Trends in Genetics

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REVIEWS

Opinion

Making a Murderer: The Evolutionary Framing of Hybrid Gamete-Killers

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Recent molecular investigations of hybrid incompatibilities have revealed fascinating patterns of genetic interactions that have been interpreted as the remnants of a history of selfish evolution. Instead of framing hybrid incompatibilities in light of genetic conflict, we advocate assuming their innocence. Researchers must build a strong theory for each case, supported by population genetic evidence, such that the role of conflict in the evolution of a hybrid incompatibility can be proven beyond reasonable doubt. This will require careful investigation of the evolutionary history of these incompatibilities, a reckoning of how the reproductive biology of study organisms impacts on the likelihood of genetic conflict, and molecular evidence of the rapid selfish spread of these alleles.

Introduction

The production of inviable or sterile offspring in interspecific hybrids is a puzzling outcome of evolution by natural selection. How can interspecific combinations of alleles generate low-fitness offspring when natural selection should prevent populations from descending into fitness valleys? The **Dobzhansky–Muller incompatibility** (DMI; see Glossary) model provides an elegant solution: epistasis among alleles that have not coexisted in the same population underlies low hybrid fitness, and therefore selection never opposed their spread. A variant model, proposed nearly three decades ago, posits that hybrid incompatibilities – particularly those that cause hybrid sterility – arise through **selfish evolution** within species [1,2]. Under this scenario, the intrinsic fertility costs of selfish elements are overcome by their distortion of transmission, but favor the evolution of suppressors; distorter–suppressor mismatches are later revealed as incompatibilities in hybrids. This selfish model was met with initial skepticism [3–6], but key studies of segregation distorters in *Drosophila* and cytonuclear male sterility in plants have led to widespread acceptance (reviewed in [7]). Indeed, as hybrid incompatibilities become increasingly accessible to molecular dissection, acceptance has moved toward assumption. '**Gamete-killers**', 'selfish evolution', and **genomic conflict** have become default evolutionary explanations in recent studies of hybrid incompatibilities (e.g., [8–11]).

Scientists are detectives at heart and, when confronted with dead gametes, we readily see the selfish hand of a 'gamete-killer'. In many cases, the invocation of a selfish past for incompatibility loci is justified. After all, natural selection below the level of the individual is powerful force, and **meiotic drivers** and other selfish segregation distorters are ubiquitous and diverse [12,13]. On the other hand, the epistatic nature of genic hybrid incompatibilities means that phenotypes observed in hybrids, such as gamete-killing, do not necessarily imply the causal genes produce the same phenotypes within species. That is, in the same way as hybrid incompatibilities can arise without a history of inviability or sterility in either lineage, hybrid gamete-killers can arise without a history of drive or selfish evolution. Thus, the plausibility of drive as a mechanism is not the same as concrete evidence of drive in a given case. We

Highlights

The molecular mechanisms and evolutionary histories of hybrid incompatibility loci are now excitingly knowable; elucidation of both aspects is crucial for robust understanding of their origins and contributions to speciation.

Neutral processes should be the null hypothesis for fertility/sterility phenomena observed in hybrids between taxa (or allopatric populations).

Selfish scenarios for the evolution of hybrid incompatibility should involve an explicit evolutionary genetic model that is grounded in the population biology (e.g., mating system) of the study organisms.

Now that genome-wide sequence data can be readily generated for large numbers of individuals, population genomic studies of incompatibility loci (particularly polymorphic ones) should be a necessary but not sufficient piece of evidence for the inference of a selfish history.

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therefore feel it is timely to renew a decades-old call [14,15] for tempered consideration and empirical testing of alternative evolutionary scenarios for the origins of hybrid incompatibility.

