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Passing the message on: inheritance of epigenetic traits

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Epigenetic modifiers play an important role in genome organization, stability and the control of gene expression. Three research groups that are exploring the transfer of epigenetic information between generations have recently published papers. Mary Alleman *et al.* have shown that RNA-directed chromatin changes mediate paramutation in maize, and Minoo Rassoulzadegan *et al.* have demonstrated that RNA also plays a role in paramutation in mice. A new aspect of epigenetic regulation has been revealed by Jean Molinier *et al.* – they have demonstrated that the memory of exposure to stress is transferred through several generations.

Transgenerational inheritance of epigenetic information

The coordinated patterns of gene expression in multicellular organisms involve both genetic and epigenetic mechanisms. Epigenetic regulation is mediated by changes in DNA methylation, chromatin structure and by non-coding RNAs that can in turn direct changes in chromatin or DNA methylation. During sexual reproduction, genetic information is transmitted from each parent to their offspring, but early experiments showed that patterns of DNA methylation in the mammalian genome were reset each generation, suggesting that epigenetic information is not inherited [1]. However, epigenetic information is not always erased between generations because it has recently been shown that epigenetic modifications of at least some sequences can be transmitted through the germline [2–5]. In plants, the situation is similar, with some epigenetic marks such as the vernalization-induced epigenetic repression of *FLC* being erased in the next generation [6], whereas heavily methylated, inactivated plant transposons are generally transmitted to the next generation in an inactive state [7]. Some plant genes are also inherited with their epigenetic information intact, for example, in paramutation (Box 1). Paramutation has been described in both plants and animals [8]. Now, two recent studies by Mary Alleman *et al.* [9] and Minoo Rassoulzadegan *et al.* [10] have revealed a role for RNA in mediating paramutation in both kingdoms. A study reported recently by Jean Molinier *et al.* suggests that the transfer of epigenetic information between generations provides a memory of environmental stresses experienced in earlier generations [11].

Uncovering the molecular basis for inter-allelic communication in paramutation

The maize *b1* locus encodes a transcription factor that regulates the anthocyanin biosynthetic pathway, resulting in purple pigmentation of plant tissues. Two alleles of this locus, *B-I* and *B′*, are involved in paramutation; these alleles are identical in both DNA sequence and DNA methylation around the promoter and proximal region of the gene and yet there is a 10- to 20-fold difference in the level of transcription between *B-I*, which has a high level of expression, and the paramutagenic *B′* alleles [12,13]. Paramutation has been linked to an 853 bp sequence, located 100 Kb upstream of the transcription start, and this sequence is tandemly repeated seven times in alleles that participate in paramutation [14]. In *B′*, which has a low level of expression, these repeated sequences are more densely methylated (M. Stam and co-workers, personal communication) and the associated chromatin is more compact than *B-I*, which has a high level of expression [15] (Figure 1a), but it is not known how the modification of these upstream sequences affects expression of the *b1* locus. Two models to explain the nature of the interaction between paramutagenic and paramutable alleles have been proposed [8]. One invokes a direct interaction between the chromatin associated with each allele whereas the other involves an indirect interaction mediated by RNA, leading to RNA-directed changes in chromatin structure.

Alleman *et al.* [9] have now added to our understanding of the molecular basis for paramutation by cloning the *Mop1* gene, mutants of which block aspects of paramutation at *b1* and other loci [16]. *Mop1* encodes an RNA-dependent RNA polymerase that is similar to the *Arabidopsis* polymerase associated with the production of short RNAs that direct chromatin modification [9]. This strongly suggests that paramutation involves an RNA-based silencing mechanism. This idea is supported by observations that both strands of the repeat element are transcribed and that short interfering RNAs (siRNAs) with homology to the repeats can be detected (M. Arteaga-Vasquez and V. Chandler, personal communication) (Figure 1a). SiRNAs were not detected in the *mop1* mutant, which is consistent with Mop1 having a role in producing a dsRNA template from which siRNAs are cleaved (M. Arteaga-Vasquez and V. Chandler, personal communication).

