNAi throughout that history is to protect the genome from both pathogenic and parasitic invaders.

Argonaute proteins, in complex with distinct classes of small RNAs, form the core of the RNA-induced silencing complex (RISC), the RNA-interference (RNAi) effector complex (*1*). The Argonaute superfamily segregates into two clades, the Ago clade and the Piwi clade (table S1). The single fission yeast Argonaute and all plant family members belong to the Ago clade, whereas ciliates and slime molds contain members of the Piwi clade. Together, these findings indicate that Piwis and Agos are similarly ancient. Animal genomes typically contain members of both clades, and it is becoming clear that this division of Argonautes reflects their underlying biology.

Ago clade proteins complex with microRNAs (miRNAs) and small interfering RNAs (siRNAs), which derive from double-stranded RNA (dsRNA) precursors (*1*). miRNA-Ago complexes reduce the translation and stability of protein-coding mRNAs, which results in a regulatory network that impacts ~30% of all genes. siRNAs in *Drosophila* arise from replicating RNA viruses and are crucial in antiviral immune responses (*2*). In *Caenorhabditis elegans*, endogenous siRNAs overlap protein-coding genes and likely participate in gene regulation (*3*). As classes, neither virus-derived nor endogenous siRNAs have yet been described in vertebrates.

The Piwi Clade

The Piwi clade is found in all animals examined so far, and its presence is tightly correlated with the emergence of specialized germ cells. Most animals separate germline and somatic cells early in development and restrict Piwi expression specifically to germ cells. In flatworms, an animal clade close to the bilaterian root, Piwis are expressed in germ cells and neoblasts, undifferentiated stem cells responsible for the remarkable regenerative capacity of these organisms (*4*). Although neoblasts are considered somatic stem cells, they are capable of giving rise to germ cells. Thus, the conserved expression pattern of Piwi proteins is a strong indication of their vital function in the germ line.

The genomes of multicellular animals encode multiple Piwi proteins. The three *Drosophila* proteins Piwi, Aubergine, and AGO3 are expressed in the male and female germ lines. Piwi is additionally expressed in the somatic cells, which are in close contact with germline cells (*5*–*8*). Expression of the three mouse proteins MIWI (PIWIL1), MILI (PIWIL2), and MIWI2 (PIWIL4) is mainly restricted to the male germ line (*9*–*12*). Although expression of *Mili* in prenatal ovaries has been reported (*9*), no function for Piwis in the female mammalian germ line has yet been demonstrated.

Consistent with their expression pattern, Piwi mutant animals exhibit defects in germ cell development. *Drosophila* Piwi is required for the maintenance of germline stem cells, both in testes and ovaries (*13*). In mouse, all three Piwi proteins are nonredundantly required for spermatogenesis (*10*–*12*). Although some somatic expression of Piwis has been reported, mutant animals lack obvious defects in the soma. On the basis of their loss-of-function phenotypes, Piwi proteins were placed in signaling pathways underlying germline development (*10*, *14*). However, genetic studies also pointed to a role for the Piwi pathway in silencing selfish genetic elements (*15*–*17*). Insight into the molecular function of Piwi proteins was stalled until the discovery of their small RNA partners.

Piwi-Interacting RNAs

The first indication of a distinct population of Piwi-associated small RNAs came from studies in *Drosophila*. The presence of 25- to 27-nucleotide (nt) RNAs homologous to the repetitive *Stellate* locus was correlated with its silencing and required the Piwi clade protein Aubergine (*15*). Profiling of small RNAs through *Drosophila* development placed *Stellate*-specific small RNAs into a broader class, derived from various repetitive elements, called repeat-associated small interfering RNAs (rasiRNAs) (*18*). A direct interaction between rasiRNAs and Piwi proteins was demonstrated by immunoprecipitation of Piwi complexes (*5*–*7*, *16*). Small RNAs resembling *Drosophila* rasiRNAs have been identified in testes and ovaries of zebrafish, which demonstrates evolutionary conservation of this small RNA class (*19*). Small RNA partners of Piwi proteins were also identified in mammalian testes and termed Piwi-interacting RNAs (piRNAs) (*20*). Although these RNAs share some features with rasiRNAs, there are also substantial differences, including a dearth of sequences matching repetitive elements. Nonetheless, on the basis of their common features, we refer to small RNAs in Piwi complexes as piRNAs with rasiRNAs being one specialized subclass.

