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REVIEW

Genetic conflicts: the usual suspects and beyond

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ABSTRACT

Selfishness is pervasive and manifests at all scales of biology, from societies, to individuals, to genetic elements within a genome. The relentless struggle to seek evolutionary advantages drives perpetual cycles of adaptation and counter-adaptation, commonly referred to as Red Queen interactions. In this review, we explore insights gleaned from molecular and genetic studies of such genetic conflicts, both extrinsic (between genomes) and intrinsic (within genomes or cells). We argue that many different characteristics of selfish genetic elements can be distilled into two types of advantages: an over-replication advantage (e.g. mobile genetic elements in genomes) and a transmission distortion advantage (e.g. meiotic drivers in populations). These two general categories may help classify disparate types of selfish genetic elements.

KEY WORDS: Red Queen, Antagonism, Mutualism, Toxin–antitoxin, Meiosis, Mitochondria, *Wolbachia*, Host–pathogen

Introduction

Social behavior involves the interaction of two or more biological entities, whether genetically related or not, in a way that affects the fitness of the individuals. Although social behavior can benefit the individuals in a group, most forms involve an element of compromise, whereby each individual's fitness may be sacrificed for the common good of all members of the society (Nowak, 2006). This sets up an intrinsic susceptibility to conflict in biological societies whereby individual adaptation for self-interest ('selfishness') can be contrary to the common good. Many societies employ active or indirect policing to ensure compliance with the 'common good' strategy (Fischer et al., 2014; Foster and Ratnieks, 2001; Hauser, 1992). Nevertheless, selfishness is just as pervasive in biological interactions as cooperation. In this review, we extend previous treatises on the subject (Burt and Trivers, 2006; Dawkins, 1976; Hurst and Werren, 2001; Hurst et al., 1996; Werren, 2011), with particular focus on the biological implications of selfishness on a cellular and molecular level. This leads to the suggestion that the diversity of selfish elements can be sorted into two categories (Burt and Trivers, 2006): those elements that over-replicate relative to the host and those that distort patterns of inheritance to increase in prevalence. These vignettes show how natural selection shapes antagonistic interactions and how such genetic conflicts shape fundamental aspects of biology.

Adaptation drives natural selection

Darwin put forth the now widely accepted idea that populations of organisms evolve by natural selection, in which individuals more suited to the environment are more likely to survive, reproduce and pass on their heritable traits to future generations. Advances in population genetics, evolutionary genetics and sequencing techniques have provided us with a rich repertoire of examples of the molecular details of such adaptations in a variety of organisms, including plants, animals and microbes (Arnegard et al., 2014; Barrick and Lenski, 2013; Carroll, 2000). We understand not only the molecular details of the adaptation process but also the molecular dynamics underlying the tempo and mode of fixation of adaptive alleles in populations (Messer and Petrov, 2013; Tenaillon et al., 2016).

The Red Queen: 'the environment' fights back

Changes in the abiotic environment of an organism – for example, variation in temperature or rainfall – are among the many factors that drive natural selection. When organisms adapt to a change in the abiotic environment, the change in the population of organisms provides no feedback to the environment, i.e. the abiotic environment is unaltered by the adaptation of the organism (Fig. 1A). However, not all adaptations are driven by changes in environment; many are driven by interactions with other groups of organisms. In this case, biological adaptations can have direct and, often, immediate fitness consequences to coevolving organisms populating an ecosystem. Here, a change in the allele frequencies in one population imposes selective pressure on another population, thereby selecting for a change in allele frequencies in the other population – coevolution. We define coevolution as the coupling of the fitness of any two replicators, such that a fitness change in one affects the fitness of the other. Here, mutualism is defined as positive epistasis between replicator fitness; an increase in the fitness of one replicator increases the fitness of the other. In contrast, conflict is defined as negative epistasis between replicator fitness; an increase in the fitness of one replicator decreases the fitness of the coevolving replicator. For instance, fitness gains via adaptation of a prey species to evade a predator species lower the fitness of the predator species. This decrease in fitness of the predator species can spur a tit-for-tat round of adaptation that may increase predator fitness and, in turn, decrease the fitness of the prey (Fig. 1B). In such antagonistic interactions where both species recurrently adapt, the fitness of the prey and predator species cannot be optimized simultaneously. The fitness incentive to the species that is 'losing' this evolutionary race (whether it be prey or predator) provides the engine to drive relentless rounds of adaptation and counter-adaptation. Indeed, this cycle is expected to continue until one of the species is driven to extinction. In this way, 'biotic forces provide the basis for a self-driving … perpetual motion of the effective environment and so of the evolution of the species affected by it' (Van Valen, 1973). This concept of recurrent antagonistic coevolution was formalized by Leigh Van Valen and termed the Red Queen's Hypothesis, inspired by Lewis Carroll's fictional character, who runs across a chessboard with Alice, only to remain in the same place despite exhausting considerable energy (Carroll and Tenniel, 1871).