To guide such tests, we highlight three points that have been sometimes brushed aside in a rush to judgment. First, we stress that hybrid incompatibilities (by definition) cause reproductive dysfunction and involve interactions among alleles. Therefore, the traditional DMI model provides a null explanation for reproductive dysfunction in hybrids. Second, because selfish evolution takes place in an organismal, ecological, and population genetic context, we must ask who gains from the loss of another allele (motive), and model whether a putative driver could actually spread throughout the study species (opportunity). This point is particularly important in self-fertilizing species in which the paucity of heterozygotes limits the potential benefit of drive. Finally, we point out that population genomic signatures of intraspecific selfish evolution leading to hybrid incompatibilities should be readily detectable, and therefore are key pieces of evidence.

Presumed Innocent – The Need for a Null

The original papers linking selfish evolution to hybrid incompatibilities [1,2] laid out a specific sequence of events. First, a selfish genetic element spreads by distorting genetic transmission to its advantage, despite individual fitness costs. Second, selection to mitigate these costs favors suppressor alleles at unlinked loci. Third, an evolutionary arms race results in rapid divergence among lineages with distinct histories of intragenomic conflict. This divergence is exposed in interspecific crosses that separate selfish genetic elements from their suppressors, resulting in both **transmission-ratio distortion** and sterility in hybrids. This is one scenario, and likely applies to many mitochondria–nucleus incompatibilities (e.g., [16]), a common cause of male sterility in plant hybrids [17]. However, it is not the only path to an epistatic incompatibility in hybrids, even when both evolutionary steps occur within one lineage (Figure 1).

An alternative model for the evolution of DMIs and transmission-ratio distortion arrives at superficially similar hybrid phenotypes without any history of selfishness. First, a 'permissive' allele at one locus spreads through a population, either by a selective advantage unrelated to drive suppression, or by drift. On this new genetic background, an allele at a second locus can evolve with no decrease in fitness, but this same variant shows deleterious effects in hybrids that lack the compensatory allele. As in the classic DMI model, both distortion and sterility are aberrant phenotypes in hybrids – neither was ever expressed within the parent species.

Similar caveats apply to many of the recently characterized 'single-locus' incompatibilities (Table 1, Key Table), which are caused by two or more linked genes with separate 'killer' and 'antidote' or 'target' functions. We highlight these single-locus systems for two reasons. First, the recent literature is full of them. Remarkably, in the past 2 years, nearly all cases of cloned hybrid-sterility genes fall into this single-locus category [9–11,18–21]. Second, we believe that the evolutionary dynamics of this class of DMIs have received too little scrutiny. In single-locus incompatibilities that arise via two or more steps (presumably, most cases in Table 1), a reasonable null expectation is that the *cis*-acting antidote (or, analogously, a nonfunctional target) evolves. This is because an indiscriminate, *trans*-acting killer allele arising an unprotected genetic background would be suicidal. If the antidote becomes fixed within a population, the killer can arise as a neutral variant (Figure 1), with gamete-killing and distortion occurring only in hybrids.

Consistent with an evolutionary scenario in which distortion in hybrids is an epiphenomenon rather than the 'ghost of conflict past', unlinked suppressors have rarely been found for the

Glossary

Dobzhansky–Muller incompatibility (DMI): an epistatic interaction between alleles from different species (or populations) that decrease viability or fertility when combined in the same genome. In combination, incompatible alleles can decrease hybrid fitness even if they do not decrease fitness as they spread within a population.
Gamete-killers: loci that cause partial sterility in hybrids (or heterozygotes) when one parental allele destroys gametes carrying the other parental allele, resulting in non-Mendelian transmission. At the molecular level, these loci often encode a *trans*-acting 'poison' that kills all meiotic products lacking a tightly linked *cis*-acting 'antidote' or sensitive 'target'.
Genomic conflict: selection (on the rest of the genome) generated by the spread of a costly selfish element.
Meiotic drivers: historically, both meiotic and gametic mechanisms of transmission-ratio distortion acting within species (i.e., evolving selfishly) are referred to as 'meiotic drive'.
Selfish evolution: an increase in the population frequency of a genetic element due to natural selection via biased transmission but without benefits (and often with costs) to individual fitness.
Transmission-ratio distortion: an observation of non-Mendelian inheritance, which implies some form of locus-specific selection between parental and offspring generations.