Piwis and piRNAs form a system distinct from the canonical RNAi and miRNA pathways. No association between Piwis and miRNAs was detected in either fly (*5*, *6*) or mouse (*21*, *22*), although piRNAs, like miRNAs, carry a 5′ monophosphate group and exhibit a preference for a 5′ uridine residue (*21*–*23*). In contrast to miRNAs, many of which are conserved through millions of years of evolution, individual piRNAs are poorly conserved even between closely related species (*21*–*23*). piRNAs in *Drosophila* (*5*, *6*) and mammals (*21*–*23*), as well as siRNA-like scan RNAs that bind Piwi proteins in ciliates (*24*), are substantially longer (24 to 30 nt) than miRNAs and siRNAs (21 to 23 nt). Unlike animal miRNAs, but similar to plant miRNAs, piRNAs carry a 2′*O*-methyl modification at their 3′ ends, which is added by a Hen-1 family RNA methyltransferase (*25*). Finally, genetic analyses in flies (*16*) and zebrafish (*19*) argue against a role for Dicer, a key enzyme in miRNA and siRNA biogenesis, in piRNA production.

The Genomic Origin of piRNAs

Most *Drosophila* piRNAs match repetitive elements and therefore map to the genome in dozens to thousands of locations. Yet mapping of those piRNAs that could be placed uniquely in the genome (e.g., piRNAs from divergent repeat copies) identified a limited set of discrete loci that could give rise to most piRNAs. These were dubbed piRNA clusters (*5*). piRNA clusters range from several to hundreds of kilobases

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in length. They are devoid of protein coding genes and instead are highly enriched in transposons and other repeats (fig. S1). The vast majority of transposon content in piRNA clusters occurs in the form of nested, truncated, or damaged copies that are likely not capable of autonomous expression or mobilization. The presence of transposable elements per se is not sufficient for piRNA production. Virtually all piRNA clusters in *Drosophila* are located in pericentromeric or telomeric heterochromatin, which suggests that chromatin structure may play a role in defining piRNA clusters (Fig. 1).