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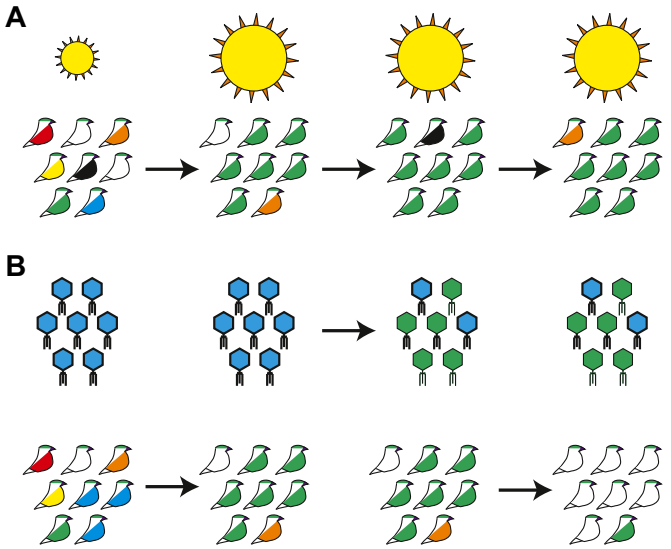

Fig. 1. Adaptation to static versus dynamic environments. (A) A change in environmental conditions (for example, a move to a higher temperature, represented as an increase in sun exposure) selects for bird genotypes (green) better adapted to the altered abiotic environment. As a result, these fit genotypes increase in frequency. Even though other genotypes might appear later in the population, selection maintains the high prevalence of the fittest genotype. The change in the allele composition of the bird population has no effect on the environmental conditions. (B) A pathogen infects a population, and selects for a resistant genotype (green) in the host population. As the green genotype increases in frequency, this selects for pathogen genotypes that can infect the most prevalent (now green) genotype. This, in turn, selects for a new resistant host genotype (white) that resists infection by the prevalent pathogen (green) genotype. Thus, cycles of adaptation in the host and pathogen populations drive perpetual cycles of adaptation, typical of Red Queen interactions.

Although framed in the classical mode of natural selection as imagined by Darwin, Red Queen interactions are distinct in one aspect: whereas Darwin anticipated natural selection to play out most intensely between individuals within species, Red Queen interactions are usually conflicts between distinct species for evolutionary supremacy. However, Darwin's vision of the struggle for existence within the species plays an important role. In fact, the competitor's coevolved response creates a negative frequency-dependent selection regime (Fig. 1B) in which the more prevalent the 'winning' prey allele becomes, the more likely it is to be targeted by the predator and become the 'losing' allele (Clarke, 1962; Hamilton, 1980). Consequently, common genotypes are targeted sequentially in the prey and predator, resulting in recurrent fluctuations in the allele composition of each species. In this way, there is competition within the prey species, but this competition is driven by selection pressure from another species. It bears mentioning that the response of mimic and model species in Batesian mimicry could be viewed from the same perspective of a Red Queen interaction (Pfennig et al., 2001).

The over-replicators: 'me before you'

Host–pathogen interactions exemplify the stark nature of conflict between distinct genetic entities for evolutionary survival. In many examples, pathogen fitness is inversely correlated to host fitness, much like the prey–predator interactions originally considered by Van Valen. In this case, over-replication of a pathogen (relative to host replication) increases pathogen fitness, often at the expense of host fitness. In response, any host tactic that slows a pathogen's replication increases host fitness.

Although they operate on organismal scales, many antagonistic interactions can be distilled into a series of molecular interactions. These interactions could be between signaling molecules and their receptors (e.g. quorum sensing molecules and their receptors; Eldar, 2011), or between proteins or RNAs. In both cases, recognition (by 'predator') versus evasion (by 'prey') shapes the paradigm of antagonism. One signature that such arms races leave on protein-coding genes of hosts and pathogens is the higher probability of fixation of an amino acid-altering (non-synonymous) mutation, if changes at that position provide a selective advantage. Using amino acid-preserving (synonymous) mutations as a proxy for neutral changes, we interpret a higher rate of fixation of non-synonymous (dN) over synonymous (dS) substitutions (or dN>dS) as an evolutionary signature that amino acid alterations were positively selected by natural selection in a recurrent fashion (Yang and Bielawski, 2000). Such a signature of positive (or diversifying) selection could occur in the context of a whole protein, a particular domain or even an individual amino acid residue. Hotspots of several neighboring positively selected protein residues are predicted to represent interaction sites that are being continually reshaped by cycles of increased binding and evasion. Implicit in this prediction is the assumption that the same protein domains have been engaged in evasion–binding cycles over millennia (Daugherty and Malik, 2012).

Infectious viruses

Because of their usability in the laboratory and importance to human health, viruses provide a prime model to study the relevance of selection signatures in host–pathogen interactions. The following sections review examples of how positive selection has been used to identify 'where' host–virus molecular interfaces are located, 'when' host–virus arms races began, and 'how' viruses adapt to combat host restriction (Fig. 2).

Where?

