In addition, mixing between mantle components can generate a range of basalt isotope compositions more varied than that seen in the mantle.

Second, can depleted material really impart distinctive helium-isotope signals into OIBs? Both helium and uranium are strongly concentrated into mantle melts. This means that, although low U/^{3}He ratios may be left behind during melting, there is very little helium left at all, especially if large amounts of melting occur. The helium-isotope signature of the depleted material is likely to be hidden by that of various other mantle components, such as subducted material and surrounding, less depleted bulk mantle that clearly also contribute to the source of OIBs. Furthermore, other signals that would characterize the depleted regions of mantle suggested by Parman[1] as the origin of OIBs, including neodymium, lead and hafnium isotopes, are typically not found in OIBs.

Third, how would such a mantle work? Mantle domains now seen in ocean islands would have been generated throughout Earth's history, and so must have been stored where mixing would not destroy them. This is a particular problem for the largest hotspots of Hawaii and Iceland, which have the lowest ^{4}He/^{3}He ratios and so would need a source as old as 4 billion years. Although it is tempting to picture separate blobs circulating in the mantle like raisins in a pudding, these would probably be destroyed by mixing[7]. And questions of how this material can be preferentially incorporated into plumes beneath ocean islands would remain. Even more perplexing, how can individual locations such as Hawaii and Iceland have basalts derived from a range of these sources, as is implied by the spread of helium data within these regions?

Overall, the picture suggested by Parman provides an elegant explanation for a fundamental characteristic of ocean-island rocks. Although there are still considerable reasons to be sceptical, the many points of correspondence between peaks in zircon ages in the crust and helium isotopes in the mantle seem to be more than a coincidence. If this observation survives further scrutiny and data collection, it will certainly be important for understanding some of the most distinctive volcanic features on Earth. ■

Don Porcelli is in the Department of Earth Sciences, University of Oxford, Parks Road, Oxford OX1 3PR, UK.
e-mail: don.porcelli@earth.ox.ac.uk

1. Parman, S. W. *Nature* **446,** 900–903 (2007).
2. Graham, D. W., Lupton, F., Albarède, F. & Condomines, M. *Nature* **347,** 545–548 (1990).
3. Parman, S. W., Kurz, M. D., Hart, S. R. & Grove, T. L. *Nature* **437,** 1140–1143 (2005).
4. Heber, V. S., Brooker, R. A., Kelley, S. P. & Wood, B. J. *Geochim. Cosmochim. Acta* **71,** 1041–1061 (2007).
5. Condie, K. C. *Earth Planet. Sci. Lett.* **163,** 97–108 (1998).
6. Kemp, A. I. S., Hawkesworth, C. J., Paterson, B. A. & Kinny, P. D. *Nature* **439,** 580–583 (2006).
7. van Keken, P. E., Hauri, E. H. & Ballentine, C. J. *Annu. Rev. Earth Planet. Sci.* **30,** 493–525 (2002).

RNA SILENCING

Genomic defence with a slice of pi

Phillip D. Zamore

In fruit flies, a few very large genes generate the small RNAs that silence parasitic DNA elements. These RNAs might also participate in an amplification circuit that increases their potency.

Nearly half of the human genome and a third of the fruit fly's consists of selfish elements called transposons, 'jumping genes' that insert themselves into new locations, mutating other genes and damaging chromosomes. These molecular parasites include simple nucleotide repeats and virus-like elements that have colonized genomes throughout evolution. In response, animals have evolved complex mechanisms to silence transposons. The fruit fly *Drosophila melanogaster* silences its transposons by a mechanism that uses small RNA 'guides'. Reporting in *Cell*[1] and *Science*[2], two research groups propose an unanticipated explanation for the production and amplification of these small, silencing RNAs.

The best known silencing pathway guided by small RNAs is RNA interference (RNAi), in which small interfering RNAs (siRNAs) trigger an immune response that defends plants and animals against viruses by destroying complementary RNA sequences[3,4]. The siRNAs bind to members of the Argonaute family of proteins — molecular 'scissors' that use the small RNA guide to bind to and cut a second RNA molecule, the 'target'. The use of RNA guides rather than protein antibodies is a key difference between the sequence-based RNAi defence pathway and our adaptive immune responses, which recognize viral proteins. The enzyme Dicer produces siRNAs by cutting long, double-stranded RNA into smaller pieces about 21 nucleotides long. One strand of each siRNA is then loaded onto an Argonaute protein, generating a RNA–protein complex that binds to a viral RNA target by base-pairing and cuts it.

Like viruses, transposons are parasites, but, unlike viruses, they are primarily transmitted by inheritance, rather than through infection. To produce enzymes that facilitate their jumping to a new location in the genome, transposons must first be copied into mRNA. The evolution of small-RNA-guided silencing mechanisms, which prevent copying of transposons into RNA sequences, allows higher organisms to defend their genes against transposons.