More surprising is the finding that this repeat element is transcribed at the same rate [9] and that siRNAs are detected (M. Arteaga-Vasquez and V. Chandler, personal

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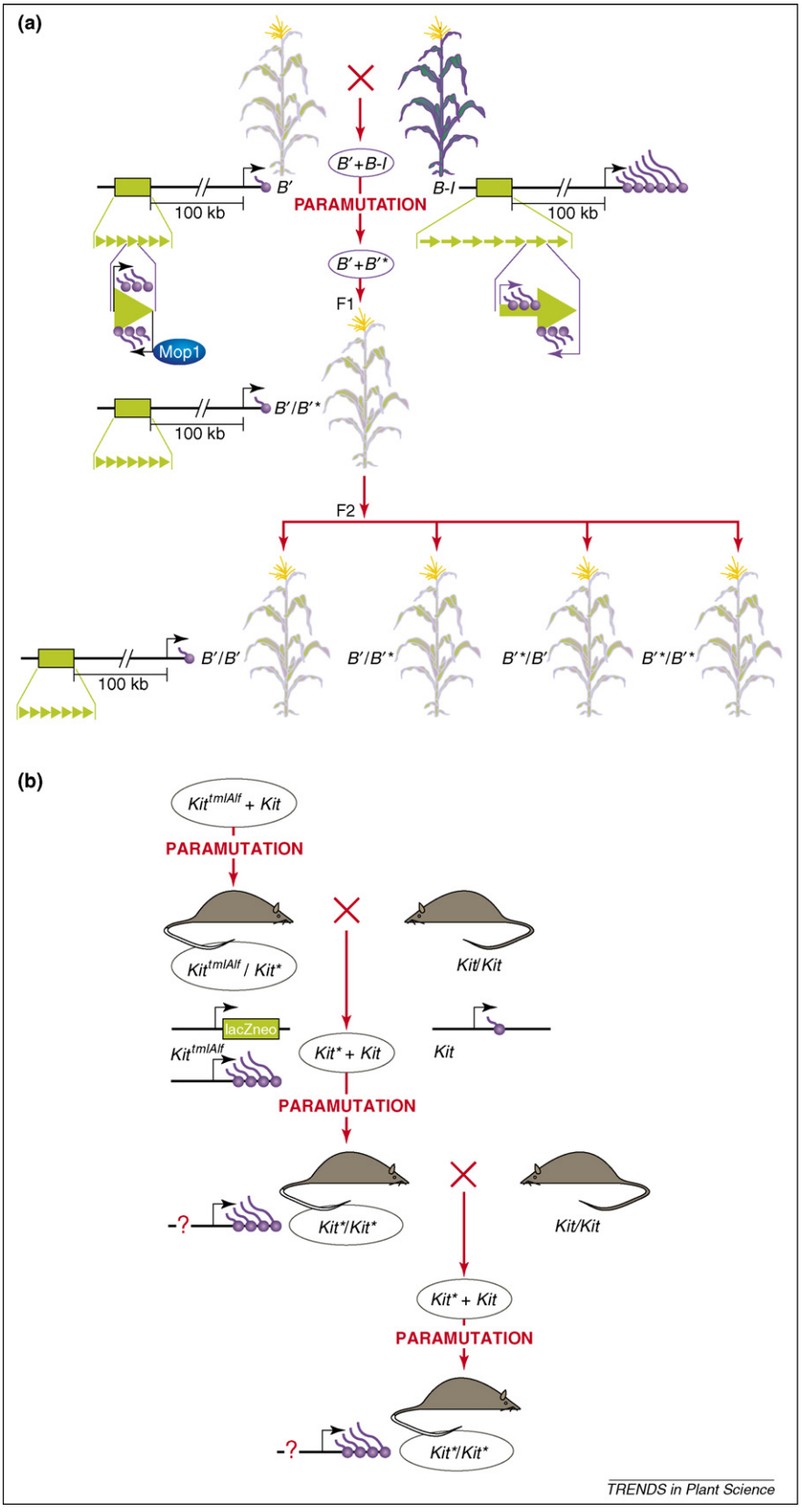

