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NEWS AND COMMENTARY

Yeast hybrid incompatibility genes

One hundred years after Bateson: a pair of incompatible genes underlying hybrid sterility between yeast species

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This year we celebrate the bicentennial of Darwin's birth and the sesquicentennial of Darwin's seminal work, *The Origin of Species*. A less-known anniversary is the centennial of William Bateson's (1909) genetic model of hybrid sterility and inviability. Bateson's model postulated that the lack of fertility and/or viability of hybrids arises from interactions among genes, a view that is generally held today. Recently, Hsin-Yi Lee *et al*. (2008) identified a pair of interacting genes, one mitochondrial and one autosomal, which contributes to sterility in hybrids in the manner predicted by Bateson a century ago.

Darwin saw hybrid sterility and inviability evolving as the by-product of other changes and not as adaptive *per se*, but lacked a genetic mechanism to illustrate this (reviewed in Johnson, 2008). Only 9 years after the rediscovery of Mendel's laws, Bateson (1909) proposed such a model. He recognized that a change at a single locus was unlikely to lead to hybrid sterility and inviability, because one or more of the nascent species would have to go through what would later be called an adaptive valley, as heterozygotes would be less fit than either homozygote (Gavrilets, 2004). If hybrid incompatibility was due to interactions among genetic changes at multiple sites, then both nascent species could evolve without either going through an adaptive valley. Bateson's model was neglected even in his own later works; most geneticists did not know of Bateson's contributions to the genetics of speciation until Orr's (1996) perspective in the journal *Genetics*. A generation after Bateson, Theodosius Dobzhansky (for example, 1937) and Herman Muller (for example, 1942) proposed and extended models similar to Bateson's. As Muller (1942) recognized, these genetic incompatibilities can involve more than two loci. Regardless of the number of loci involved, these Bateson–Dobzhansky–Muller (BDM) incompatibilities form the basic paradigm for much of the current theory on the evolution of reproductive isolation, and therefore the formation of species (for example, Porter and Johnson, 2002; Gavrilets, 2004; Unckless and Orr, 2009).

Substantial evidence exists for such BDM incompatibilities contributing to the sterility and inviability of interspecific hybrids across many taxa (Coyne and Orr, 2004). Until recently, that evidence consisted of chromosomal segments from one species interacting with different chromosomal segments from another species. Even when one gene affecting hybrid incompatibility was characterized, its partners were left unidentified. Working with hybrids between *Drosophila melanogaster* and *D. simulans*, Brideau *et al*. (2006) showed that interactions between the *lethal hybrid rescue* (*Lhr*) gene from *D. simulans* and the *hybrid male rescue* (*Hmr*) gene from *D. melanogaster* contributed to the inviability of these hybrids. Until the study by Lee *et al*., the *Lhr–Hmr* interaction was the only clear example of such a BDM incompatibility. Moreover, *D. melanogaster* and *D. simulans* are a relatively old pair of species, which have undergone substantial functional divergence; the species normally do not produce any fertile hybrids and it is likely that hundreds of genes are involved in the sterility and inviability of their hybrids (Johnson and Kliman, 2002).

The yeast species *Saccharomyces cerevisiae* and *S. bayanus* are closely related and somewhat intercrossable. To examine the genetic basis of sterility of hybrids between these species, Lee *et al*. constructed chromosomal replacement lines; each contained one specified chromosome from *S. bayanus* with the rest of the genetic background being from *S. cerevisiae*. Most of these replacement lines were able to grow. Although chromosome 13 replacement lines were viable and could be maintained as haploids, they were completely defective in sporulation and therefore sterile. Moreover, these chromosome 13 lines could not be grown in media that contained just glycerol, suggesting an additional defect in oxidation.

To find genes that could rescue the respiratory defect, the researchers screened a genomic library from *S. cerevisiae*; all of the clones that restored oxidation contained the *AEP2* gene, which resides on chromosome 13. Additional work confirmed that the addition of the *AEP2* allele from *S. cerevisiae* was able to rescue the sporulation and respiratory defect of the chromosome 13 lines, showing that the *S. bayanus* allele of this gene had a role in hybrid sterility. It is interesting that the Aep2 protein is located in the mitochondria.

Based on the results of Lee *et al*. from genetic analyses, *AEP2* does not interact with a single autosomal genetic factor to yield the BDM incompatibility; the sterility could be due to interactions with a cytoplasmic factor or with multiple autosomal genes. Given that the Aep2 protein resides in the mitochondria, a mitochondrial gene seemed most likely to be the interactor. To find this interactor, the investigators took advantage of the rich knowledge base of functional biology established in *S. cerevisae*. As previous studies suggested that the protein Aep2 facilitates the translation of *OLI1* mRNA by binding to its 5′untranslated region (UTR), Lee *et al*. hypothesized that *OLI1* interacted with AEP2. Two key observations from their studies support their hypothesis: (1) the 5′ UTR of *OLI1* diverged substantially between the two yeast species and (2) translation of *OLI1* mRNA is impaired in chromosome 13 substitution lines. So, an interaction between the Aep2 protein from *S. bayanus* and *OLI1* mRNA from *S. cerevisiae* is likely to be the cause of sporulation and respiration defects seen in chromosome 13 replacement lines, and is therefore a BDM incompatibility.

How could this incompatibility evolve? Although the BDM model is agnostic regarding whether the changes that lead to such incompatibilities are neutral or adaptive, empirical evidence from Drosophila hybrid sterility and hybrid inviability studies strongly suggest that these changes were driven by natural selection (Johnson and Kliman, 2002; Coyne and Orr, 2004; Brideau *et al*., 2006; see also; Unckless and Orr, 2009). Experimental evolution studies in yeasts also show the evolution of partial hybrid

sterility and inviability during adaptation to new environments (Dettman *et al*., 2007). The investigators suggest ecological factors, namely *S. bayanus* adapting to nonfermentable carbon sources, as the likely source of this selection. In contrast to most of the hybrid incompatibility genes in Drosophila, no signature of positive selection driving the evolution of *AEP2* was detected. The ratio of the rates of replacement to synonymous site changes (0.24) is far less than the equality expected under neutrality. This finding is not a strong evidence against selection having a role in the evolution of this genetic incompatibility, as negative selection could obscure any effect of positive selection on the replacement/synonymous evolution rate. Further examination such as comparing divergence and polymorphism (for example, McDonald and Kreitman, 1991) is necessary.

In his commentary for *Nature* on Lee *et al*.'s study, Louis (2009) highlighted that other genes are likely to be involved in the reproductive isolation between the two yeast species, and that they could act by different mechanisms. We do not know when the *AEP2–ORI1* changes occurred during the speciation process or if these changes were ever a barrier to hybridization between the yeast species. Nonetheless, such an interaction is a further proof of principle of the model proposed by Bateson (1909) and extended by Dobzhansky (1937), Muller (1942) and subsequent geneticists. It shows that the model applies in yeast where, surprisingly, previous studies have failed to find evidence for BDM incompatibilities (Greig, 2009). We do not yet know the range of phenomena associated with these BDM incompatibilities. The nuclear–cytoplasmic interaction of *AEP2* and *ORLI1* in yeast differs considerably from the X autosomal interaction seen in the *Lhr–Hmr* incompatibility seen in Drosophila. Perhaps general patterns will emerge, as more pairs of such interacting genes are uncovered during the second century of Bateson's model.

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