In some higher organisms, the RNAi pathway provides a crucial defence mechanism against transposons[5–7]. But for fruit flies the genome is guarded by the Piwi-associated interfering RNA (piRNA) pathway[8]. At the heart of this pathway lies a specialized set of Argonaute proteins produced in the germ cells. Flies have five Argonaute proteins: Ago1, which uses small RNAs called microRNAs to regulate gene expression; Ago2, which uses siRNAs to fight viral infection; and three closely related Piwi proteins — Piwi, Aubergine and Argonaute3 (Ago3) — which use piRNAs to silence transposons and other parasitic DNAs. In flies, piRNAs are also called repeat-associated siRNAs, or rasiRNAs.

The Hannon[1] and Siomi[2] laboratories separately set out to identify small RNAs bound to each of the three fly Piwi proteins, in the hope that their sequences would reveal how rasiRNAs are made and function. Their findings are simply spectacular, suggesting that rasiRNAs arise from a small number of trigger loci — huge 'genes' that produce small RNAs against many selfish genetic elements — and that they are amplified through reciprocal cycles of cleavage by pairs of Piwi proteins (Fig. 1, overleaf).

To identify the RNAs bound to the three *Drosophila* Piwi proteins, each laboratory used antibodies to purify Piwi, Aubergine and Ago3 from the fly's ovaries, along with their associated rasiRNAs. Hannon and colleagues[1] identified 60,691 different rasiRNAs. It is difficult to pinpoint the site of origin of any one rasiRNA to a single genomic location, because nearly identical copies of specific transposons litter the entire genome. However, the set of rasiRNA sequences identified by these authors was so large that around 12,000 could be assigned to unique sites. These sites formed just 142 clusters, with a single cluster on the right arm of chromosome 2 comprising about 21% of all the unique rasiRNAs.

Another cluster corresponded to a genetic locus called *flamenco* on the X chromosome, which was previously shown to repress the jumping of the *gypsy*, *Idefix* and *ZAM* transposons. Since its discovery[9], *flamenco* has posed a puzzle because no protein-encoding gene resides at this locus. The new results indicate that *flamenco*, instead of producing a protein, is the source of rasiRNAs that target multiple types of transposon. These rasiRNAs may come from an enormous precursor RNA molecule, as mutations lying at the beginning of the locus disrupt *flamenco*-derived rasiRNAs some 168,000 nucleotides away. Loss of *flamenco* function activates transposons, such as *gypsy*, that lie within it, although most *gypsy* transposons reside outside this locus. However, it has no effect on transposons that are not found in *flamenco*. Thus, *flamenco* seems to have evolved as a master regulator of *gypsy*, *Idefix*

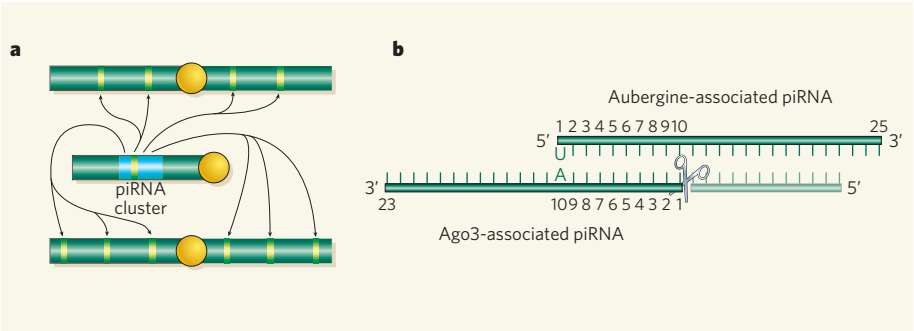

Figure 1 | piRNA-mediated silencing of transposons. **a**, A few trigger loci generate piRNAs, which target transposons (yellow) elsewhere in the genome and prevent their transcription. **b**, Complementary binding of Aubergine- and Ago3-associated piRNA sequences results in their amplification, ensuring efficient silencing of transposons.

and *ZAM* transposons and is the primary, if not the sole, source of rasiRNAs against these selfish elements.

Most rasiRNAs correspond to the antisense strand of transposons and can therefore bind to, and presumably destroy, the RNA transcripts of transposons[1,8]. These antisense rasiRNAs bind to Piwi and Aubergine. The two new papers[1,2] report that the small RNAs bound to Ago3 are nearly all of the sense orientation. Of the 353 Ago3-associated rasiRNAs identified by Siomi's group[2], the first 10 nucleotides of 16 sequences could be paired with rasiRNAs bound to Aubergine. And more than 11,200 (48%) of the Ago3-associated sense rasiRNAs identified by Hannon's group[1] could form an offset couple with at least one antisense rasiRNA.