Figure 1. The molecular basis for paramutation at the maize *b1* locus and the *Kit* gene in mouse differ. **(a)** Paramutation of the *b1* locus has been linked to an 853 bp sequence located 100 Kb upstream of the transcription start; there are seven copies of this sequence in tandem array (green arrows) in alleles involved in paramutation [14]. The paramutagenic *B′* and paramutable *B-I* alleles are identical in sequence and DNA methylation around the promoter, but *B-I* is more highly expressed than *B′* [indicated by the number of purple balls (RNA polymerases) at each allele]. *B-I* plants are deeply pigmented whereas *B′* plants are a pale purple. *B′* is stable and causes paramutation of *B-I* to *B′** whenever the two alleles are present in the same nucleus, indicated here as an oval. The expression of *B′* and *B′** is identical; the * indicates that this allele entered the heterozygote as a high expressing *B-I* allele, and was converted by *B′* to become *B′**, which is stably transmitted to the F2 progeny, which are all pale purple. In the low expressing *B′*, the repeated sequences are both more densely methylated (M. Stam and co-workers, personal communication) and the associated chromatin is more compact (indicated by arrow head) compared with the highly expressing *B-I* where the sequence is present in open chromatin (indicated by the arrow). In both *B′* and *B-I* the repeated sequences are transcribed from both strands and the corresponding siRNAs (not shown) are present in both alleles (M. Arteaga-Vasquez and V. Chandler, personal

Box 1. Important features of paramutation

One of the laws established by Gregor Mendel during his study on the inheritance of traits states that alternative versions of genes (also known as alleles) account for the variation in inherited characters. During gamete formation these variant alleles separate and pass, unchanged by their association with each other, from one generation to the next. In the phenomenon known as paramutation, this law of segregation is violated (reviewed in Ref. [8]). The key feature of paramutation is that particular variant alleles, termed paramutagenic alleles, cause a change in the expression of other, paramutable alleles of the same gene whenever the two alleles are present in the same nucleus (Figure 1). This change is stable through both mitotic and meiotic divisions, so the paramutated allele shows this same altered level of expression in the next generation (Figure 1). What is more, this newly paramutated allele frequently acquires paramutagenic capabilities and influences the expression of susceptible (paramutable) alleles in subsequent crosses. Some alleles of loci that show paramutation are not influenced by the paramutagenic variant; these alleles are known as neutral alleles. Paramutation-like phenomena occur not only between naturally occurring alleles of endogenous genes, but also between transgenes or between a transgene and an endogenous gene [8]. Although most commonly reported for plants, paramutation-like phenomena have also been observed in mice [10,35].

communication) in all genotypes, including *B-I*, *B′* and a neutral allele that has only one copy of this sequence and does not participate in paramutation. These intriguing observations suggest that alleles of *b1* can be 'immune' to RNA-directed chromatin modifications under some circumstances, and perhaps that chromatin itself can modulate the effect of RNA-directed chromatin changes. A similar finding has been reported for the *FWA* locus of *Arabidopsis*, expression of which is regulated by RNA-directed DNA methylation of two direct repeats located in the *FWA* promoter [17].

Mop1 is not just important for paramutation because homozygous *mop1* mutants are small, late flowering and rather unhealthy plants. Some *mop1* plants show developmental defects that behave like (epi)mutations at unlinked loci [16], rather like the *Arabidopsis ddm1* mutant [18]. The developmental defects in *mop1* mutants could be caused by the reactivation of transposable elements [19]. *mop1* mutants lack small RNAs with homology to *MuDR*, and *Mop1* is required to maintain DNA methylation and silencing of *MuDR* [20].

Although this elegant piece of research has opened the way to a greater understanding of the molecular basis for paramutation, several questions remain. *B-I* is unstable and spontaneously converts to *B′* at a low frequency, but what provides the trigger for the spontaneous conversion of *B-I* to *B′*? Why, once converted to *B′* does it effect paramutation in all cases? Why don't neutral alleles participate in paramutation given that they too produce siRNAs with homology to the repeat sequence? What feature(s) of paramutation facilitates the transgenerational inheritance of the paramutagenic state? Are homologues of other members of the RNA-directed chromatin modification pathway such as *Arabidopsis* DCL3, AGO4, POLIV or DRM proteins required for paramutation? A requirement for these proteins would strengthen the case for an RNA-directed chromatin change.

RNA also plays a role in paramutation in mice

Rassoulzadegan *et al.* [10] have described a paramutation-like phenomenon in mice. In this case, paramutation was observed in heterozygous mice carrying a wild-type *Kit* tyrosine kinase receptor gene and a null allele, Kit^{tm1Alf}, that was created by the insertion of a lacZ-neo cassette just downstream of the *Kit* translation start (Figure 1b). The Kit tyrosine receptor kinase plays an essential role in germ cell differentiation, haematopoeisis and melanogenesis. Homozygous null mice die soon after birth, and heterozygotes have a white tail tip and white feet, indicative of the reduced activity of the Kit kinase. Surprisingly, the genetically wild-type progeny of the Kit^{tm1Alf}/+ heterozygotes also sported white tail tips, typical of their heterozygous parent. This suggests that the wild-type allele was modified (*Kit* to *Kit**) in the heterozygote, rather reminiscent of the conversion of *B-I* to *B′** in maize (Figure 1). The white tail tip phenotype was also inherited by progeny in the next generation for which neither parent carried the Kit^{tm1Alf} allele (Figure 1b), indicating that, like the newly arising *B′**, *Kit** is also paramutagenic.