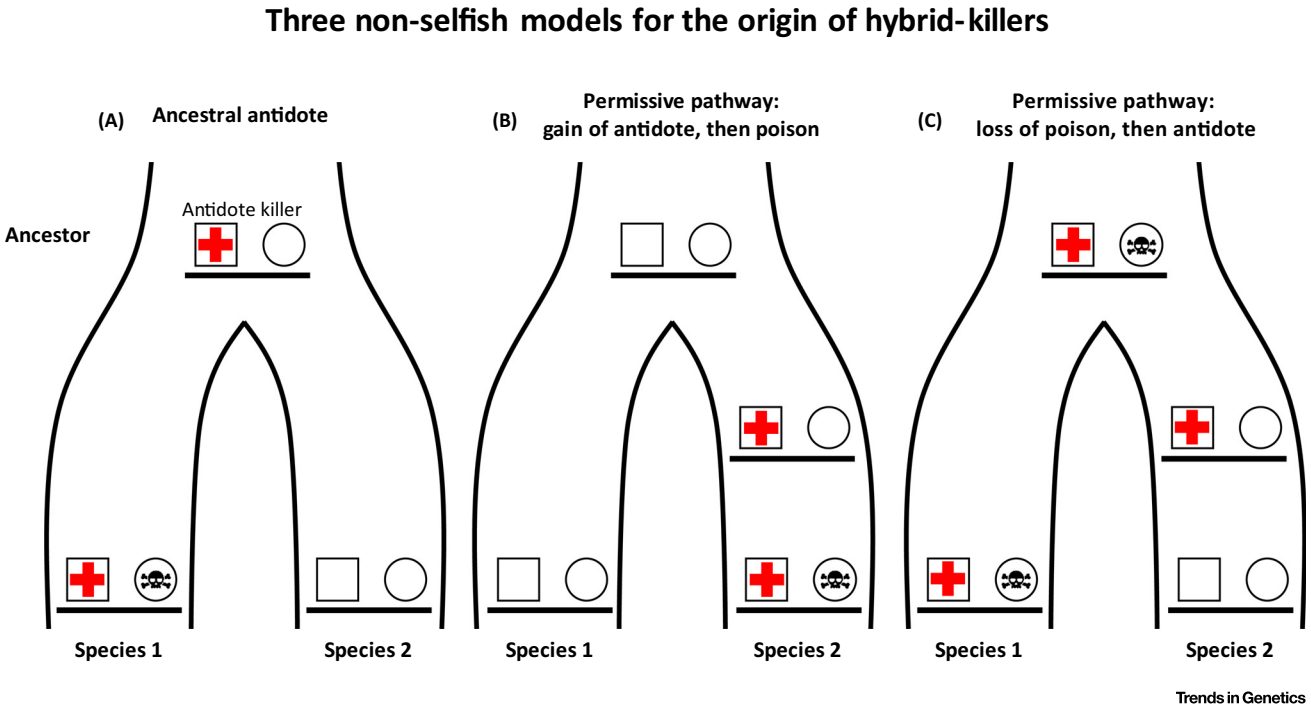

Figure 1. Evolution of Gamete-Killers in Hybrids Does Not Need to Involve a History of Selfish Evolution within Species. In this cartoon example, two linked genes – the antidote (square) and the killer (circle) – cause transmission-ratio distortion and partial sterility in hybrids between species 1 and species 2. Gametes that inherit a functional killer allele (circle with skull and crossbones) secrete a 'poison' but are protected from its effects because they also carry a functional antidote allele (square with red cross). Gametes with this functional killer–antidote haplotype gain a transmission advantage over gametes with the alternative, non-killer allele (empty circle) that do not carry a protective, functional antidote (empty square). Note that these evolutionary pathways are equivalent for gamete-killers that function instead via killer–target systems (i.e., the functional antidote allele is replaced with a nonfunctional target allele and the nonfunctional antidote allele is replaced by a functional target). (A) An ancestral species is fixed for functional antidote and nonfunctional killer alleles (the latter might simply be absent). Species 1 evolves a functional killer allele, but the killing phenotype is not expressed because the species is also fixed for the antidote. Species 2 evolves a loss-of-function antidote allele, but the killing phenotype is not expressed because the species lacks a functional killer gene. (B) An ancestral species is fixed for nonfunctional alleles of both the antidote and the killer. Species 1 retains the ancestral haplotype and does not express the killing phenotype. Species 2 evolves and fixes a functional antidote before evolving a functional killer allele; with this mutational order, the killing phenotype is never expressed. (C) An ancestral species is fixed for functional alleles of both the antidote and the killer. Species 1 retains the ancestral haplotype and does not express the killing phenotype. Species 2 evolves loss-of-function mutations in the killer, followed by the antidote: with this mutational order, the killing phenotype is never expressed.

distorters listed in Table 1, suggesting they have few costs within species. Furthermore, of the two cases in which unlinked suppressors are known, one has recently evolved in the laboratory [21], and the other is modulated by a separate 'spore-killer' [22], further reinforcing the idea that it is not the cost of drive that has favored the evolution of unlinked suppressors of these alleles in nature. Moreover, unlike the *SD* (segregation distorter) locus in *Drosophila* [23] or the *t* haplotype in mice [24] – loci that inspired the original theory linking distorters to DMIs – these single-locus gamete-killers have no homozygous costs (lethality or sterility). It is notable, then, that in all but one case [9,18] there are no molecular signatures of the rapid evolution expected under an arms-race scenario. Finally we note that, for most of the systems in Table 1, definitive crossing or transgenic experiments to test whether transmission-ratio distortion occurs within species/strains have not yet been done.