A 10-nucleotide offset between the beginning of a small RNA guide and a second RNA molecule has a special meaning. Argonaute proteins cut target RNAs by measuring 10 nucleotides from the beginning of their RNA guide to the site of cleavage on their target. Such a pairing scheme suggests that the starting nucleotide of each antisense rasiRNA is defined by a cut that is guided by a corresponding sense rasiRNA. Reinforcing this view, nearly all the antisense rasiRNAs begin with the nucleotide U, whereas the sense rasiRNAs show no bias for beginning with U, A, C or G. Instead, the tenth nucleotide of the sense rasiRNAs was almost always A, which would allow it to pair with the first nucleotide — U — of an Aubergine- or Piwi-bound antisense rasiRNA (Fig. 1b).

Imagine, then, that a mother fly protects her offspring by providing her developing eggs with some of her Aubergine- and Piwi-bound antisense rasiRNAs. These could then generate sense rasiRNAs by cleaving the RNA transcripts of transposons, thereby simultaneously silencing them and initiating a cycle of rasiRNA amplification. The sense rasiRNAs bound to Ago3 would then cleave the long, antisense transcripts produced by master regulatory loci such as *flamenco*, producing new antisense rasiRNAs that would bind to Aubergine or Piwi. If antisense transcripts from master regulatory loci are generally more abundant than sense transcripts from transposons — a reasonable assumption as transposons are normally silenced — then the pool of rasiRNAs would, as observed, be disproportionately antisense.

Of course, the model proposed by these authors[1,2] only explains how the start of each rasiRNA is defined. How the 3′ end of the rasiRNA is made remains to be discovered. And what of piRNAs in humans? piRNAs were recently discovered in immature mouse, rat and human sperm cells[10], and in zebrafish testes and ovaries[11], although they were mostly not associated with transposon sequences. What piRNAs do in mammalian sperm is unknown, but, like fly piRNAs, they derive from large genomic clusters. And like fly piRNAs[8], they do not seem to be made by Dicer. Perhaps all piRNAs are made and amplified by reciprocal cycles of Piwi-catalysed slicing of sense and antisense transcripts. Stay tuned for further detailed sequence analyses. ■

Phillip D. Zamore is in the Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, Massachusetts 01605, USA.
e-mail: phillip.zamore@umassmed.edu

1. Brennecke, J. *et al. Cell* **128,** 1089–1103 (2007).
2. Gunawardane, L. S. *et al. Science* **315,** 1587–1590 (2007).
3. Fire, A. *et al. Nature* **391,** 806–811 (1998).
4. Hamilton, A. J. & Baulcombe, D. C. *Science* **286,** 950–952 (1999).
5. Ketting, R. F., Haverkamp, T. H., van Luenen, H. G. & Plasterk, R. H. *Cell* **99,** 133–141 (1999).
6. Tabara, H. *et al. Cell* **99,** 123–132 (1999).
7. Djikeng, A., Shi, H., Tschudi, C. & Ullu, E. *RNA* **7,** 1522–1530 (2001).
8. Vagin, V. V. *et al. Science* **313,** 320–324 (2006).
9. Prud'homme, N., Gans, M., Masson, M., Terzian, C. & Bucheton, A. *Genetics* **139,** 697–711 (1995).
10. Kim, V. N. *Genes Dev.* **20,** 1993–1997 (2006).
11. Houwing, S. *et al. Cell* **129,** 69–82 (2007).

NEUROBIOLOGY

Feeling right about doing right

Deborah Talmi and Chris Frith

Reason and emotion come into conflict in making all kinds of judgements. Results of work with brain-damaged patients constitute one line of evidence that the emotional component is not to be dismissed.

In resolving moral dilemmas, should emotion be our guide? This is a question prompted by various research avenues, including work described in the paper by Koenigs *et al.*[1] on page 908 of this issue.

In a typical moral dilemma, we have to choose between the lesser of two evils. Causing the death of one person is bad, but causing the death of five people is even worse. So, if you are on a runaway trolley with no other options, many people say that it is better to switch to the left fork in the track, resulting in the death of one person, than to carry on along the right fork and kill five. But what if there was no fork in the track and the only way to stop the trolley killing five people was to throw a large person, who happens to be standing next to you, under the wheels? From a utilitarian point of view the dilemma is the same: should we sacrifice one person for the sake of five? But, given this version of the dilemma, most people will choose not to throw their companion to his death. Why the difference?

There is increasing evidence that there is a strong emotional component to our moral intuitions, and that this determines, to a large degree, how we make moral judgements[2]. Thus the benefit from sacrificing a single life for the greater good must be pitted against the emotional aversion associated with the taking of life, particularly when we are face-to-face with our victim. Measurement of brain activity while people are presented with these dilemmas confirm this intuition: the moral dilemma involving throwing our companion onto the track elicits more activity in emotion-processing regions of the brain than the standard runaway-trolley problem (see ref. 3 for a review).

The implication of these ideas is that people with impaired emotional responses will have altered moral intuitions. Koenigs and his colleagues[1] have tested this hypothesis with a group of patients with damage to part of the brain called the ventral medial prefrontal cortex (VMPFC). As is typical after such damage, the autonomic nervous system in these patients showed reduced responses to emotionally charged pictures and, according to their spouses, the patients showed reduced feelings of empathy and guilt. When confronted with moral