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SHORT REVIEW

Epigenetic, transposon and small RNA determinants of hybrid dysfunctions

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Accumulating evidence suggests that hybrid genetic dysfunctions accrue not only because of sequence divergence of incompatible alleles but also result from a broad variety of mechanisms related to the maintenance of chromatin integrity. For example, it has been observed that hybridization in plants and mammals disrupts patterns of DNA methylation and imprinting. These epigenetic changes can be associated with transcriptional activation and mobilization of transposable elements in hybrids. It raises a question of how these alterations are matched by small regulatory RNAs, such as piwi-interacting RNAs, which play a potent role in both suppressing transposable elements and epigenetic control. The review offers a handful of glimpses into these complex dynamics.
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'The weakest link in the chain is also the strongest. It can break the chain.'

Stanisław Jerzy Lec

How new species originate is a central question in biology. Clearly, this question will not be solved without an understanding of the molecular underpinnings behind postzygotic reproductive isolation, including hybrid dysfunctions such as inviability and sterility. Although there has been some progress in characterizing genes related to postzygotic isolation, this is just a tip of the iceberg. Dobzhansky–Muller's model of genetic incompatibilities has long provided a useful theoretical framework for speciation genetics, but it is becoming increasingly clear that the model is too general to generate more specific predictions regarding the genetic mechanisms involved.

Accumulating evidence indicates that the merging of two distinct genomes typically sets in motion extensive modifications of the genome and transcriptome, creating cascades of novel gene expression patterns (Michalak and Noor, 2003; Wu *et al*., 2003; Ranz *et al*., 2004; Auger *et al*., 2005; Hegarty *et al*., 2006), regulatory interactions and new phenotypic variation (Riddle and Birchler, 2003; Adams and Wendel, 2005a, b), chromosomal rearrangements (Rieseberg *et al*., 2003; Metcalfe *et al*., 2007), transposable element mobilization (Liu and Wendel, 2000; Shan *et al*., 2005; Ungerer *et al*., 2006), miRNA deficiency (Michalak and Malone, 2008) and DNA methylation changes (Waugh O'Neill *et al*., 1998; Vrana *et al*., 2000; Salmon *et al*. 2005; Josefsson *et al*., 2006).

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Contrary to other reviews of speciation genetics that typically enumerate examples of so-called 'speciation genes,' this review focuses on a broad class of genetic processes related to maternal effects, epigenetic changes, activity of transposable elements and small RNAs in interspecies hybrids. This by no means suggests that these genetic factors are more important in creating hybrid genetic incompatibilities than others (for example, protein–protein interactions). Instead, the intention is to draw more attention to the fact that elements related to chromatin integrity may contribute to Dobzhansky–Muller incompatibilities (DMI). For example, Lethal hybrid rescue (Lhr), which interacts with Hybrid male rescue and causes hybrid inviability in *Drosophila*, is known to colocalize with Heterochromatin Protein 1 along heterochromatic repetitive segments (Brideau *et al*., 2006).

This mini review is separated into three parts devoted to epigenetic programming, mobile elements and small noncoding RNAs. However, this distinction is largely artificial, as all these factors constitute a highly interacting network. Interspecific hybridization is common in plants, and experimental hybridization has traditionally been the main method of horticulture. Until the recent development of comparative genomics; however, hybrid and speciation genetics of plants lagged behind animal genetics research. Currently, speciation genetics of plants enjoys its renaissance capitalizing on massive data related to gene expression, polyploidization and hybridization and plant systems such as *Arabidopsis* are emerging as new model genera for speciation (reviewed by Bomblies and Weigel, 2007). This review takes advantage of these developments and thus relies heavily on plant case studies.

Epigenetic reprogramming in hybrids

When two different genomes are combined in a hybrid zygote, they must respond to massive regulation changes

corresponding to 'genomic shock' (Comai *et al*., 2003; Wang *et al*., 2006). In plants, hybridization is commonly associated with subsequent genome duplication (allopolyploidy), and these two processes have their distinct contributions to global changes of gene expression. To dissect transcriptional effects of hybridization and polyploidization, Hegarty *et al*. (2006) compared floral gene expression in allohexaploid *Senecio cambrensis* with that in its parent species, *S. vulgaris* (tetraploid) and *S. squalidus* (diploid) and their triploid F1 hybrid, *S. x baxteri*. They demonstrated that *S. x baxteri* showed the most dramatic transcriptome changes relative to parental taxa and that genome duplication exerts ameliorating effects on expression patterns altered by hybridization, the latter result confirmed with profiling of synthetic lines of *S. cambrensis*.