Ideally, future experiments should investigate whether gamete-killers detected in hybrids are also effective against non-killing variants that co-occur in natural populations (as in [25]). One compelling case is the *wtf4* gene, which has been shown to cause spore-killing not only in crosses between two strains of fission yeast but also within one of the strains (in

Key Table

Table 1. Recent Molecular Dissections of 'Single-Locus' Incompatibilities Have Provided Little Concrete Evidence for Selfish Evolution, but in Several Systems the Case Is Still Open

Single-locus incompatibility	Species	Mating system	Genetic basis	Phenotype	Evolutionary history[a]	Population genomic evidence	Refs
Sa	*Oryza sativa japonica* and *O. sativa indica*	Selfing	Three genes: one target and two killers	Male gamete-killing; male sterility	C	Supports non-selfish alternatives	[30]
S5	*O. sativa japonica* and *O. sativa indica*	Selfing	Three genes: one antidote and two killers	Female gamete-killing; female sterility	C	Supports non-selfish alternatives	[31]
Sc	*O. sativa japonica* and *O. sativa indica*	Selfing	Multiple tandemly duplicated genes	Male gamete-killing; male sterility	B	Equivocal; selfish evolution possible in the outcrossing ancestor *O. rufipogon*	[10]
S1	*O. sativa* and *O. glaberrima*	Selfing	Multiple genes	Male and female gamete-killing; sterility	A or B	Supports non-selfish alternatives	[19,20]
qHMS7	*O. sativa japonica* and *O. meridionalis*	Selfing	Two genes: pollen-expressed antidote and sporophytic toxin	Male gamete-killing; male sterility	B	Equivocal; selfish evolution possible in the outcrossing ancestor *O. rufipogon*	[11]
wtf4	*Schizosaccharomyces pombe* and *S. kambucha*	Homothallic; likely low outcrossing[b]	One gene: alternative transcripts encode antidote and poison	Spore-killing; sterility	?	Equivocal; formal proof of selfish evolution is needed	[9,18]
wtf13	*Schizosaccharomyces pombe* and *S. kambucha*	Homothallic; likely low outcrossing[b]	One gene: alternative transcripts encode antidote and poison	Spore-killing; sterility	?	Equivocal; formal proof of selfish evolution is needed	[21]
Spok1/Spok2	*Podospora anserine* strains S and T	Heterothallic; mixed mating	Two genes: each encodes both antidote and poison	Spore-killing; sterility	?	Equivocal; formal proof of selfish evolution is needed	[22]
zeel-1/peel-1	*Caenorhabditis elegans* strains CB4858 and N2	Selfing	Two genes: zygotic antidote and paternal toxin	Embryonic lethality	?	Supports non-selfish alternatives	[27,28]
sup-35/pha-1	*C. elegans* strains DL238 and N2	Selfing	Two genes: zygotic antidote and maternal toxin	Embryonic lethality	C?	Equivocal; formal proof of selfish evolution is needed	[29]