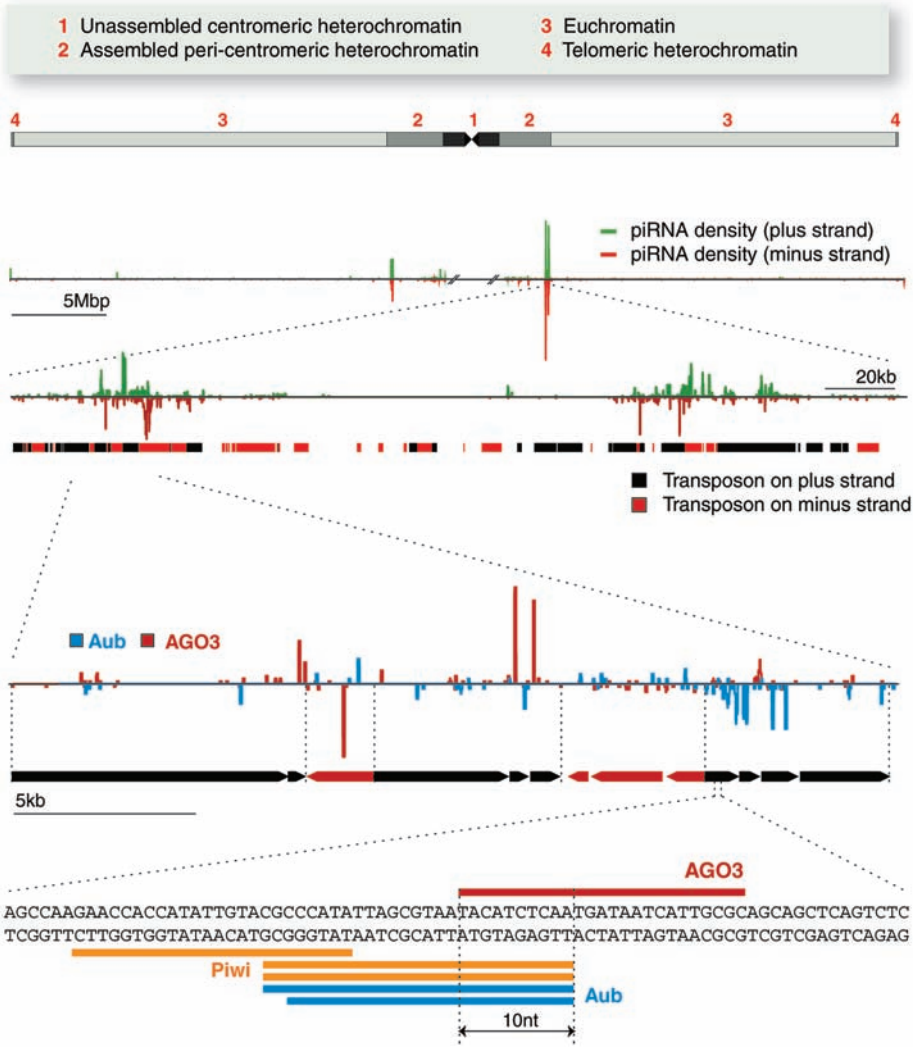

Fig. 1. Features of piRNA clusters. Overview of *Drosophila* chromosome 2 and progressively more detailed view of a major piRNA cluster.

Prominent piRNA loci are also found in mammals (*21*–*23*, *26*) and zebrafish (*19*). Mammalian piRNAs can be divided into two populations. Pachytene piRNAs appear around the pachytene stage of meiosis, become exceptionally abundant, and persist until the haploid round spermatid stage, after which they gradually disappear during sperm differentiation (*21*, *22*). Pachytene piRNAs are relatively depleted of repeats, and even those that do match annotated transposons are diverged from consensus, potentially active copies (fig. S1). Prepachytene piRNAs are found in germ cells before meiosis (*26*). These share the molecular characteristics of pachytene piRNAs but originate from a different set of clusters that more closely match those of *Drosophila* and zebrafish in repeat content.

Generally, clusters in flies and vertebrates give rise to piRNAs that associate with multiple Piwi proteins. Mouse pachytene piRNAs join both MILI and MIWI complexes (*27*). Similarly, *Drosophila* clusters produce piRNAs, which associate with all three Piwi proteins (*5*). However, some clusters generate piRNAs that join specific Piwi proteins, likely because these clusters and the Piwi proteins with which their products associate display specific temporal and special expression patterns. For example, *Drosophila* piRNAs originating from the *flamenco* cluster are found almost exclusively in Piwi complexes, and that is the only family member that is present in the somatic cells of the ovary (*5*), where *flamenco* is predominantly expressed.

Unlike trans-acting siRNAs in plants, piRNAs do not arise from clusters in a strictly phased manner but rather originate from irregular positions forming pronounced peaks and gaps of piRNA density (Fig. 1). piRNA populations are extremely complex, with our recent estimates placing the number of distinct mammalian pachytene piRNAs at >500,000.