What are the mechanisms underlying these and similar genome-wide changes to gene expression in newly formed hybrids? Reprogramming through epigenetic modifications, such as DNA methylation and chromatin remodeling, provides a very potent candidate mechanism. One line of evidence that hybridization leads to epigenetic alterations comes from disruption of imprinting in hybrids (Vrana *et al*., 1998; Bushell *et al*., 2003; Josefsson *et al*., 2006). In deer mouse (*Peromyscus*), two hybrid phenotypes are produced that are dependent on the direction of crossing: when a female *P. maniculatus* is crossed with a male *P. polionotus*, the offspring is undersized; in the reciprocal cross, the offspring is oversized, producing a sixfold difference in placental weight between the two hybrid types (Dawson, 1965). Vrana *et al*. (1998) showed that the oversized hybrids predominantly lost imprinting of paternally expressed genes (*Peg3*, *Mest*, *Snrpn*), thus leading to their overexpression, as predicted by the parent–offspring conflict model. According to this model, alleles of paternal origin are selected to extract more resources than it would be advantageous for the mother's other current or future offspring (Trivers, 1974).

The oversized *Peromyscus* hybrid progeny typically does not survive as it leads to the mother's death at parturition. The very few that have survived postnatally and have been oversized were females, obeying Haldane's rule. However, this pattern of hybrid viability is consistent with Haldane's rule not as a consequence of deleterious X-linked recessive alleles, as predicted by dominance theory, but rather as results from the epigenetic regulation of X-linked genes. Specifically, Vrana *et al*. (2000) found that oversized inviable hybrids arise from a combination of a maternally expressed X-linked Locus (*Mexl*), or its *P. polionotus* allele and a paternally expressed autosomal locus (*Peal*), or its *P. maniculatus* allele. Fine-resolution mapping of these loci is in progress (Loschiavo *et al*., 2007). Imprinting effects are comparable with the hemizygosity of X-linked genes, and therefore it is tempting to extend the logic used to explain the large-X effect to imprinted sequences, which in mammals make up a non-trivial part of the genome ($\sim$0.1%) (Vrana *et al*., 2000).

A major prezygotic pollination barrier in flowering plants is genetic self-incompatibility (SI). SI is best known as an intraspecies mechanism against self-fertilization, and its role in reproductive isolation between species may be somewhat surprising. Nevertheless, the disruption of SI is a critical event in hybridization of self-incompatible species, as it produces self-fertile hybrids. SI is determined by allele-specific interaction between two proteins, the stigma-expressed S-locus receptor kinase (SRK) and its pollen ligand, the S-locus cysteine-rich protein (SCR, also known as SP11) (Nasrallah, 2005; Takayama and Isogai, 2005). Nasrallah *et al*. (2007) showed SI disruption in the stigmas of *Arabidopsis thaliana x A. lyrata* hybrids and their neo-allotetraploid derivatives and in the pollen of *Capsella rubella x C. grandiflora* and their homoploid progenies. In these two systems, two different mechanisms were responsible for loss of SI: aberrant processing of SRK transcripts in *Arabidopsis* and suppression of SCR in *Capsella*. Interestingly, SI was restored along with the parental SRK transcript profile in first-generation backcross *Arabidopsis*. As SI breakdown was reversible and no changes in DNA sequence were identified to underlie the pattern, it was concluded that these modifications were epigenetic (Nasrallah *et al*., 2007).

Arabidopsis arenosa is another species that hybridizes with *A. thaliana* (Figure 1). These two species have hybridized in nature to form the allotetraploid species *A. suecica* (Kamm *et al*., 1995). Postzygotic isolation between *A. arenosa* and *A. thaliana* affects seed abortion, as seeds from the *A. thaliana x A. arenosa* cross result in endosperm overgrowth and arrested or abnormal embryo development (the reciprocal cross is impossible owing to pollination failure). Josefsson *et al*. (2006) observed that seed inviability strongly correlated with increasing relative paternal genome dose, suggesting that maternal genomic excess suppressed incompatibilities in hybrids. They also found that maternal genomic contribution (and thus seed viability) was inversely correlated with expression of *ATHILA*, predominantly pericentromeric retroelements. The normally silenced *ATHILA* (but not other transposable elements tested) were derepressed in hybrids, but only paternal (not maternal) copies were expressed.