[a]Options A, B, and C refer to the evolutionary pathways depicted in Figure 1.
[b]Reference [39].

Schizosaccharomyces pombe kambucha, 50% of spores die in a heterozygous antidote mutant [9]). However, even with compelling experimental evidence that gamete-killing can take place in within-species crosses, it is important to note that the population genetic conditions for selfish evolution are much more restrictive than for the null model in Figure 1: a new killer allele might spread selfishly within species, but only if the antidote is polymorphic and the killer arises in coupling phase with a functional antidote (Figure 2).

We note that none of our arguments above are definitively exculpatory, and selfish evolution may indeed be responsible for some of the incompatibilities in Table 1. For example, the

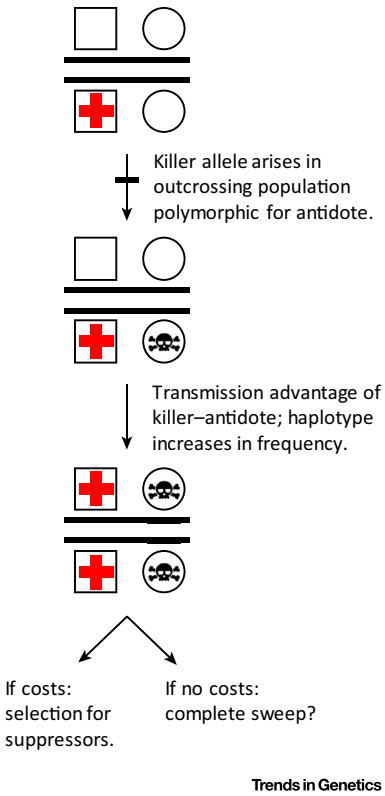

Figure 2. Selfish Evolution via Gamete-Killing Requires Several Population Genetic Conditions. In killer–antidote systems, the killer allele can increase in frequency only if it arises after the antidote (otherwise, gametes would be suicidal). In addition, the killer allele enjoys a transmission advantage only in populations that are polymorphic for the linked antidote gene: if the antidote is fixed, there can be no killing phenotype. Finally, the transmission advantage of the killer allele occurs only in heterozygotes, and therefore the likelihood of it spreading is low in highly inbreeding populations. When these population genetic conditions are met, the killer–antidote haplotype can spread via selfish evolution. If the host organism incurs a fitness cost (via reduced fertility), there will be selection for unlinked suppressor alleles to mitigate these costs. If costs are minimal, the killer–antidote haplotype might sweep to fixation, restoring gamete fertility and Mendelian transmission.

absence of unlinked suppressors of drive might reflect a history in which low-cost distorters became fixed too quickly for suppressors to evolve. In addition, instead of requiring a killer allele to arise on a haplotype bearing an antidote, the antidote and killer could both arise in one mutational step. This scenario is plausible in some cases (e.g., [9,18,21]), but the evolutionary origins of single-locus gamete/spore-killing have not yet been demonstrated in any system. However, at the moment, the burden of proof for elevating these plausibility arguments into strong evidence falls on the researchers indicting selfish evolution in the evolution of hybrid incompatibilities.