Biogenesis of piRNAs

The lack of a dependence on Dicer (*16*, *19*) and the profound strand asymmetry of mammalian pachytene clusters indicate that piRNAs are not generated from dsRNA precursors. In *Drosophila*, most piRNA clusters generate small RNAs from both strands; however, there are exceptions, such as the *flamenco* locus, where piRNAs map almost exclusively to one genomic strand (fig. S1) (*5*). In zebrafish, piRNAs can map to both genomic strands; however, within any given region of a cluster, only one strand gives rise to piRNAs (*19*).

Given these considerations, two plausible models emerge. The first is the generation of piRNAs by sampling of long single-stranded precursors. Alternatively, piRNAs could be made as primary transcription products. Evidence for the former is the lack of a 5′ triphosphate group and the observation that a single P-element insertion at the 5′ end of the *flamenco* cluster prevents the production of piRNAs up to 160 kb away (*5*). This strongly supports a model in which a single transcript traverses an entire piRNA cluster and is subsequently processed into mature piRNAs.

Processing of small RNAs from long single-stranded transcripts is not unprecedented. Indeed, miRNAs are processed from precursors that often span several kilobases and that can encode several individual miRNAs (*27*). Pronounced peaks in piRNA density within a cluster also hint at the existence of specific processing determinants; however, the nature of these signals is yet to be resolved.

The machinery that produces piRNAs from cluster-derived transcripts must be somewhat flexible, as different Piwi proteins in flies and mammals each incorporate a distinct size class of small RNA (*5*, *21*, *22*). Data from flies and mammals suggest a model in which piRNA production begins with single cleavage of a primary piRNA cluster transcript to generate a piRNA 5′ end. piRNAs may be sampled virtually from any position within a cluster with the only preference being a 5′ uridine residue. After incorporation of the cleaved RNA into a Piwi, a second activity generates the 3′ end of the piRNA with the specific size determined by the footprint of the particular family member on the RNA.

Piwi and Aubergine complexes contain piRNAs antisense to a wide variety of *Drosoph-*

ila transposons, and these show the strong 5′ U preference noted for mammalian piRNAs (*5*, *6*, *16*). In contrast, AGO3 associates with piRNAs strongly biased toward the sense strand of transposons and with no 5′ nucleotide preference (*5*, *7*). piRNAs in AGO3 show a characteristic relation with piRNAs found in Aub complexes, with these small RNAs overlapping by precisely 10 nt at their 5′ ends (Fig. 2A). Accordingly, the AGO3-bound piRNAs were strongly enriched for adenine at position 10, which is complementary to the 5′ U of Aub-bound piRNAs (*5*, *7*). These observations indicated the existence of two distinct piRNA populations, possibly with different biogenesis mechanisms, and led to the hypothesis that cluster-derived transcripts and transcripts from active transposons interact through the action of Piwi proteins to form a cycle that amplifies piRNAs that target active mobile elements (*5*).

The cycle (called the Ping-Pong amplification loop) (Fig. 2B) begins with a transposon-rich piRNA cluster giving rise to a variety of piRNAs. In most clusters, a random arrangement of transposon fragments would initially produce a mixture of sense and antisense piRNAs, likely populating Piwi and Aub. When encountering a complementary target, a transposon mRNA, Piwi/Aub complexes cleave 10 nt from the 5′ end of their associated piRNA (*6*, *7*). This not only inactivates the target but also creates the 5′ end of new AGO3-associated piRNA. Loaded AGO3 complexes are also capable of cleaving complementary targets (*7*); one place from which such targets could be derived is the clusters themselves. Cleavage of cluster transcripts by AGO3 would then generate additional copies of the original antisense piRNA, which would enter Aub and become available to silence active transposons. The combination of these steps can form a self-amplifying loop. Signatures of this amplification loop are also apparent in zebrafish (*19*) and in mammalian prepachytene piRNAs (*26*). This transposon-silencing pathway, with both genetically encoded and adaptive components, has many conceptual similarities to adaptive immune responses.