Seed development in *Arabidopsis* is negatively regulated by a polycomb repressive complex (PRC) containing *MEDEA* and *FIE* genes. Paternally imprinted *MEDEA* is predominantly expressed in the endosperm and the embryo, where it targets *PHERES1*, a maternally imprinted gene whose repression of the maternal copy is dependent on the PRC complex (Köhler *et al*., 2005). Interestingly, maternal *MEDEA* was shown to regulate its own imprinting on the paternal chromosome (Gehring *et al*., 2006; Jullien *et al*., 2006). Paternal imprinting of *MEDEA* and maternal imprinting of *PHERES1* were lost in hybrids (Josefsson *et al*., 2006). Maternal *PHERES1* deregulation was shown to functionally contribute to hybrid seed inviability, as knocking out maternal *PHERES1* rescued hybrid seed survival.

Hybridization is known to affect genome-wide patterns of DNA methylation in synthetic *Arabidopsis thaliana x A. arenosa* allotetraploids (Madlung *et al*., 2002) and *Solanum tuberosum x S. kurtzianum* diploids (Marfil *et al*., 2006), extending much beyond imprinted genes. Similarly, synthetic hybrids of wheat (*Triticum aestivum*) exhibit rapid and widespread loss of genomic fragments and methylation alterations (Ozkan *et al*., 2001; Shaked *et al*., 2001). However, there is no evidence that global changes of methylation are associated with hybridization in placental mammals (Roemer *et al*., 1999).

Figure 1 (**a**) *Arabidopsis thaliana* (autotetraploid), (**b**) *A. arenosa* (outcrossing tetraploid) and (**c**) resynthesized allotetraploids (in 8th generation of selfing) (Photo by Z Jeff Chen).

Transposable element derepression during hybridization

Activation of transposable elements as a result of hybridization is by no means limited to *ATHILA* in *Arabidopsis*. Barbara McClintock predicted as early as in the 1980s that hybridization in plants might activate quiescent transposons and result in genome restructuring (McClintock, 1984). Another example of transposable element (TE) mobilization comes from intergeneric hybridization between rice (cultivar Matsumae) and wild rice (*Zizania latifolia*). Shan *et al*. (2005) used a repeated pollination procedure to generate a series of morphologically distinct inbred lines of rice with introgressed genomic DNA from wild rice, and showed that *mPing* miniature inverted-repeat transposable element (MITE) and its transposase-encoding partner, *Pong*, were mobilized in these lines. In contrast, these two MITEs remained immobile in control lines sharing the same parentage to the experimental lines but possessing no introgressed DNA.

A striking example of retrotransposon proliferation is provided by three hybrid species of sunflowers, *Helianthus anomalus*, *H. deserticola* and *H. paradoxus*, which are products of ancient hybridization between *H. annuus* and *H. petiolaris* (Ungerer *et al*., 2006). These hybrid species have a nuclear genome at least 50% larger than that of either parental species, despite the fact that both hybrid and parental species are diploids and all have the same number of chromosomes ($n = 17$). Ungerer *et al*. (2006) showed that the difference in genome size between hybrid and parental species is largely explained by the increased abundance of Ty3/gypsy-like LTR retrotransposon sequences in hybrids.

In contrast to plants, it seems that TE mobilization in hybrids between animal species is less frequently observed, despite direct attempts at detecting it (for example, Coyne, 1986, 1989; Hey, 1988). This made some stay skeptical about the plausibility of reproductive isolation as a consequence of TE movement (Coyne, 1989; Coyne and Orr, 2004). Nevertheless, spectacular examples of TE activation in animal hybrids do exist. An interspecific hybrid between two species of Australian wallaby (*Macropus eugenii* and *Wallabia bicolor*) shows dramatically extended centromeres due to proliferation of additional centromeric material consisting of an unmethylated, endogenous retroviral element (retroelement) (Waugh O'Neill *et al*., 1998). Similar centromeric aberrations were also observed in hybrids between two other marsupial species, *Macropus rufogriseus* and *M. agilis* (Metcalfe *et al*., 2007).

In *Drosophila*, most examples of hybrid dysgenesis were provided by intraspecies crosses of *D. melanogaster* and *D. virilis* (see below Small RNAs and fertility

defects). However, there is at least one interspecies cross documented to have resulted in activation of TE, namely that between *D. buzzatii* and *D. koepferae* (Labrador *et al*., 1999).