In contrast to *B′* and *B′**, *Kit** was shown to have an increased rate of transcription (Figure 1b) associated with the accumulation of aberrant transcripts with homology to the 5′ end of the *Kit* gene. These transcripts accumulated in the Kit^{tm1Alf}/+ heterozygotes and, one would predict, would also accumulate in the *Kit**/*Kit** progeny, although no RNA analysis of these progeny was presented. The relationship between the presence of aberrant transcripts and paramutation is unclear, but it is reminiscent of post-transcriptional gene silencing in plants where RNA degradation products sometimes accumulate [21–23]. A high level of aberrant *Kit* transcripts were detected in sperm, and the authors propose that the presence of these transcripts allow the conversion of a wild-type *Kit* allele in the zygote. This is supported by the finding that injection of RNA from Kit^{tm1Alf}/+ into one-cell embryos triggered paramutation of *Kit*.

These observations are intriguing but raise several questions. Is the deregulation of *Kit** associated with small double-stranded RNA, as reported recently in humans [24]? Is there an accumulation of aberrant *Kit* transcripts in *Kit** oocytes, which also confer a paramutagenic effect in the zygote? Is the transgenerational effect of *Kit** a special case because *Kit** is expressed and plays a role in developing germ cells?

Transgeneration memory of stress in plants

During their lifetime, plants are exposed to many different environmental conditions, including both abiotic (e.g.

Figure 1 Continued communication). Mop1, an RNA-dependent RNA polymerase, plays a role in both the initiation and maintenance of the paramutated state [9]. (a) Adapted from Ref. [8]. **(b)** Heterozygous Kit^{tm1Alf}/+ mice have a white tail tip and show deregulated expression of the wild-type allele, which is modified to become *Kit** [10]. Aberrant *Kit** transcripts accumulate in the sperm, and transmission of these aberrant transcripts to the zygote is proposed to cause paramutation of the incoming wild-type *Kit* gene, giving rise to progeny with white-tipped tails (*Kit*/Kit**). We predict that *Kit** has elevated expression associated with the accumulation of aberrant transcripts in these progeny (indicated by the '?'), although this has not been reported. Paramutagenicity can be passaged through either male or female gametes and persists through several generations.

