Poisons, antidotes, and selfish genes

Genes masquerade as essential to development to ensure their transmission

By **Nitin Phadnis**

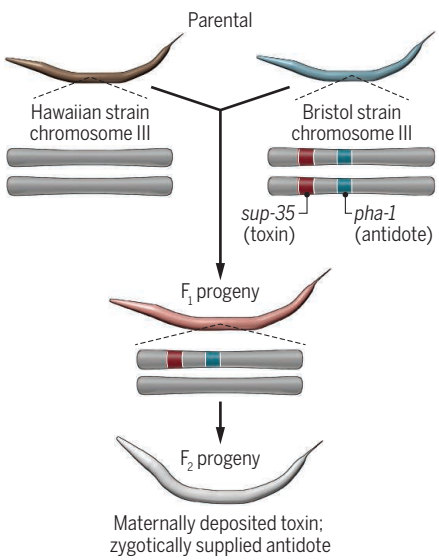
Selfish genetic elements are parasitic replicators that are specialists in ensuring their own transmission despite conferring no benefit, or even exacting a cost, on their bearers. They come in many flavors, such as transposable elements, segregation distorters, female meiotic drivers, and so-called B chromosomes (or accessory chromosomes) (*1*). Such selfish elements provide the strongest support for the gene-centric view of evolution, as popularized by Richard Dawkins in *The Selfish Gene* (*2*). On page 1051 of this issue, Ben-David *et al.* (*3*) chase down a serendipitous observation of an anomaly in genetic crosses to unmask a toxin-antidote type of selfish system in worms.

With the exception of transposable elements, which are abundant and easy to detect, little is known about the genetics of many broad classes of selfish genetic elements and the strategies that they deploy to manipulate cellular processes to their own advantage. This is, however, beginning to change. When performing genetic crosses between strains of the worm *Caenorhabditis elegans*, Ben-David *et al.* observed something that looked suspiciously like the work of a selfish system. During crosses to specifically move a region on chromosome V from a standard laboratory strain isolated from Bristol, UK, into a Hawaiian strain of the same species, another unlinked region from chromosome III also persisted despite attempts to exclude it. Through a series of genetic analyses, the authors identified two neighboring genes—the embryonic lethal gene *pha-1* and a gene that encodes a suppressor of *pha-1* called *sup-35*—as perpetrating invasive spread of the chromosome III region.

The identification of *sup-35* and *pha-1* reveals their remarkable mode of action. The *sup-35* gene product is a poison that *C. elegans* mothers from the Bristol strain deposit in their embryos. The poison kills the resulting larvae by interfering with the proper development of their pharynx. Unless the mothers also supply an antidote to their progeny, how can natural selection even tolerate such filicidal behavior? Indeed, the antidote *pha-1* is expressed in the developing zygote and protects against the poison, allowing the worms to develop normally. The Hawaiian strain does not carry either *sup-35* or *pha-1*; only the Bristol strain does. When these two strains are crossed, the resulting first-generation offspring (F_1) have one copy of the Bristol and Hawaiian chromosome III each (see the figure). When these F_1 females produce haploid eggs, all of the progeny will die because the *sup-35* maternal toxin is present. Only progeny that inherit Bristol chromosome III, however, can express the *pha-1* antidote and survive; those that inherit Hawaiian chromosome III die. This mechanism explains how Bristol chromosome III manages to readily invade the population in crosses between the two strains.

A toxin-antidote system

Only F_2 zygotes with the Bristol chromosome express PHA-1 and can rescue themselves from the SUP-35 toxin deposited into all eggs by the F_1 mother.



Studying the mechanisms of selfish genes that "beat the system" is like apprenticing with a master cheater to gain a deep understanding of the rules of the game. These approaches are, therefore, likely to provide unique insights into the inner workings of biological systems. *pha-1* is not an obscure gene; it has been characterized as essential for the proper development of the worm pharynx (hence its name) (*4*, *5*). How does the Hawaiian strain manage to thrive in the absence of a developmentally essential gene? This is now obvious in light of the selfish dynamics: *pha-1* only masquerades as an essential gene, but exists solely because it is brutally efficient at transmitting itself to the next generation at the cost of killing half of the progeny of heterozygous mothers. Indeed, evolutionary analysis shows that the *sup-35* and *pha-1* system is a recent innovation in Bristol worms and is absent in this strain's ancestors. This raises the shocking possibility that many genes that are well studied and thought to be essential may have originated as selfish genes.

Only a few years ago, another independent toxin-antidote system was discovered that involves two genes, *peel-1* and *zeel-1* (*6*). In this system, *peel-1* is a paternally deposited toxin that is delivered through sperm, and *zeel-1* is the zygotically acting antidote (*7*). Such individual toxin-antidote systems only kill a fraction of the progeny of hybrids between populations. If many such independent systems constantly evolve within populations, a cross-firing of many separate systems may lead to the complete destruction of hybrids between populations. This scenario is consistent with the idea that selfish-gene dynamics may hold the key to the origins of new species (*8*, *9*).

In an era of emerging artificial gene drive systems, it makes sense to first understand natural drive systems that are shaped and tested by evolution. It is now the right time for many broad and understudied classes of selfish genetic elements to yield their jealously guarded secrets. ■

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