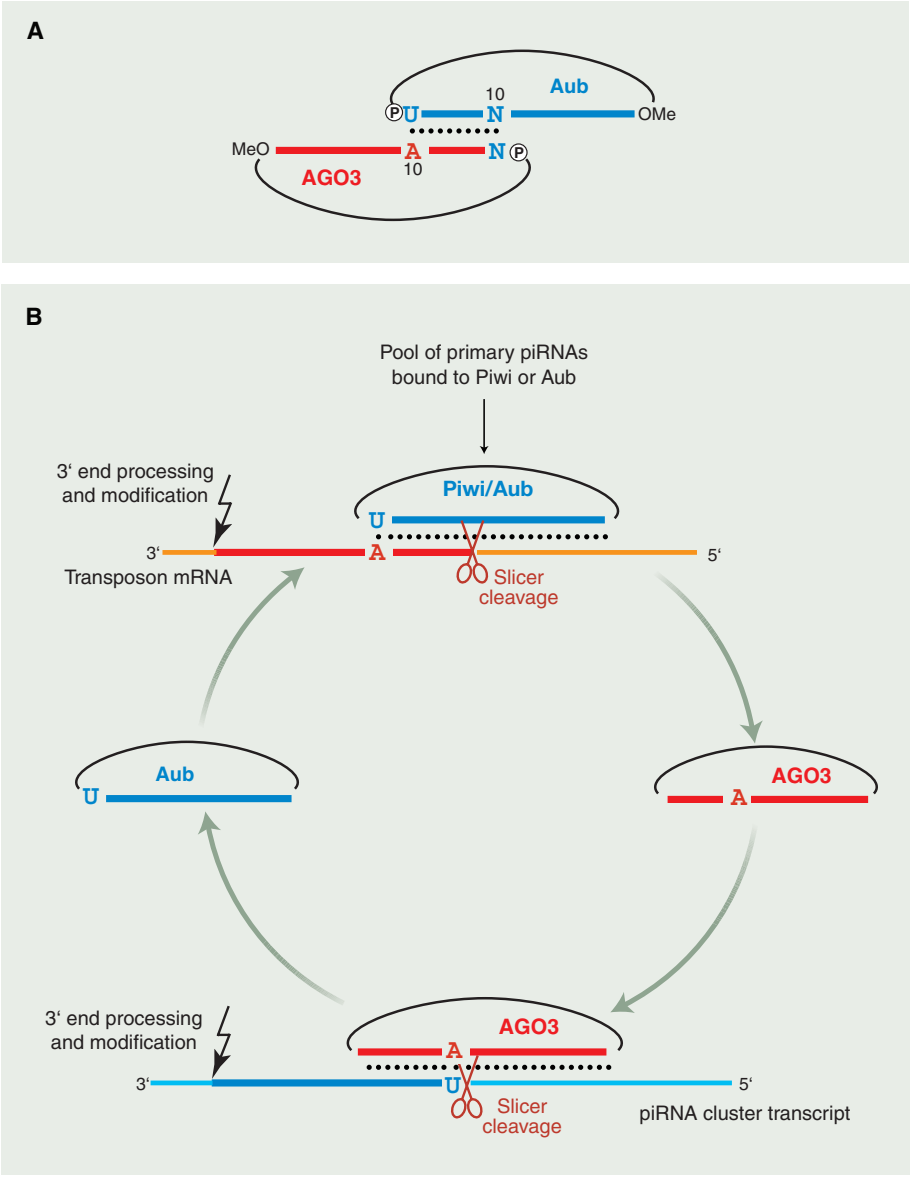

Fig. 2. Properties and biogenesis of piRNAs. (**A**) Features of Aub- and AGO3-associated piRNAs in *Drosophila*. Indicated are the 5′ U bias in Aub-bound piRNAs, the 10A bias in AGO3-bound piRNAs, the 5′ phosphate, and the 3′ O-methylation. (**B**) Ping-Pong model of piRNA biogenesis in *Drosophila*. Primary piRNAs are generated by an unknown mechanism and/or are maternally deposited. Those with a target are specifically amplified via a Slicer-dependent loop involving AGO3 and Aub.