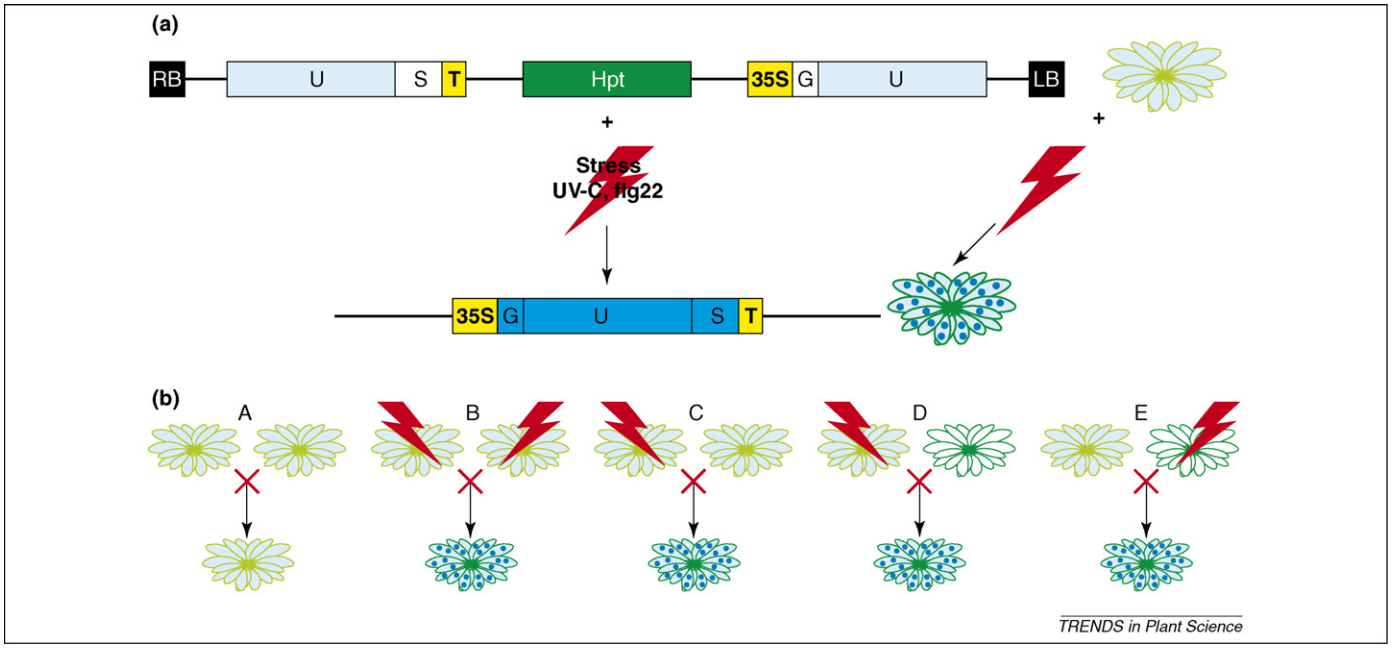

Figure 2. Somatic homologous recombination is enhanced in the progeny of UV-C- and flg22-treated *Arabidopsis* plants. **(a)** One of the recombination substrates used to visualize somatic homologous recombination in response to UV-C or flg-22 [11]. The homologous region of the construct is shaded light blue; plants carrying this construct are coloured light blue, which also represents the background level of recombination. Upon stimulation with UV-C or flg-22, homologous recombination produces a functional copy of the GUS gene (dark blue). Plants showing an elevated frequency of somatic homologous recombination are shown with dark-blue spots on a pale-blue background. The red lightening bolt indicates an applied stimulus, UV-C or flg-22. Abbreviations: GUS, β-glucuronidase gene; Hpt, hygromycin-resistance gene; 35S, 35S promoter; T, terminator sequence; RB and LB, right and left borders of construct. **(b)** The colour scheme of the *Arabidopsis* plants and additional features are the same as described in (a). A: control cross between two non-stressed transgenic plants that produce off-spring with the same background frequency of homologous recombination. B: cross between two stressed transgenic plants producing offspring with an increased level of homologous recombination that is similar to the level in selfed S_1 from a treated parent. C: treated transgenic plant crossed with a non-treated transgenic plant. D: treated transgenic plant crossed with a non-treated wild type (white *Arabidopsis* plants). E: non-treated transgenic plant crossed with a treated wild-type plant. Progeny from the crosses described for C, D and E have a comparable frequency of homologous recombination as the progeny from B and selfed S_1 from a treated parent. The level of homologous recombination is independent of whether the male or female germline carries the transgene or is stressed.

temperature, light, water and salt) and biotic (e.g. pathogens) stresses. Plants adapt to the changing environment by altering gene expression and, surprisingly, in some cases, by destabilizing the genome [25–29]. Increased rates of somatic recombination have been observed in response to various stresses [25–28], including viral infection, which results in a systemic signal leading to increased homologous recombination in non-infected leaves [28]. Now Barbara Hohn's laboratory has demonstrated that increased somatic homologous recombination in response to stress can be inherited by successive generations [11], implying a novel mechanism under the control of an unknown epigenetic phenomenon.

Somatic recombination was monitored using *Arabidopsis* plants carrying various recombination substrates consisting of two partially overlapping homologous sequences ('GU' and 'US') of the β-glucuronidase (GUS) gene, separated by a hygromycin resistance gene (Figure 2a). Homologous recombination between the two gene fragments produces a functional GUS gene that can be visualized by histochemical staining; the number of blue sectors is indicative of the recombination frequency. Consistent with previous reports [26], treatment with ultraviolet-C (UV-C) increased the frequency of somatic homologous recombination by between two- and four-fold in six independent GUS reporter lines compared with the non-treated controls [11]. Similar results were obtained when plants were treated with flg22 [11], a conserved peptide from flagellin that mimics a pathogen attack [30]. An inactive flg22 analogue from *Agrobacterium tumefaciens* [30] did not affect the recombination frequency.

