**The gene family that cheats Mendel**

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**ABSTRACT**

**Genes in the *wtf* family of fission yeasts boost their own spread at the expense of their less fortunate *wtf*-less siblings through production of poisons and antidotes, creating reproductive barriers in the process.**

**TEXT**

Gregor Mendel’s now famous law of segregation states that in a diploid organism, half the gametes will carry one allele and half the other; thus, both parental alleles have an equal likelihood of being transferred to their children (Mendel, 1866). And like all biological laws, this one too has its exceptions as certain alleles have evolved ways to kill sibling gametes that do not carry them, achieving transmission to offspring at frequencies much higher than would be expected from equal segregation (Burt & Trivers, 2006). Genes harboring alleles that increase their own propagation have been identified in plants, fungi, and animals, including humans, and come by various names, such as selfish drivers, meiotic drivers, and gamete or spore killers.

Despite the diversity of selfish drivers described, characterization of their mechanisms of action has remained elusive, except in a few cases that can generally be classified as belonging to either the poison-antidote or the killer-target models (Fig. 1). In the poison-antidote model, an antidote is produced that neutralizes the effects of the poison. These effects can be produced by the same gene (a single-gene model) as with the *Spok* genes of *Podospora anserina* (Grognet et al., 2014) or by two distinct genes (two-gene model) as in *Neurospora* (Hammond et al., 2012). In contrast, in the killer-target model a gene favors its own transmission by killing gametes that carry a ‘target’ locus; for example, the segregation distortion (*Sd*) gene in *Drosophila* acts by killing sperm that contain a sensitive *Responder* (*Rsps*) locus, identified by its high numbers of a sequence repeats (Larracuente & Presgraves, 2012).

Aiming to gain mechanistic insights into the function and evolution of selfish drivers, two research groups led by Sarah Zanders at the Stowers Institute for Medical Research in the United States and Li-Lin Du at the National Institute of Biological Sciences in China turned to the genetically tractable fission yeasts *Schizosaccharomyces kambucha* and *S. pombe* (Hu et al., 2017; Nuckolls et al., 2017). These yeast species are genetically nearly identical, and some researchers do not consider them as separate species, but hybrids between the two are often sterile. In fact, spores derived from crosses between different isolates of *S. pombe* are often inviable, suggesting a very recently emerging reproductive barrier. Previous work by the Zanders group suggested that at least three spore killer genes are responsible for these barriers (Zanders et al., 2014).

To elucidate the genetic identity of these spore killers, Zanders and colleagues conducted introgression studies to isolate a region of the 3rd chromosome that caused selfish drive. By knocking out *wtf4,* a member of a large and cheekily-named gene family found at the center of this region they determined that spores lacking the gene show reduced survival. The authors hypothesized that *wtf4* either functions as a killer-target or as a poison-antidote system (Fig. 1)*.* Upon further testing, Nuckolls and co-workers showed that *wtf4* does not appear to be targeting another locus in the genome. Rather, *wtf4* produces both a poison and an antidote through the generation of two alternative transcripts that differ in their start sites.

But how does the poison act on the surrounding spores but not the antidote? To answer this question, they created fluorescent versions of the *wtf4* poison and antidote proteins and visualized their localizations inside gametes as well as in their surroundings. These elegant experiments showed that whereas the poison protein can cross gametes’ membranes, the antidote protein is stuck within the cell (Nuckolls et al., 2017).

Du and colleagues identified two other genes, which they named *cw9* and *cw27*, from the same *wtf* gene family that act as spore killers in crosses between different strains of *S. pombe*. By examining the spore viability of heterozygote and homozygote deletion mutants of each gene in diploid *S. pombe* strains, they showed a reduction in viability in heterozygotes but not in homozygotes, indicating that both genes are selfish drivers. Hu and coworkers then asked whether the two genes can rescue the other’s spore killing ability by examining a diploid strain that contained heterozygote deletion mutants for both genes. The loss of spore viability was more severe than the losses observed in the single heterozygote deletion mutants of either gene, suggesting that the two genes do not rescue each other and act independently to drive (Hu et al., 2017).

In summary, the data provided by the Zanders and Du groups reveal several genes in a unique gene family responsible for the targeted killing of sibling spores that do not carry them via a novel mechanism of action involving alternative transcription. This work, done in the genetically tractable fission yeast, enriched our understanding of the mechanisms of the genes that break Mendel’s acclaimed genetic law. Future work in this area will not only help us understand the role of selfish elements on reproductive isolation and speciation, but knowing the biomolecular basis of these phenomena may lead to a better appreciation for the role of these kind of mechanisms in infertility in species as diverse as plants, fungi, and animals including humans.

**FIGURES**

**Figure 1. The poison-antidote and killer-target models of selfish drive.** In the poison-antidote model, a toxin (skull-and-crossbones) is produced that can neutralized by an antitoxin (pill). (**A**) Both products can be produced by the same gene (boxes) via alternative transcription, as illustrated by the work of the Zanders and Du groups in *Schizosaccharomyces* yeasts (Nuckolls et al., 2017; Hu et al., 2017). (**B**) Alternatively, different genes produce the poison and antidote, which is the case for the *Neurospora* spore killers (Hammond et al., 2012). (C) In the killer-target model, a toxin is still produced but lethality occurs when the toxin interacts with specific target alleles of another locus; an example of this model is offered by the segregation distorter system in *Drosophila* (Larracuente et al., 2012).

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