Our first attempt at testing the hypothesis that hotspots of positive selection represent protein interaction surfaces or, more precisely, antiviral specificity domains came from studies of the antiviral protein TRIM5alpha. Previous work from the Sodroski lab discovered that the *TRIM5alpha* gene underlies the protection of rhesus macaque cells against HIV-1 infection (Stremlau et al., 2004). In contrast to rhesus TRIM5alpha, human TRIM5alpha provided only modest restriction of HIV-1 (Stremlau et al., 2004). A single segment in the B30.2 domain of TRIM5alpha containing five amino acid residues was shown to have undergone recurrent positive selection in Old World monkeys and hominoids (Sawyer et al., 2005). A swap of these five residues was sufficient to swap the antiviral potencies of human and rhesus TRIM5alpha against HIV-1. Parallel studies showed that just a single amino acid residue was sufficient to mediate this swap of antiviral specificity (Stremlau et al., 2005; Yap et al., 2005). Thus, evolution-guided analyses identified interaction surfaces based not on conservation (which is often a metric employed for site-directed mutagenesis studies) but rather on rapid evolution, i.e. apparent lack of conservation (Fig. 2A). More recently, we showed that a hotspot of positive selection defines the antiviral specificity domain of the MxA antiviral protein (Mitchell et al., 2012). Again, a single positively selected residue conferred gain-of-antiviral specificity onto an ineffective but otherwise-wildtype ortholog. Studies from several other antiviral genes have demonstrated the utility of such an

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approach to study the interaction of viruses with the innate immune antiviral systems of mammals and provide a powerful complement to traditional biochemical techniques (Daugherty and Malik, 2012; Meyerson and Sawyer, 2011).

When?

While a recurrent signature of positive selection can be a powerful guide for delineating antiviral specificity domains, a signature of episodic positive selection (positive selection in a subset of the considered taxa) can be equally informative to 'date' the origin of evolutionary arms races (Emerman and Malik, 2010). For instance, our finding that the antiviral gene *SAMHD1* underwent intense positive selection in one lineage of Old World monkeys (the Cercopithecinae) suggested the concurrent origin of SAMHD1-antagonizing activity in viruses (Lim et al., 2012). Intriguingly, such an activity exists in the Vpx/Vpr protein encoded by some simian lentiviruses (including HIV-2), which almost exclusively infect Cercopithecinae. Together, these two findings allow us to date the origin of the Vpx–SAMHD1 arms race to the common ancestor of the Cercopithecinae (Fig. 2B) (Lim et al., 2012). Similarly, using episodic positive selection as an evolutionary echo of a previous infection has allowed more accurate dating of the origin of lentiviruses (Compton et al., 2013) and hepaciviruses (Patel et al., 2012). Such dating would be imprecise using only sequences of the viruses because their rapid evolution leads to an under-estimation of viral age, often by several orders of magnitude (Holmes, 2008; Patel et al., 2011; Wertheim and Worobey, 2009).

How?

Many RNA viruses such as poliovirus mutate rapidly, enabling rapid exploration of adaptive landscapes (Vignuzzi et al., 2006). This allows RNA viruses to overcome many challenges imposed by immune systems (Aebischer et al., 1991; Ciurea et al., 2000) or human-engineered antivirals (Melnick et al., 1961). Yet, a cost accompanies this high rate of mutation: the higher the mutation rate, the more likely a progeny virus is to carry a deleterious mutation (Crotty et al., 2001; Eigen and Schuster, 1977). Nonetheless, higher mutation rates are overall beneficial to RNA viruses in the context of host infections, wherein the viral populations have to continually adapt (Domingo et al., 2012) (Fig. 2C, top).

In contrast to RNA viruses, DNA viruses have modest mutation rates, similar to those of the hosts they infect (Drake, 1999). How do these 'slowly evolving' viruses keep pace with the changing immune repertoires of their hosts? One important clue came from experimental evolution studies of the vaccinia virus, a model poxvirus, and its antagonism of the human antiviral protein PKR (protein kinase R). Vaccinia virus encodes K3L, a weak antagonist of human PKR that is, in contrast, very effective against PKR orthologs from other primates (Elde et al., 2009). When passaging vaccinia virus in human cells, the K3L locus rapidly underwent genomic expansion, producing larger amounts of the K3L antagonist and overcoming PKR by a mass-action effect, despite incurring a cost from its increased genome size (Elde et al., 2012). However, the 'accordion-like' expansion of the K3L gene locus also provided substantially more targets on which Darwinian mutation-selection could act. Once a more effective K3L protein evolved within the gene expansion, the accordion rapidly collapsed to eliminate the cost of the genome expansion. In cases like vaccinia virus, gene accordion-like intermediate states may be obligatory for positive selection even if the final product of the selection is a single amino acid alteration (Fig. 2C, bottom). Such copy number alterations may provide the genetic fodder for many