Function of Piwi Proteins and piRNAs

Studies of piRNAs have pointed to a conserved function in the control of mobile genetic elements, and this is consistent with the defects in transposon suppression observed in Piwi mutants (*15*–*17*). One line of evidence comes from studies of loci that exert control over specific transposons in flies. The *flamenco* locus represses transposition of the retrotransposons *gypsy*, *ZAM*, and *Idefix* (*28*, *29*). *flamenco* maps to the pericentromeric heterochromatin on the X chromosome. Genetic analysis failed to reveal a protein-coding gene underlying *flamenco* function; however, the discovery that *flamenco* is a major piRNA cluster provided a molecular basis for its ability to suppress several unrelated retroelements. *flamenco* spans at least 180 kb and is highly enriched in many types of repetitive elements, including multiple fragments of *gypsy*, *ZAM*, and *Idefix*. In *flamenco* mutants, *gypsy* is desilenced, and essentially all piRNAs derived from this cluster are lost (*5*). Thus, *flamenco* is an archetypal piRNA cluster that encodes a specific silencing program, which is parsed by processing into individual, active small RNAs that exert their effects on loci located elsewhere in the genome.

Genetic studies of Piwi mutants suggested involvement in germline development in both invertebrates and vertebrates (*8*, *10*–*12*, *30*). *Drosophila piwi* is required in germ cells, as well as in somatic niche cells, for regulation of cell division and maintenance of germline stem cells (*8*). The *aubergine* phenotype resembles so-called spindle-class mutants that demonstrate meiotic progression defects (*30*). The defects in spindle-class mutants are a direct consequence of Chk2 and ATR (ataxia telangiectasia mutated and Rad3-related) kinase dependent meiotic checkpoint activation, and the phenotypes of *aub* mutants are partially suppressed in animals defective for this surveillance pathway (*31*).

In mice, loss of individual Piwi proteins causes spermatogenic arrest (*10*–*12*). In *Miwi* mutants, germ cells are eliminated by apoptosis after the haploid, round spermatid stage (*10*). However, in *Mili* (*11*) and *Miwi2* (*12*) mutants, earlier defects appear as meiosis is arrested

around the pachytene stage. In flies, mammals, and zebrafish, no phenotypic abnormalities have yet been detected outside of the germ line, in accord with the expression pattern of Piwis.

A key question is whether the diverse effects of Piwi mutations can be explained solely through the actions of Piwi proteins in transposon control or whether other Piwi functions exist. In *Drosophila*, studies of hybrid dysgenesis linked transposon activation to severely impaired gametogenesis. Mutation of a single piRNA cluster, *flamenco*, results in defects in germ and follicle cell development and complete sterility (*32*). Defects in *aub* mutants are linked to DNA damage checkpoint signaling that is probably activated in response to double-strand breaks arising from transposon activity (*31*). In mammals, germ cell loss in *Mili* and *Miwi2* mutants has been correlated with transposon activation (*12*, *26*). Other studies also support the idea that severe defects in germ cell development can be a direct consequence of transposon activation. For example, *Dnmt3L*-deficient animals show demethylation of transposable elements, which lead to their increased expression, as well as meiotic catastrophe and germ cell loss (*33*), a combination of phenotypes similar to those seen in *Mili* and *Miwi2* mutants.

