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The (new) new synthesis and epigenetic capacitors of morphological evolution

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Abstract

A new study shows that the piRNA-binding protein Piwi interacts with Hsp90 and suppresses phenotypic variation in *Drosophila melanogaster* by preventing the expression of hidden epigenetic variation. This suggests that Hsp90 and Piwi function are dampened in times of stress to increase genetic and epigenetic variability, providing a last-ditch mechanism for a species to survive.

In 1942, Julian Huxley wrote an influential book, *Evolution: The Modern Synthesis*, that influenced generations of geneticists¹. The basis of the ‘modern synthesis’, also called the ‘new synthesis’, is that it reconciles Mendelian genetics with gradual evolution by means of natural selection of existing genetic variation. Now, on page 153 of this issue, Haifan Lin and colleagues report the existence of mechanisms that normally prevent the expression of hidden epigenetic variation², suggesting that the new synthesis should be expanded to incorporate both genetic and epigenetic sources of variation on which selection can act.

Piwi suppresses genetic variation

The Piwi-interacting RNA (piRNA) binding protein Piwi³, which is in the Argonaut family of small-RNA slicing proteins, was recently found to prevent transposon mobilization in the male germline by ‘slicing’ (cleaving) transposon RNAs^{4,5}. Then, Specchia *et al.*⁶ showed that reducing the expression of Hsp90, a chaperone that helps signaling proteins fold properly, disrupts piRNA-mediated silencing and leads to transposon activation. Specchia *et al.*⁶ proposed that loss of piRNA can increase genetic variation through transposon mobilization, and this newly induced genetic variation can be genetically assimilated over many generations to increase the fitness of the organism. This work suggests that Piwi is an adaptively inducible ‘canalizer’. ‘Canalization’ is a term proposed by Conrad Waddington in 1942 to explain how assimilation of specific alleles in a population stabilizes a phenotype from environmental stress to produce developmental robustness⁷. The beneficial effect of transposon mobilization is not a new idea; Barbara McClintock proposed in her Nobel Prize seminar in 1983 that transposon mobilization in times of stress can be a last-ditch mechanism of genome reorganization⁸.

Piwi suppresses epigenetic variation

Vamsi Gangaraju *et al.*² now show that Piwi also suppresses epigenetic variation and forms a protein complex with Hsp90. They propose that a combined genetic and epigenetic increase in diversity in times of stress can dramatically increase phenotypic variation on which selection can act. They used a sensitized assay that detects loss of epigenetic silencing of a dominant gain-of-function allele of Kruppel (*Kr^{irregular facets-1}*; *Kr^{If-1}*) in the developing eye⁹. It is already known that maternal deficiency of Hsp90, or of Trithorax-group chromatin remodeling proteins, causes loss of repression of *Kr^{If-1}* and development of ectopic large bristle outgrowths (ELBOs) from one or both of the eyes⁹. Gangaraju *et al.*² show that combined maternal and zygotic loss of Piwi causes the ELBO phenotype in *Kr^{If-1}* flies, suggesting that Piwi has similar functions to Hsp90. The authors further show that Hsp90 interacts with Piwi in a multiprotein complex and regulates Piwi phosphorylation².

In addition to the exciting finding that Piwi functions in a complex with Hsp90, the authors show that *Kr* mRNA expression itself is increased in the heads of flies with ELBOs². As *Kr^{If-1}* is a spontaneous mutation that is presumably caused by a transposon insertion (the allele has not yet been fully characterized), an attractive model is that Piwi silences the *Kr^{If-1}* allele by targeting its transposon for cleavage, similar to how it silences other transposons (Fig. 1a). Piwi is thought to silence transposons in two sequential steps: first by slicing the transposon transcripts and then by interacting with heterochromatin protein-1 (HP1) and directly repressing transcription of the transposons¹⁰ (Fig. 1a). If *Kr^{If-1}* is caused by a transposon insertion, then recruitment of Piwi and HP1 to the *Kr^{If-1}* locus may repress expression of Kruppel in the developing eye and prevent ELBO formation (Fig. 1a). If Hsp90, Piwi or both are inactivated, by the Hsp90 inhibitor geldanamycin, by genetic loss or by exposure to stress, then transposons are expressed and mobilized, *Kr^{If-1}* is expressed and ectopic Kruppel in the eyes causes the ELBO phenotype (Fig. 1b).

Although this is an attractive hypothesis to explain how loss of Piwi might cause transposon mobilization, Piwi may be involved in a more complex epigenetic mechanism, such as DNA looping or localization to 'Polycomb bodies', which are distinct nuclear loci where repressive Polycomb complexes aggregate¹¹. We found, for instance, that the Kruppel localization pattern in the developing eye is indistinguishable in *Kr^{If-1/+}* flies regardless of whether the ELBOs are present or not (D.M. Ruden & V. Sollars, unpublished data), suggesting that the eye outgrowth phenotype is not a simple result of Kruppel overexpression. In summary, the results of Gangaraju *et al.*² provide evidence for a model in which Piwi functions as an adaptively inducible canalizer to both suppress transposon-mediated mutagenesis and suppress epigenetic variation.

The (new) new synthesis

These findings make clear that epigenetic and mutagenic processes are not an alternative to genetic adaptation. Rather, they are mechanisms induced in response to some stimulus, and the changes can potentially be transmitted across generations. Thus, there is a need for a '(new) new synthesis' or 'ultramodern synthesis' that incorporates the range of responses an organism makes to environmental change. The theory should take into account genetic and epigenetic adaptation, the timescales of these processes, the potential for reversibility and the interplay between individual and population processes.

Roles for epigenetic and mutagenic mechanisms in evolutionary theory are not new. These concepts can be traced back to another influential, but more controversial, paper published in 1942, in which Conrad Waddington defined epigenetics as "the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype

into being” and argued that there is a bidirectional interaction between the environment and genes⁷.

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Figure 1.

Proposed model of Hsp90- and Piwi-mediated suppression of variation. **(a)** In the nonstressed state, Hsp90 binds Piwi and regulates its phosphorylation (P). Piwi slices transposon RNAs (represented by short lines) and binds HP1 to repress transcription of both endogenous transposons and the presumed transposon in the Kr^{lf-1} allele. **(b)** In the stressed state, inactive Hsp90 and inactive Piwi allow expression of both transposons and Kr^{lf-1} .