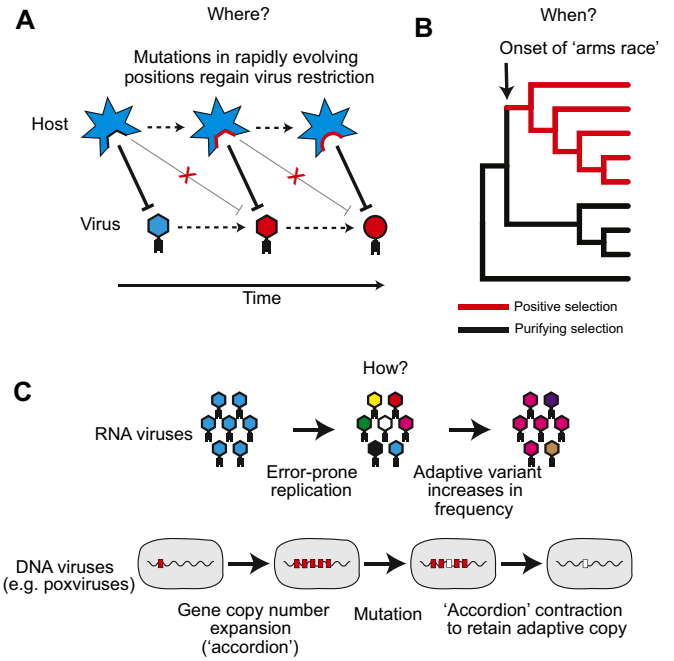

Fig. 2. Rapid evolution of amino acid sequences identifies interface and timing of host–virus conflict. (A) Where? Host restriction factors block the replication of pathogenic viruses, but this places pressure on the virus, which selects for variants that evade host restriction (red hexagon virus, red circle virus). Similarly, host variation at the interaction interface that restricts evasive viruses is selected for (red surface on host factor), shifting selection back to the virus. As there is always a benefit to adapt to evade (on the virus side) or restrict (on the host side), there is no stable equilibrium and always an advantage to adapt. Often, the difference between a restrictive and ineffective host factor may be determined by a single amino acid change, as described for TRIM5alpha and MxA. (B) When? Positive selection can date the origin of a host–pathogen arms race. Episodic positive selection in a subset of primate species suggests the initiation of the 'arms race' began in the common ancestor of these species, as seen in the Cercopithecinae subfamily of Old World monkeys when an ancestral lentivirus gained the ability to antagonize SAMHD1. (C) How? Top: error-prone RNA viruses adapt through generating a diverse pool of offspring, some of which contain adaptive mutations that evade or counteract host restriction. These adaptive mutations increase in frequency in the virus population. Bottom: in the genomes of more slowly evolving DNA viruses like the poxviruses, the copy number of genes frequently expands. If one duplicate gene samples a mutation that increases the fitness of the virus (for example, the white variant evades host restriction), this variant will be selected for and the copy number expansion may contract to contain only the newly adaptive (white) gene variant.

subsequent adaptations (Brennan et al., 2014). Similar copy number expansions have been observed in many 'slowly evolving' organisms including bacteria, yeast, *Plasmodium* and even mammalian cells (Bergthorsson et al., 2007; Demuth and Hahn, 2009; Dunham et al., 2002; Kugelberg et al., 2010; Nair et al., 2008; Pränting and Andersson, 2011; Singer et al., 2000; Stambuk et al., 2009; Sun et al., 2009).

The scourge of transposable elements

Natural selection acts on all replicators – any autonomous or partially autonomous replicating entity (Koonin and Starokadomskyy, 2016), whether it be a specific allele of a gene, a chromosome, a genome or even a group of genomes. In this context, transposable elements represent the ultimate (and perhaps original) selfish DNA elements (Doolittle and Sapienza, 1980; Orgel and Crick, 1980; Orgel et al., 1980). Transposable elements are nucleic acid sequences containing the information required to

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replicate in the context of a host genome. Like infectious viruses, these selfish elements evolve because they encode the ability to make more of themselves.

Although they reside within host genomes, transposable elements need to over-replicate relative to the host genome to ensure they stay one step ahead of mutational inactivation. The substantial proportion of transposable elements in host genomes stands testament to their prolific over-replication. For example, half (or more) of the human and over 80% of the maize genome arose from transposable element activity (de Koning et al., 2011; Jurka et al., 2005; Lander et al., 2001; Schnable et al., 2009). Their transposition and presence in large proportions imperils many aspects of host fitness, including genome stability and fertility (Beck et al., 2011; Boissinot et al., 2001; Bourc'his and Bestor, 2004; Malki et al., 2014; Montgomery et al., 2007; Song and Boissinot, 2007). Like infectious viruses, the relationship between transposon fitness and host fitness is complex. At low levels of replication, a transposon may have minimal effects on host fitness. However, transposable elements with enhanced ability to replicate in the germline will increase in frequency, becoming more likely to impact the fitness of the host. In the host, any gene variants that limit transposon activity in the germline (perhaps the only tissue that really needs protecting from element activity) will be selected in the face of active transposition. Like other Red Queen interactions, this conflict between selfish element and host genomes is self-propagating. More transposon copies mean higher transposon fitness but lower host fitness, and vice versa.