Overall, genetic and biochemical data indicate that a substantial component of Piwi biology is dedicated to transposon control. However, there are also properties of the Piwi pathway that are difficult to explain solely on the basis of transposon regulation. Pachytene piRNAs in mammals are depleted of transposon sequences, and even those that form part of this population are highly diverged and unlikely to function in transposon suppression. Consistently, no activation of transposons has been detected in *Miwi* mutants (*27*). Thus, the function of pachytene piRNAs remains a mystery, as does the basis of postmeiotic arrest in the *Miwi* mutants. Global translational control plays important roles during mammalian spermatogenesis, with the expression of many mRNAs being posttranscriptionally regulated. Loss of *Miwi* has been linked to changes in the abundance of several mRNAs important for development of haploid cells (*10*). The extreme diversity of pachytene piRNAs may allow MIWI and MILI complexes to exert broad effects on the transcriptome through a miRNA-like mechanism.

Summary and Perspective

It is becoming increasingly clear that an ancient and conserved function of the Piwi and piRNA pathway is to protect the genome from the activity of parasitic nucleic acids. Even in ciliates, which diverged earlier than the common ancestor of plants and animals, parallels to the piRNA pathways of flies and mammals are clear. In *Tetrahymena*, the scanning hypothesis for DNA elimination (*34*) suggests that a complex population of small RNAs is first generated from the micronuclear genome and subsequently filtered through interactions with the old macronuclear genome. The small RNAs that emerge from this process specify repeat silencing, in this case by elimination from the newly forming and transcriptionally active macronucleus. DNA elimination depends upon a Piwi protein, Twi1, but unlike the case in vertebrates and *Drosophila*, also on a Dicer protein (*35*).

Comparisons to ciliates reveal that, during evolution, the core Piwi and piRNA machinery may have adopted both different strategies for producing and filtering small RNA triggers and different strategies for ultimately silencing targets. In *Drosophila*, the Ping-Pong model strongly suggests a posttranscriptional component to transposon silencing. However there is also evidence for impacts of Piwi proteins on chromatin states (*36*). In mammals, Piwi proteins have been implicated in DNA methylation (*12*, *26*), a function that may be exerted either directly or indirectly.

Plants lack Piwi proteins and have adapted a different RNAi-based strategy for transposon control. In *Arabidopsis*, the Ago subfamily protein Ago4 is programmed with a complex set of transposon-derived small RNAs (*37*). In contrast to flies and mammals, in which piRNA loci serve as a genetically encoded reservoir of resistance to mobile elements, each individual transposon copy seems to produce small RNAs in plants. Although the precise mechanisms that funnel expressed repeats into this pathway and exclude protein coding genes have yet to be determined, there are hints that chromatin marks may help to concentrate small RNA production at particular sites. This resembles the situation for centromeric repeats in *S. pombe* where specific histone modifications recruit RNAi components to maintain heterochromatin through a local, self-reinforcing loop of small RNA production (*37*) that is in many ways analogous to the Ping-Pong amplification loop for piRNAs. Yeast and fly systems differ in their strategies for producing complementary substrates. Where yeast and plants use RNA-dependent RNA polymerases to produce antisense repeat sequences, *Drosophila* and mammals encode them from piRNA loci.

Although much remains to be learned about Piwi proteins and their functions throughout evolution, one must wonder whether this pathway is providing a glimpse into the ancestral functions of RNAi. It seems almost certain that the evolution of genomic parasites followed closely the emergence of self-replicating genomes. Thus, the development of heritable, but also adaptive, systems of parasite resistance would have been essential to maintaining fitness. Given the dire consequences of transposon activation in higher organisms, for example, hybrid dysgenesis in *Drosophila* and sterility in mammals, it is likely that colonization by mobile elements provides a driving force in speciation, as subpopulations adapt to coexist with specific invaders. The Piwi and piRNA pathway may thus have played a long-standing and important role in maintaining species cohesion by allowing adaptation of populations to new mobile elements and preventing reproductive isolation.