Small RNAs and fertility defects

Derepression of TEs in hybrids may result from a lack of specificity of maternally contributed small RNAs. This was shown in some intraspecific *Drosophila melanogaster* crosses, in which *P*, *I* and *hobo* elements were mobilized, resulting in sterility of the offspring from crosses between males carrying these TEs and females lacking them (for example, Kidwell, 1985; Yannopoulos and Stamatis, 1987). In the reciprocal cross between females carrying these elements and males lacking them, TE repression is unperturbed and the offspring is fully fertile. Clearly, maternal inheritance maintains TE repression, which can be transmitted to the next generation, even if the maternal TE copies are defective or not transmitted themselves (Ronsseray *et al*., 1993; Stuart *et al*., 2002). Direct evidence for maternally transmitted small interfering RNA in TE repression has been provided for *Drosophila virilis* strains (Blumenstiel and Hartl, 2005). Hybrid dysgenesis (manifested as male sterility) in this species is associated with mobilization of *Penelope*, a retroelement containing an intron, and comobilization of other unrelated elements including class I LTR, non-LTR and class II DNA members. Approximately 23 nt long sense and antisense RNAs homologous to *Penelope* are maternally (but not paternally) loaded in embryos through the female germ line in the presence of a specific non-dysgenic X chromosome. Dysgenic sons are produced by mothers who lack the X chromosome and fail to provide embryos with the *Penelope*-derived siRNA.

It is tempting to speculate that small RNA pathways, such as RNAi, miRNA and piwiRNA (piRNA), are instrumental to hybrid dysgenesis and maternal effects. The recent discovery and characterization of piRNA are particularly exciting in the context of male sterility and transposon repression (reviewed by O'Donnell and Boeke, 2007). These 24- to 30-nt long RNAs are derived primarily from transposons and other repeated sequence elements, generated by a Dicer-independent mechanism (as opposed to siRNA and miRNA) and complex with a subset of Argonaute proteins related to Piwi, which are crucial to germ line development and fertility (O'Donnell and Boeke, 2007). In *Drosophila*, piRNAs were first described as repeat-associated small interfering RNAs (rasiRNA) (Aravin *et al*., 2003). The most abundant *Drosophila* piRNAs originate from the antisense strand of retrotransposon sequences and preferentially interact with the Argonaute proteins Piwi and Aubergine (Aub), whereas sense-strand piRNAs preferentially associate with Argonaute 3 (Ago 3). Piwi, Aub and Ago3 form a complex with piRNAs that guide cleavage of the target RNA, leading to gene silencing.

Remarkably, *Drosophila* piRNA pathway mutations have resulted in the reduction of male fertility, overexpression of retrotranposons and *piwi* mutations have led to mobilization of at least one class of transposon in the male germ line (reviewed by Klattenhoff and Theurkauf, 2007). As piRNAs are also produced from

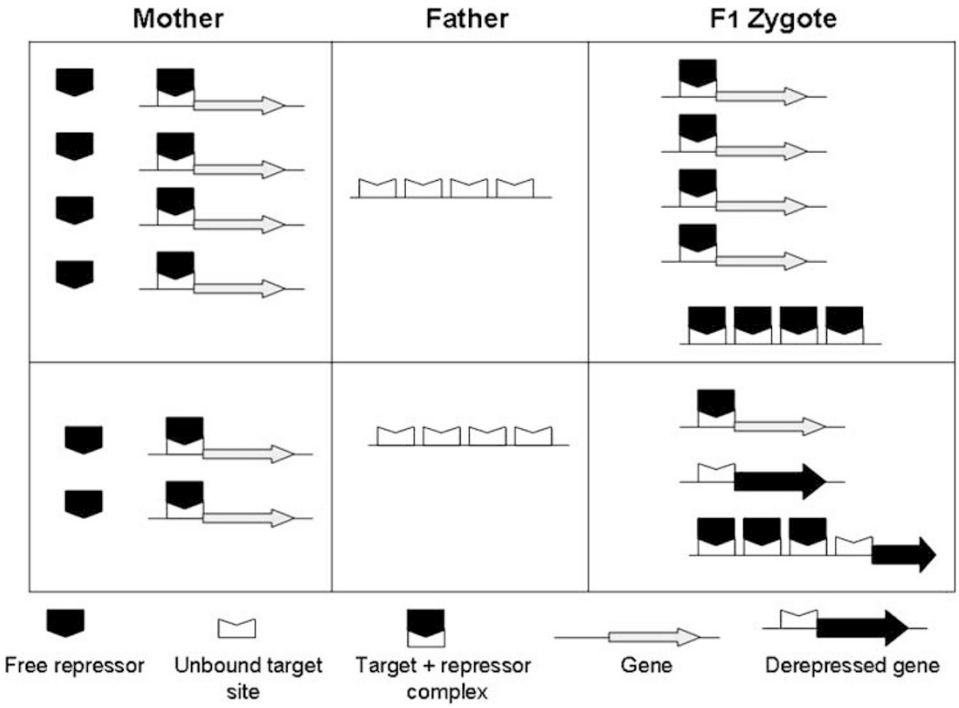

Figure 2 Dosage-dependent induction model of chromatin-mediated hybrid failure (after Josefsson *et al*., 2006). Two reciprocal crosses are depicted: 4n × 2n (top) and 2n × 4n (bottom), where n has originally represented the ploidy level, but it may also refer to any difference in the repressor gene copy, its transcript abundance or binding efficiency. During zygote formation, the female gamete must provide a sufficient quantity of the repressor (for example, siRNA) to saturate the available binding sites in the male gamete. If an insufficient amount of the repressor is delivered, both paternal and maternal unbound target sites (for example, mobile elements) will escape silencing, resulting in their derepression.