Many aspects of host control of transposable elements are analogous to host control of viruses. Indeed, many restriction factors that were originally discovered because of their activity against viruses (including retroviruses) were subsequently shown to be potent restrictors of retrotransposons (transposable elements that mobilize via an RNA intermediate and reverse transcriptase activity) (Goodier et al., 2015; Hu et al., 2015; McLaughlin et al., 2014; Moldovan and Moran, 2015; Muckenfuss et al., 2006). However, one mechanism that is unique to transposon control stems from the fact that the transposons are resident within host genomes (among eukaryotic viruses, only retroviruses have this obligate requirement of host genome integration). Thus, curbing transposon transcription has the potential to stop the cycle of transposition in its tracks. This control is especially evident in the germline, where host genomes use a variety of silencing strategies (including DNA and histone modifications) that are specifically targeted to transposable elements (Molaro and Malik, 2016). The *KRAB-Zinc Finger* (*KZNF*) genes found in mammalian genomes provide one stunning example of the selection on host genomes to restrict transposons. In humans, there are more than 400 *KZNF* genes, which via gene duplication have a dramatically expanded repertoire of DNA-binding specificities (Najafabadi et al., 2015; Vaquerizas et al., 2009; Weirauch and Hughes, 2011). Many individual KZNF proteins are targeted to individual transposon families (Castro-Diaz et al., 2014; Jacobs et al., 2014; Turelli et al., 2014). Upon binding, the KZNF proteins interact with transcriptional silencing machinery to suppress transposon expression (Wolf and Goff, 2009). Thus, KZNF proteins act as malleable adaptors to allow the host silencing machinery to keep pace with a changing landscape of transposons. Indeed, the prevalence of these genes in mammalian genomes is likely explained by a history of adaptation and counter-adaptation at the level of DNA-binding specificity (Thomas and Schneider, 2011).

Although the conflict between transposons and the host genome can be cast in exclusively Darwinian terms, a highly successful transposon runs the risk of lowering host fitness to the point where it drives the host, and therefore itself, extinct. However, the host is always counter-evolving to limit transposon replication, and the nature of Red Queen interactions commands that there is always selection for transposons to evade these restriction mechanisms and replicate, or face extinction. In a sense, the Red Queen forbids a 'happy medium' in which transposons increase their prevalence but not to the point of host extinction. Consistent with this notion, only a few transposable element copies account for the bulk of transposition activity in human genomes (Beck et al., 2011; Brouha et al., 2003). Further, there are well-documented examples of extinction of entire families of transposons in host genomes (Cantrell et al., 2008; Grahn et al., 2005), which could reflect especially potent host restriction or perhaps the random loss of these elements.

It was not always recognized that transposable elements are, in fact, selfish genetic elements. Indeed, almost coincident with the seminal discoveries of transposable elements by Barbara McClintock came the suggestion that transposable elements or 'control elements' were beneficial to the genome, whether in the form of a stress response or for some other purpose. However, the presence and proliferation of such elements could be explained purely by considering them as selfish parasites without the requirement to invoke any beneficial function to the genome (Doolittle and Sapienza, 1980; Orgel and Crick, 1980; Orgel et al., 1980). Yet, despite their deleterious potential, the residence of transposons in host genomes provides a resource for genetic innovation in host genomes. While the bulk of transposable element insertions suffer the ignominy of mutational abrasion, some copies have been protected against mutation, suggesting that host genomes have domesticated these insertions for their own purpose. There are some spectacular examples in which protein-coding genes domesticated from transposon insertions have been usurped for host roles, from mediating the genomic rearrangements required for antibody diversification (Agrawal et al., 1998; Hiom et al., 1998), to placental reproduction (Dupressoir et al., 2012), to centromere function (Smit and Riggs, 1996; Tudor et al., 1992) and genome defense (Benit et al., 1997; Best et al., 1996; McLaughlin et al., 2014; Yan et al., 2009). In addition to domestication for their protein-coding function, networks of transposable element insertions distributed across the genome have been domesticated to orchestrate transcriptional programs. Indeed, some spectacular biological novelties that arose during mammalian evolution can be attributed to this 'copy-and-paste' transcriptional network (Lynch, 2016), from placental function to innate immunity (Chuong et al., 2016; Feschotte, 2008; Kunarso et al., 2010; Wang et al., 2007). In rarer cases, transposable elements have been domesticated for their transposition activity. Perhaps the best-known example comes from *Drosophila* genomes, which employ retrotransposons to perform the chromosome end-protection function provided by telomerase in most eukaryotes (Mason and Biessmann, 1995; Sheen and Levis, 1994). Although some would view these examples as a form of symbiosis, the selfish DNA perspective would make the strong case that these are simply evolutionary 'spoils of war', in which host genomes exploit every resource at their disposal.

The study of transposable elements exemplifies why the context of natural selection is so important. Viewed from the genic perspective, transposable elements embody the Darwinian struggle for existence and evolutionary dominance in the genome, even if their activity lowers the fitness of their host. What distinguishes transposons from conflicts between warring genomes in host–virus arms races is the fact that these elements are inherited together with the rest of the host genome.