A Theory of the Case – Mating System Matters

Neither DMIs nor selfish gamete-killers are understandable without a gene-centric view of evolution, and any scenario for their origins requires a population genetic model. Thus, the reproductive biology of the focal species/population matters a great deal for framing alternative scenarios. Selfish gamete-killers increase in frequency by outcompeting alternative alleles in heterozygotes. Theory shows that such elements are disfavored in highly inbreeding populations – where there is minimal gamete competition or sexual conflict, and a selfish mutant has no way to spread beyond its initial lineage [26]. Nonetheless, many recently identified single-locus hybrid distorters are in highly self-fertilizing taxa (e.g., *Arabidopsis*, domesticated rice, androdioecious nematodes), calling into question the importance of selfish processes in their evolution (e.g., [8,10,11,20,27–31]). One way to skirt this contradiction is to posit that distorters/gamete-killers arose in outcrossing ancestors; this is a testable hypothesis in some systems, but no more intrinsically plausible than the non-selfish alternatives described above. Given these complications, we argue that mating system and other population genetic and

ecological factors must be considered in discussions of how gamete-killers contributing to hybrid incompatibilities might evolve.

The objection that selfish evolution in predominantly selfing taxa undercuts the motive for meiotic drive – and therefore begs for an alternative explanation – has been raised before. In their genetic dissection of the *peel/zeel* paternal-effect killer system maintained by balancing selection in the highly self-fertilizing nematode, *Caenorhabditis elegans*, Seidel and colleagues [27,28] note that the rarity of heterozygotes limits the selfish benefit of the killer allele. As an alternative, they argue that the balanced polymorphism acts as an 'incompatibility trap', with selfing allowing incompatible alleles (that only become deleterious after outcrossing) to accumulate away from the watch of natural selection. Surprisingly, this reasoned consideration of mating system is often absent from more recent claims of selfish evolution in *C. elegans* and other primarily selfing species (e.g., [29]).

Rules of Evidence – The Proof Is in the Population (Genomics)

Fortunately, alternative models of the evolution of hybrid incompatibilities often make clear predictions that can be tested with population genomic and quantitative genetic data. We can now begin to address key questions about the origins of incompatible alleles: what is the order of mutations (drivers followed by suppressors, or vice versa)? Is transmission-ratio distortion expressed within species and, if so, is there evidence of associated fitness costs? Is there population genomic evidence of selection on putative drivers and/or suppressors? The last question is newly accessible with inexpensive next-generation sequencing approaches, and highly definitive. Numerous intraspecific drivers show strong signatures of recent selective sweeps [32–34], and similar patterns should be evident if and when DMIs arise from intraspecific selfish evolution. For example, loci underlying a cytonuclear hybrid incompatibility in yellow monkeyflowers (*Mimulus*) show signatures of selection that are consistent with a history of selfish mitochondrial evolution and nuclear coevolution within one species [16].

There is little direct population genomic evidence that any of the recently reported hybrid gamete-killers evolved to kill (Table 1). In rice (*Oryza* spp.), the two single-locus gamete-killers that have been reconstructed both appear to have evolved on compensatory backgrounds [30,31], and in another the killer haplotype exists only in selfing species [20]. Two additional cases in rice, both involving gamete-killers polymorphic in the outcrossing ancestor *O. rufipogon*, remain open [10,11]: if the killer and antidote genes both segregate within populations (Figure 2), this system is also amenable to direct tests of selfish evolution as a driver of hybrid incompatibilities. In the fission yeast *S. pombe*, the spore-killing *wtf* genes are members of a recently expanded and rapidly evolving gene family [9,18]. Although it is tantalizing to speculate that drive is the cause of this evolutionary dynamism, population genetic evidence is so far equivocal. The existence of many antidote-only *wtf* genes [9,18] could suggest that this function evolves first. If so, more work will be necessary to determine whether outcrossing rates in *S. pombe* (which is homothallic) are sufficient to maintain polymorphism of the antidote long enough that a linked *wtf* killer can gain an advantage (as in Figure 2). Alternatively, the two functions might arise simultaneously, with the poison degenerating later, an evolutionary scenario made more likely by the fact that killer *wtf* genes produce both poison and antidote (using different transcriptional start-sites [9,18,21]). Irrespective of their evolutionary history, it will be important to establish the population and ecological conditions that could allow a selfish *wtf* variant to spread. Similarly, a population genetic framework would help to make the case for selfish evolution in the pseudo-homothallic (i.e., semi-outcrossing) fungus *Podospora anserina*, which carries several single-gene spore-killers, including *Spok1* and *Spok2* [22].

