Molecular Mechanisms of Reproductive Isolation

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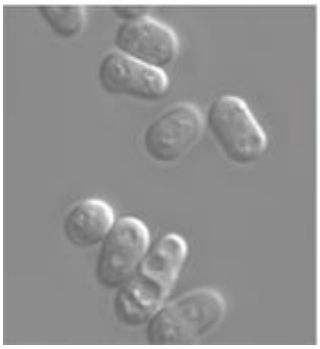
GE Zentner

Schizosaccharomyces pombe



Schizosaccharomyces kambucha

Image provided by Dr. Sarah Zanders

Images of cells of the yeast species used in this work.

When two individuals of recently diverged species mate, the hybrid offspring is often infertile. This hybrid sterility is one of the first reproductive isolation mechanisms to develop between two recently diverged species, but the molecular bases of this phenomenon have been elusive. To examine the underlying causes of hybrid sterility, postdoctoral fellow Dr. SaraH Zanders and colleagues in the laboratories of Drs. Gerald Smith and Harmit Malik (Basic Sciences Division) studied the genetic structure of hybrids formed by crossing two species of fission yeast, *Schizosaccharomyces pombe* (Sp) and *Schizosaccharomyces kambucha* (Sk). These two species are 99.5% identical at the level of DNA sequence but, when mated, produce mostly inviable gametes. The researchers found that a combination of chromosomal rearrangements and selfish genetic elements are major causes of hybrid infertility.

Dr. Zanders and colleagues first mated Sp and Sk haploid cells to produce both pure and hybrid diploids, then stimulated the diploids to undergo meiosis and generate spores (gametes). Spores

derived from the Sk/Sp hybrid displayed at least a 24-fold reduction in viability versus either of the pure diploids. Further analysis revealed that this marked decrease in spore viability was not due to defective meiosis, as Sk/Sp hybrids initiated and completed both meiotic divisions with timing and efficiency similar to the pure diploids. Interestingly, viable spores produced by Sk/Sp hybrids grew slowly, and the authors found a high frequency of aneuploidy in these spores.

The researchers next examined meiotic recombination in Sk/Sp hybrids, as defects in recombination can lead to aneuploidy. They determined that hotspots of meiotic recombination are well conserved between the two species, arguing that differing recombination hotspots are not causative of hybrid incompatibility in this system. Repair of DNA double-strand breaks was also grossly normal in the hybrid.

Next, the authors assayed recombination frequencies in pure and hybrid diploids. Recombination frequencies for several pairs of loci decreased substantially in Sk/Sp diploids. Resequencing of the Sk genome revealed that a large fragment of chromosome 1 is inverted in Sp, which might lead to inviable outcomes of meiotic recombination. Strikingly, in the hybrid, linkage was also detected between two loci located on two different chromosomes in both of the pure species, suggesting a chromosomal rearrangement. This possibility was verified using a Southern blot. From these analyses, the authors concluded that chromosomal rearrangements are a major player in establishing hybrid incompatibility.

Analysis of the parental alleles transmitted to each viable gamete revealed that, for all tested marker alleles, that the Sk allele was inherited more frequently, arguing for a mechanism of incompatibility independent of chromosomal rearrangements. As yeast meiosis is symmetric (that is, all four genotypes generated through meiosis can be packaged as spores), there must be a selective death of spores that inherit Sp alleles. The authors termed this phenomenon 'drive' of Sk alleles, as they bias allelic transmission following meiosis. Further analysis revealed that each Sk chromosome contains such a driving allele.

This study presents two predominant molecular mechanisms driving reproductive incompatibility between two recently diverged species: chromosomal rearrangements and meiotic drive alleles. "Our paper demonstrates how quickly evolutionary forces, including sexual conflicts, can drive changes in the genome that cause infertility. It also reveals how prevalent such conflicts can be within a genome, even though they are not always easily detectable. This is an important perspective on human infertility and aneuploidy rates," said Dr. Zanders.

Zanders SE, Eickbush MT, Yu JS, Kang J-W, Fowler KR, Smith GR, Malik HS. 2014. Genome rearrangements and pervasive meiotic drive cause hybrid infertility in fission yeast. *eLife* 3:e02630.