The transmission distorters: 'eliminate or outrace the competition'

Biology is replete with examples of selfish genetic entities that can enhance their own fitness at the expense of genetic neighbors (Burt and Trivers, 2006; Hurst et al., 1996). As discussed above, transposable elements increase in fitness by over-replicating (relative to the host genome), but genetic entities can also accomplish the same increase in fitness by eliminating or outracing the competition.

Toxin–antidote systems: 'stick together or die'

Many selfish genetic elements in bacteria are inherited on plasmids. As the fidelity of plasmid segregation is not as high as that of the bacterial chromosome, the selfish genetic element is not guaranteed transmission to both daughter cells following cell division. Over time, this loss after cell division means a smaller and smaller fraction of bacterial cells in the population harbor the selfish genetic element. To ensure that they are not inevitably 'lost by dilution', some selfish genetic elements have evolved mechanisms which ensure only cells that inherit that selfish element are successfully propagated. In its simplest configuration, this is accomplished by a two-component system: a diffusible trans-acting toxin that is transmitted to both daughter cells, and a cis-acting short-lived antidote that only exists in the daughters still harboring the selfish genetic element (Unterholzner et al., 2014). Any daughter cells that lost the selfish genetic element are killed by the action of the stable toxin moiety; those still harboring the element are protected by the continued production of the antidote (Fig. 3A).

Although many selfish toxin–antidote systems (also sometimes referred to as 'addiction modules', as they are hard to get rid of) operate on the basic principles outlined in Fig. 3A, there is a dizzying array of mechanisms the toxins manifest in their killing action (Unterholzner et al., 2014). To ensure that bacterial cells are always susceptible to toxin action, toxin proteins typically attack essential cellular processes within bacterial cells, such as translation and DNA replication, or essential components like cell walls, membranes or cytoskeleton. Because the targeted proteins involved in these essential processes are typically evolutionarily constrained, it is extremely unusual for bacterial cells to evolve to 'evade' toxin action. Although all toxins discovered to date are proteins, antitoxins include proteins, small non-coding RNAs that bind and sequester toxins, small RNAs that prevent the translation of toxin mRNAs, and antitoxin proteins that competitively bind cellular targets of toxins (Unterholzner et al., 2014).

The description of the general principles of toxin–antitoxin systems enabled the observation of similar characteristics in many systems not previously considered 'selfish'. One example of such reframing comes from the pioneering work of Kobayashi and colleagues, who argued by analogy to toxin–antidote systems that the bacterial restriction–modification (R–M) systems, previously believed to be bacterial symbionts used for phage defense, may instead be selfish genes (Kobayashi, 1996, 2001; Takahashi et al., 2002) (Fig. 3B). Although R–M systems could be domesticated for host defense, it could be argued that this is not their raison d'être (like transposons, discussed above). For instance, R–M systems borne on the bacterial chromosome might primarily act in host defense against phage; maximizing the success of the bacterial chromosome that bears them maximizes their evolutionary success. In contrast, when their inheritance is decoupled from that of the bacterial chromosome (for example, on a plasmid), the primary action of R–M systems might be the selfish elimination of cells that have lost the R–M-bearing plasmids.

The same principles that underlie toxin–antidote systems in bacteria and fungi are also evident in selfish genetic elements in animals that manifest their 'killing action' post-zygotically. For example, the *peel* paternal-effect lethal gene from *Caenorhabditis elegans* encodes a sperm-delivered toxin that causes embryonic lethality unless it is rescued by a zygotically expressed antidote encoded by the *zeel* gene (Seidel et al., 2011). As expected, the *peel–zeel* 'toxin–antidote' genes are found in close genetic linkage. Similarly, the maternal-effect lethal M (Medea) factor genes present in natural populations of the flour beetle *Tribolium castaneum* cause the lethality of all hatchlings that do not inherit the M factor genes, either paternally or maternally (Beeman et al., 1992). *Tribolium castaneum* populations in India also harbor a second selfish element, the paternal effect lethal H factor genes. Intriguingly, the presence of H factors makes flour beetles immune to the maternal-effect lethality of M factor genes, suggesting that H factors suppress the 'antidote' system of M factors, leading to a suicidal action of the M factor genes (Thomson and Beeman, 1999). Although the molecular details of the M and H factor genes remain to be worked out (but see Lorenzen et al., 2008), these genetic factors are likely to be closely linked toxin–antidote genes that over-proliferate in natural populations via their selfish action.

Meiotic drive: challenging Mendel

Similar biological principles to 'toxin–antidote' bacterial systems may apply to eukaryotic meiosis, the cellular division that enables diploid organisms to produce haploid gametes. In keeping with Mendelian laws of inheritance, any allele or gene present on only one of the homologous chromosomes is transmitted to 50% of the resulting gametes. However, if the gene were to act selfishly, analogous to the toxin–antidote systems of bacteria, it could improve its evolutionary success by eliminating gametes that do not inherit it (Fig. 3C). Indeed, sperm- or spore-killers that act following meiosis have been found in several species of fungi and animals (Lindholm et al., 2016; Raju, 1994). In most cases, their presence testifies to their selfishness rather than any benefit they provide to the host genome (Kusano et al., 2003). Their toxic action is prevented from 'self-killing' (Lindholm et al., 2016) either via an antidote protein that is expressed in close genetic linkage (Hammond et al., 2012) (Fig. 3C) or by the absence of a 'susceptibility' locus that is present on all other competing chromosomes (Fig. 3D) (Wu et al., 1988).