The frequency of homologous recombination remained elevated in selfed progeny of irradiated plants, indicating that there was a 'memory' of exposure to UV-C. All the progeny of irradiated plants inherited the memory of UV-C exposure, which persisted through four generations of selfing, suggesting that the 'memory' of being placed under stress is an epigenetic phenomenon rather than having a genetic basis. A series of reciprocal crosses where only one parent was treated or where only the treated parent carried the transgene (Figure 2b A–D) showed that epigenetic control of homologous recombination is dominant and can be inherited through either the male or the female germline. Perhaps the most fascinating observation was that somatic homologous recombination increased in the progeny of a cross between a non-treated transgenic plant and a treated wild-type plant (Figure 2b, E). This intriguing result indicates that plants treated with UV-C or flg22 do not need to carry the transgene to transmit a dominant effect on recombination and that the treatment does not directly change the epigenetic status of the transgene locus.

So what does this mean for plants in the wild that are exposed to a variety of different stresses? Data from experiments using this reporter system suggest that environmental influences change the stability of plant genomes and that this change is inherited by their progeny. Because the germline of a plant is created late in development, new

traits arising in meristematic tissue can be passed to the next generation where they can be subject to selection [31]. Potential substrates for homologous recombination are the numerous disease resistance genes located in clusters throughout the genome, allowing the creation of new resistance genes by sequence exchange between the genes in the same or different clusters [31].

The nature of the epigenetic mechanism controlling the frequency of homologous recombination is unknown. Paramutation (Box 1) of the transgene itself can be ruled out because the frequency of homologous recombination increases even when the parent exposed to the stress does not contain the recombination substrate [11]. However, the possibility remains that a paramutation-like phenomenon could affect an endogenous gene(s) and that altered expression of this gene(s) might stimulate increased frequencies of homologous recombination at the transgene and other loci.

Chromatin changes can provide the basis for epigenetic memory and it has recently been shown through the use of *Arabidopsis* mutants affecting chromatin remodelling that chromatin structure plays a role in restricting the frequency of homologous recombination [32–34]. Specifically, Angela Kirik *et al*. [32] have recently characterized a new allele of the *Arabidopsis* gene *FASCIATA1* (*fas1-4*) that encodes the p150 subunit of CHROMATIN ASSEMBLY FACTOR 1. *fas1-4* has less heterochromatin and a more 'open' chromatin conformation and shows severe developmental abnormalities. When the *fas1-4* mutant was crossed with a line carrying the recombination substrate (Figure 2a), the frequency of homologous recombination in homozygous *fas1-4* mutant segregants increased ~100-fold, a frequency at least 20-fold higher than that induced by stress. This suggests that chromatin conformation is a key factor limiting homologous recombination in plants, and could play a role in the enhanced rate of recombination in stressed plants.

The most important question to be addressed before one can conclude that enhanced homologous recombination has evolved to promote plant survival in response to stress is whether there is a similar increase in somatic recombination at endogenous sequences in response to stress or in *fas1-4* mutants. To help understand what could be controlling the transgenerational 'memory' of a stress, one could ask whether the memory of stress is transmitted from a stressed genome to a non-stressed genome in such a way that the non-stressed genome now 'remembers' the stress, and can, in turn, transmit this memory. If this occurs then this would be suggestive of a paramutation-like phenomenon.

Concluding remarks

So what, if anything, links these three examples of transgenerational inheritance? The emerging evidence suggests that both examples of paramutation involve RNA-directed changes in chromatin structure. Because chromatin appears to be important in regulating homologous recombination, it is interesting to speculate that changes in chromatin could play a role in passing on the 'memory' of being exposed to environmental stresses. This change could also be mediated by RNA because previous experiments reporting enhanced recombination in response to viral infection showed that infection produces a systemic signal (perhaps an RNA) that moves ahead of the virus [28].

But what are the consequences of the transfer of epigenetic information from one generation to the next? Paramutation in plants is often associated with repeated sequences and so it is tempting to speculate that paramutation reflects the activity of a genome defence mechanism targeting repetitive DNA such as transposons. This is supported by the observation that *Mop1* is essential for the maintenance of silencing of at least the *Mu* class of DNA transposon [20]. In contrast to paramutation, which affects gene expression in a sequence-dependent manner, the decrease in genome stability in response to environmental stress might be sequence independent. The frequency of somatic homologous recombination reported here is low, but on a population-wide scale could generate novel traits that provide a selective advantage in a changing environment. The challenges for the future are to unravel these mechanisms and to determine whether endogenous sequences behave just like the transgenes used in these studies.

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