We note that, although evidence of positive selection is consistent with a history of selfish evolution, it is also expected for changes that benefit the host, such as adaptation to ecological challenges or natural enemies. Thus, evidence of positive selection is an essential part of any case for selfish evolution of hybrid incompatibilities, but is not sufficient in the absence of other evidence of selfishness.

Objection! Single-Locus Selfish Genes Should Easily Cross Species Boundaries

Before closing, we note a simple and often-overlooked objection to the idea that single-locus selfish genetic elements, even if causal of incompatibilities, can act as 'speciation genes'. If such selfish alleles spread rapidly within species owing to their transmission advantage, we expect them to cross species boundaries more readily than non-selfish variants across the rest of the genome (as in [35]). Similar objections apply to male-sterilizing mitochondria in flowering plants, which can spread across species boundaries by the same selfish mechanism that they spread within populations (assuming the corresponding nuclear restorers do not fix ahead of them) [17,36].

Overzealous prosecution of the selfish case without an explicit evolutionary model has led researchers to build complex arguments that stretch well beyond the evidence. For example, in humans, selective sweeps and a dearth of ancestry from archaic populations in X-linked ampliconic genes have been interpreted as evidence of both selfish evolution and hybrid incompatibilities [37,38]. However, if ampliconic genes on sex chromosomes have been subject to selfish sweeps in humans, why invoke hybrid incompatibilities to explain the lack of introgression? Exactly as the selfish properties of *MDox* and *Dox* promote, rather than prevent, their selfish spread across *Drosophila* species [35], transmission-ratio distortion that favors modern human alleles would presumably prevent unselfish archaic alleles from spreading in the first place, or, for more recent sweeps, erase any signature of past introgression.

Concluding Remarks

Over the past decades it has become increasingly clear that internal conflict within the genome can be a significant contributor to patterns of genomic diversity and divergence. The potential importance of conflict for patterns of organismal development, meiosis, and syngamy are profound. Thus, it is understandable that researchers would be excited to invoke selfish evolution as a driver of hybrid incompatibilities. However, we argue that the facts (as known so far) rarely implicate intraspecific gamete-killers beyond a reasonable doubt. We caution that dysfunctional hybrid phenotypes such as gamete-killing do not necessarily originate within species, and we highlight alternative 'non-selfish' routes to the evolution of hybrid incompatibilities. Going forward, we urge researchers to evaluate selfish scenarios using explicit evolutionary genetic models grounded in the population biology (e.g., mating system) of the study organisms. We are optimistic that this approach will yield exciting new insights into many unanswered questions (see Outstanding Questions).

Outstanding Questions

In systems with abundant hybrid gamete-killers (e.g., domesticated rice and fission yeast), how often do we detect population genetic signatures of selfish evolution in natural populations?

What are the normal functions of incompatibility alleles within species? Is transmission-ratio distortion an aberrant hybrid phenotype or does it occur between individuals collected from the same natural population? Are there fitness costs of gamete-killers in nature?

What are the mutational steps to 'single-locus' gamete-killers? Must the antidote arise first to prevent suicide, or can a weak killer evolve on an antidote-less background? In the case of single-gene killers, do poison and killer functions arise together *de novo*?

Do hybrid gamete-killers share particular molecular features/mechanisms? How often are gene duplication and conversion involved? Does horizontal transfer facilitate the evolution of poison–antidote systems?

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