The action of spore-killers is obviously beneficial to their own evolutionary success, but comes at a cost to the rest of the genome, which loses nearly half its otherwise-fertile gametes as a result of the selfish action of one locus. This sets up a genetic conflict between the toxin–antidote system and the rest of the genome, with the latter under selective pressure to evolve genetically unlinked suppressors to suppress the killing action of this selfish genetic element (Hartl, 1975). Because of their general isolation from recombination and the ease of experimentally detecting biased sex ratios, many drive-suppressor systems have been discovered on the sex chromosomes of animals (e.g. *Drosophila*). When suppressed and no longer able to manifest their selfish action, such genetic elements are predicted to decay with mutation in a manner similar to inactive transposable elements. In instances where they have not fully decayed but are nonetheless successfully suppressed, their presence can be revealed by crosses between closely related species which may genetically separate the toxin–antidote locus from its suppressor (Tao et al., 2001, 2007a,b; Zanders et al., 2014).

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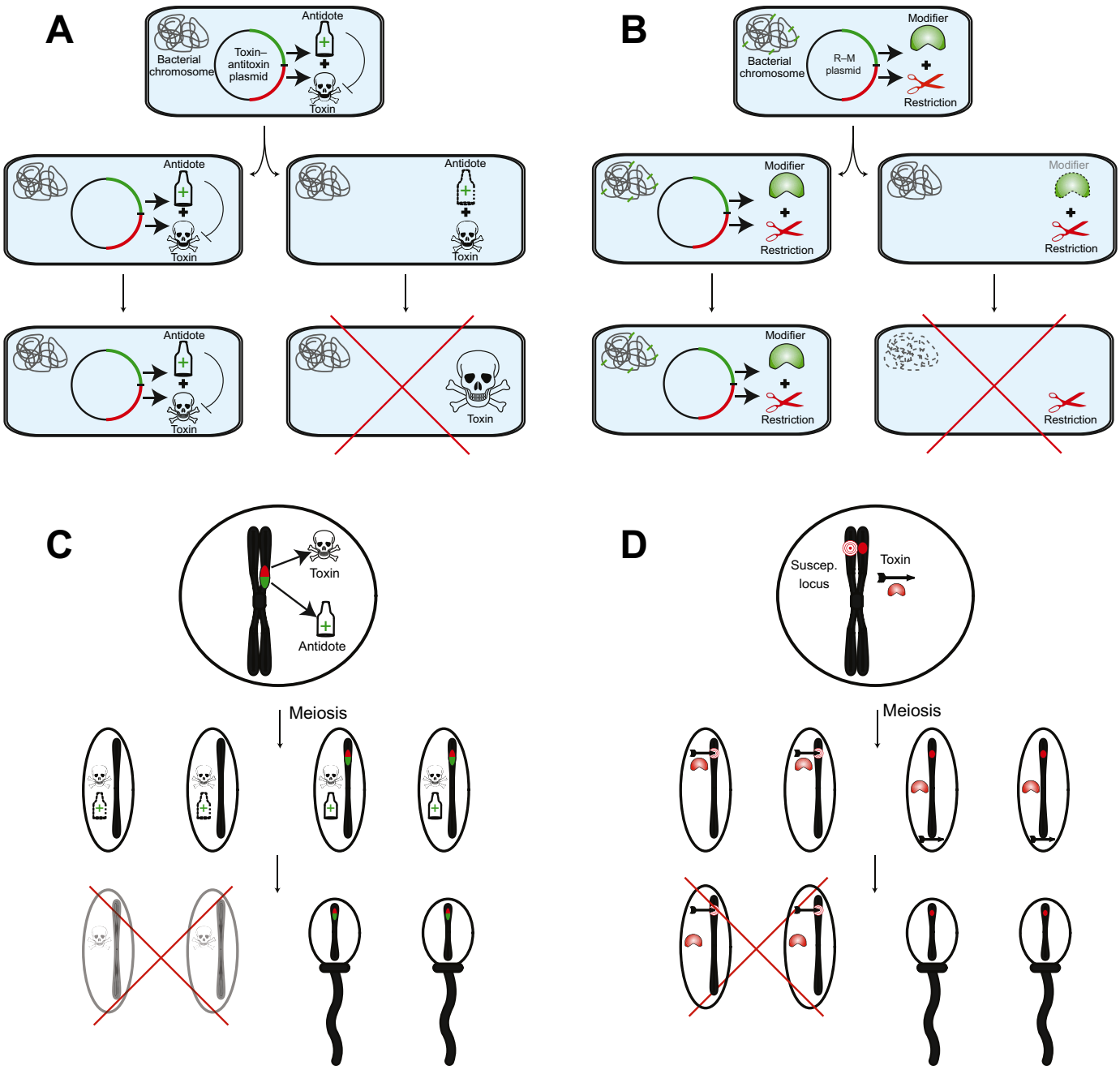