the Y-linked *Suppressor of Stellate* (*Su(Ste)*) locus, mutations in the piRNA pathway cause overexpression of X-linked *Stellate* genes, whose protein product assembles into crystals in the testes.

In the mouse, the Argonaute protein family can be divided into Ago and Piwi subclasses. There are four Ago members (AGO1-4) and three piwi members (MIWI, MILI/PIWIL2 and MIWI2/PIWIL4). Ago members are typically expressed ubiquitously and are associated with miRNAs and siRNAs, whereas Piwi members are more specific for germline and stem cells and bind piRNAs. Knockout mutations in the *Miwi* and *Mili* genes suppress piRNA production, derepress retrotransposon transcriptional activity and lead to abnormal spermatogenesis and male sterility (reviewed by Klattenhoff and Theurkauf, 2007). Mammalian spermatogenesis can be divided into three phases: (i) mitosis, when germline stem cells (spermatogonia) are self-renewed to produce primary spermatocytes, (ii) meiosis, when the primary spermatocytes progress to haploid spermatids and (iii) spermiogenesis during which round spermatids mature and are morphologically reorganized into spermatozoa. The timing of developmental arrest of *Mili* and *Miwi* mutants is correlated with the temporal expression of Mili and Miwi proteins. Mutations in *Mili* and *Miwi2* are arrested at the early pachytene spermatocyte phase, whereas *Miwi* mutants progress to the round-spermatid but do not complete spermiogenesis.

Conclusions: toward a chromatin model of hybrid genetics

It is now becoming clear that it is virtually impossible to discuss roles of transposable elements in hybrid dysgenesis separately from epigenetic mechanisms and small RNA pathways, and the distinction used in this review is inevitably artificial. For example, retroelement activation in the wallaby interspecies cross is associated with substantial DNA undermethylation (Waugh O'Neill *et al*., 1998, but see Roemer *et al*., 1999), which is consistent with the idea of methylation as the host defense system against proliferation of mobile elements. Small RNAs, such as siRNAs and piRNAs may have primarily evolved as a means of repressing TEs. The complexity of interactions is additionally increased by the fact that non-coding small RNAs are active players in epigenetic regulation, presumably by providing sequence-specific interface between a DNA sequence and its epigenetic state. For example, Yin and Lin (2007) showed that Piwi promotes euchromatic histone modifications and piRNA transcription in subtelomeric heterochromatin.

The model of Dobzhansky–Muller incompatibilities assume that hybrid dysfunctions result from negative epistatic interactions between alleles that have diverged in different populations or species. Josefsson *et al*. (2006) proposed a DMI extension, the 'dosage-dependent induction' to model quantitative interactions between maternal and paternal factors and explain the dosage sensitivity that they observed in *Arabidopsis* hybrids (Figure 2). This verbal model assumes that females and males differ in the number of regulator and target sites and that the female gamete must deliver a sufficient amount of repressive factors to saturate binding sites originating from the male gamete. If the amount is insufficient, both maternal and paternal target sites will escape silencing. For example, if there is differential deposition of maternally loaded small RNAs between species, or if these small RNAs differ in their capabilities to suppress their targets, derepression of mobile elements or other failures to maintain chromatin integrity will be manifested. This model provides new testable predictions. For example, maternal postzygotic effects should be accompanied by differences in maternal contributions of transcripts. If the piRNA pathway in hybrids is affected, this should result in derepression of mobile elements. Finally, if these effects are dosage-dependent, then increased maternal contribution to the zygote should result in partial or complete suppression of hybrid dysfunctions, as observed in *Arabidopsis*.

If methylation mechanisms and small RNAs are fine-tuned to keep mobile elements in check, then this antagonistic interplay can be subject to an evolutionary 'arms race.' Genomic imprinting can also be engaged in potential kinship–parental antagonism at the genomic level, which may explain the rapid evolution of reproductive isolation in mammals compared to other nonviviparous vertebrate groups (Zeh and Zeh, 2000; Haig, 2004). Given the high potential for rapid divergence between species, the chromatin-mediated factors described here are excellent candidate elements of Dobzhansky–Muller genetic incompatibilities.

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