References and Notes

1. N. H. Tolia, L. Joshua-Tor, *Nat. Chem. Biol.* **3**, 36 (2007).
2. X. H. Wang *et al.*, *Science* **312**, 452 (2006).
3. J. G. Ruby *et al.*, *Cell* **127**, 1193 (2006).
4. P. W. Reddien, N. J. Oviedo, J. R. Jennings, J. C. Jenkin, A. Sánchez Alvarado, *Science* **310**, 1327 (2005).
5. J. Brennecke *et al.*, *Cell* **128**, 1089 (2007).
6. K. Saito *et al.*, *Genes Dev.* **20**, 2214 (2006).
7. L. S. Gunawardane *et al.*, *Science* **315**, 1587 (2007).
8. D. N. Cox *et al.*, *Genes Dev.* **12**, 3715 (1998).
9. S. Kuramochi-Miyagawa *et al.*, *Mech. Dev.* **108**, 121 (2001).
10. W. Deng, H. Lin, *Dev. Cell* **2**, 819 (2002).
11. S. Kuramochi-Miyagawa *et al.*, *Development* **131**, 839 (2004).
12. M. A. Carmell *et al.*, *Dev. Cell* **12**, 503 (2007).
13. D. N. Cox, A. Chao, H. Lin, *Development* **127**, 503 (2000).
14. A. Szakmary, D. N. Cox, Z. Wang, H. Lin, *Curr. Biol.* **15**, 171 (2005).
15. A. A. Aravin *et al.*, *Curr. Biol.* **11**, 1017 (2001).
16. V. V. Vagin *et al.*, *Science* **313**, 320 (2006).
17. M. Savitsky, D. Kwon, P. Georgiev, A. Kalmykova, V. Gvozdev, *Genes Dev.* **20**, 345 (2006).
18. A. A. Aravin *et al.*, *Dev. Cell* **5**, 337 (2003).
19. S. Houwing *et al.*, *Cell* **129**, 69 (2007).
20. V. N. Kim, *Genes Dev.* **20**, 1993 (2006).
21. A. Aravin *et al.*, *Nature* **442**, 203 (2006).
22. A. Girard, R. Sachidanandam, G. J. Hannon, M. A. Carmell, *Nature* **442**, 199 (2006).
23. N. C. Lau *et al.*, *Science* **313**, 363 (2006).
24. K. Mochizuki, N. A. Fine, T. Fujisawa, M. A. Gorovsky, *Cell* **110**, 689 (2002).
25. J. V. Hartig, Y. Tomari, K. Forstemann, *Genes Dev.* **21**, 1707 (2007).
26. A. A. Aravin, R. Sachidanandam, A. Girard, K. Fejes-Toth, G. J. Hannon, *Science* **316**, 744 (2007).
27. D. P. Bartel, *Cell* **116**, 281 (2004).
28. N. Prud'homme, M. Gans, M. Masson, C. Terzian, A. Bucheton, *Genetics* **139**, 697 (1995).
29. S. Desset, C. Meignin, B. Dastugue, C. Vaury, *Genetics* **164**, 501 (2003).
30. J. E. Wilson, J. E. Connell, P. M. Macdonald, *Development* **122**, 1631 (1996).
31. C. Klattenhoff *et al.*, *Dev. Cell* **12**, 45 (2007).
32. M. Mevel-Ninio, A. Pelisson, J. Kinder, A. R. Campos, A. Bucheton, *Genetics* **175**, 1615 (2007).
33. D. Bourc'his, T. H. Bestor, *Nature* **431**, 96 (2004).
34. K. Mochizuki, M. A. Gorovsky, *Curr. Opin. Genet. Dev.* **14**, 181 (2004).
35. C. D. Malone, A. M. Anderson, J. A. Motl, C. H. Rexer, D. L. Chalker, *Mol. Cell. Biol.* **25**, 9151 (2005).
36. S. I. Grewal, S. C. Elgin, *Nature* **447**, 399 (2007).
37. R. K. Slotkin, R. Martienssen, *Nat. Rev. Genet.* **8**, 272 (2007).

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Supporting Online Material

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Fig. S1
Table S1

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