Hybrid dysgenesis: from darkness into light

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Hybrid dysgenesis: from darkness into light: a commentary on 'Hybrid dysgenesis in *Drosophila melanogaster*: rules of inheritance of female sterility' by William R. Engels

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One of the many striking insights to have come from sequencing complete genomes is the realization that transposable elements make up a large proportion of the DNA of most eukaryotes. These elements are far from minor players on the genomic stage. They have had a major role in genome evolution and are a significant source of genome instability. Transposable elements are driven to high copy number by transposition, but their activity is difficult to study experimentally as most copies are defective, and the few that are transpositionally competent move infrequently. This is good for the host organism, but not for anyone wanting to study them.

A small number of transposable elements in *Drosophila* transpose at high levels in the progeny of particular crosses. This results in genetic instability manifest by reduced fertility of one or both sexes and a high frequency of germ line mutations, a phenomenon known as hybrid dysgenesis (Kidwell, 1977). *P–M* hybrid dysgenesis, for example, is seen when males of a *P*-type strain are crossed with females of an *M*-type strain, but not in the progeny of the reciprocal cross.

At the heart of hybrid dysgenesis is a breakdown in the control of transposition. This was not immediately apparent and for several years hybrid dysgenesis was regarded as a strange phenomenon that appeared to run counter to accepted 'rules' of genetics. Bill Engels was one of the first to address this, and his analysis of the genetic basis for the difference between *P* and *M* strains established a paradigm for subsequent research (Engels, 1979). In an elegant series of experiments, Engels was able to show that hybrid dysgenesis could be explained by the interaction of polygenic chromosomal factors that appeared to be inherited in a Mendelian fashion, and a maternally inherited cytoplasmic state that he called 'cytotype'. He proposed that the cytotype of *M* strain females is permissive for the activity of the chromosomal factors, *P* factors, which, in dysgenic flies, would be inherited from *P* strain males. The cytotype of a *P* strain would be non-permissive, thus accounting for the non-reciprocal nature of hybrid dysgenesis. He further suggested that *P* cytotype is determined by *P* factors themselves, explaining why *P* strains are genetically stable. Finally, he proposed that *P* factors might be transposable elements, as was thought to be the case for chromosomal factors responsible for a second form of hybrid dysgenesis, *I–R* hybrid dysgenesis (Picard, 1976).

The suggestion that the chromosomal determinants responsible for *P–M* hybrid dysgenesis are transposable elements was confirmed by the identification of insertions of repeated sequences in the *white* gene in white-eye mutations isolated from the progeny of *P–M* dysgenic flies (Rubin *et al.*, 1982). These insertions appeared to be deletion derivatives of a longer element, probably the *P* factor itself. This was cloned and shown to have *P* factor activity by injection into *M* strain embryos, an experiment based on Engel's insights into the role of cytotype in controlling *P* factor activity. The flies resulting from these embryos exhibited some of the characteristics of hybrid dysgenesis. The injected DNA destabilized *P* elements inserted at the *singed* locus in a mutant that revert in *P–M* dysgenic flies, and the putative *P* factor transposed from plasmid to chromosomal DNA (Spradling & Rubin, 1982). This observation led to the development of *P* elements for transformation and mutagenesis (Rubin & Spradling, 1982), perhaps the most significant technological development in modern *Drosophila* research.

The molecular basis of *P* cytotype has been a more difficult nut to crack, and is still not completely understood. Production of mRNA for transposase, the *P* factor-encoded protein required for transposition, requires three splicing events, the third of which is blocked in somatic cells by a splicing factor (Siebel & Rio, 1990), explaining why *P–M* dysgenesis does not affect somatic cells. *P* factor RNA retaining the third intron codes for a 66 kDa truncated form of transposase that represses transposase activity if

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expressed in the germ line (Misra & Rio, 1990). Since the 66 kDa protein is normally present in ovaries as well as somatic cells of *P* strain females, perhaps because of a low level of the splice inhibitor in the germ line, it could be responsible for *P* cytotype.

The picture has become more complex since the recent discovery that a particular class of small RNAs, the piRNAs, is targeted specifically at transposable elements (Girard *et al*., 2006; Grivna *et al*., 2006; Vagin *et al*., 2006). Some insertions of *P* elements near the telomere of the *X* chromosome led to maternally inherited repression of *P* element activity (Biemont *et al*., 1990; Ronsseray *et al*., 1991), a characteristic of *P* cytotype. This is alleviated by mutations in genes of the piRNA pathway (Reiss *et al*., 2004; Josse *et al*., 2007), suggesting that piRNA may also contribute to *P* cytotype (Brennecke *et al*., 2007). The relative contributions of the 66 kDa protein and piRNA to *P* cytotype are unclear, but 30 years after it was characterized genetically by Engels, we are well on the way to understanding it molecularly.

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