Fig. 3. Selfish genetic elements that distort transmission in their own favor by eliminating the competition. (A) Toxin–antidote genes inherited on episomes (plasmids) encode two components: a long-lasting toxin and a more unstable antitoxin. Constant protection from the toxin therefore requires constant production of the antitoxin. If a bacterial cell does not inherit the toxin–antidote plasmid, it is 'killed' by the action of the persistent toxin once the unstable antidote degrades. Thus, the toxin–antidote gene pair acts as a selfish genetic element, ensuring its own preferential transmission. (B) Restriction–modification (R–M) plasmids were initially widely believed to represent a form of symbiosis, where they act to protect the host genome against invading phage. The modification protein acts to modify the bacterial chromosome, protecting it from the DNA-endonuclease activity of the restriction enzyme. However, on an episome, R–M systems act more as a classic toxin–antidote system (outlined in A), ensuring their own transmission via similar dynamics to the canonical toxin–antidote systems. (C) Toxin–antidote systems can also act following meiosis in eukaryotes. Loci that encode toxin–antidote systems are protected from toxin action by producing a constant supply of the short-lived antidote, whereas homologous sister products of meiosis that lack the locus are eliminated owing to the action of the toxin. Such 'spore-killers' are quite abundant in fungi, although only a handful have been completely characterized at the molecular genetic level. (D) In a variation of the toxin–antidote systems, toxin genes can act preferentially on chromosomes bearing a susceptibility locus (e.g. Responder satellite in *Drosophila melanogaster*) but do not act on themselves owing to the absence of this locus. As a result, such systems can drive themselves to high frequency by eliminating competitor chromosomes bearing the susceptibility locus and so preventing them from efficiently completing gametogenesis.

Racing to the finish line in female meiosis

The post-meiotic gametogenesis program that produces sperm and spores is symmetric (alleles transmit in a Mendelian fashion). It is rendered asymmetric by the selfish action of toxin–antidote genetic loci. In contrast, the gametogenesis program that produces eggs or ovules in plants and animals is inherently asymmetric as only one of four meiotic products is transmitted to the egg, and the other products become evolutionarily 'dead-end' polar bodies. More than six decades ago, seminal studies by Marcus Rhoades in maize showed that genetic elements could exploit this asymmetry to increase their own transmission (Rhoades, 1942). He showed that maize knob elements, composed of large blocks of highly repetitive DNA (Peacock et al., 1981), possessed the ability to subvert the second meiotic division to ensure a greater-than-Mendelian transmission bias during meiosis. Notably, the knob elements themselves do not contribute a fitness advantage to maize genomes; they persist in populations solely through their greater ability to compete during meiosis (Buckler et al., 1999). Generally, any genetic locus that can subvert meiosis could ensure a transmission advantage.

The finding that maize knobs manifest a neocentromeric activity that distorts transmission in the second meiotic division of female meiosis (Dawe and Cande, 1996) led to the suggestion that centromeres, the essential chromosomal sites for spindle microtubule attachment, might similarly compete for meiotic transmission during the first meiotic division of plants and animals (Henikoff et al., 2001). In *Mimulus* species, an expansion of the centromeric satellite region is genetically associated with increased meiotic transmission in female meiosis but offset by costs to male fertility (Fishman and Saunders, 2008) and general fitness (Fishman and Kelly, 2015). A complementary cell biological study in mice showed that a greater ability to attract centromeric proteins was associated with a female meiotic transmission advantage (Chmátal et al., 2014). Together, these studies support a model in which increased centromere size confers a greater ability to recruit kinetochore proteins, an increased number of microtubule attachments, and eventually a greater likelihood of segregation to the egg versus the polar bodies (Henikoff et al., 2001; Ross and Malik, 2014). Notably, 'centromere-drive' could have deleterious consequences on male meiosis and general viability, in part due to deleterious alleles hitchhiking to high frequency via linkage to driving centromeres. Much like the case of selfish genetic elements that manifest following male meiosis, centromere-drive in female meiosis is expected to elicit genetic suppressors from the genome (Henikoff et al., 2001). We proposed that these genetic suppressors could be allelic variants of kinetochore proteins, whose altered DNA-binding preference may render them less susceptible to recruitment by 'cheating' centromeric DNA arrays. Thus, DNA binding by kinetochore proteins is the molecular interface that provides the battleground for the genetic conflict of centromere drive.

Although selfish centromeres largely follow the same general principles as other selfish elements that subvert inheritance patterns, two key differences make them unique. First, female meiosis is asymmetric, but centromeres do not create this asymmetry – they are merely adept at exploiting the inherent asymmetry of plant and animal female meiosis. Why such asymmetry exists and evolved multiple times is itself a topic of great interest and conjecture. Second, unlike other toxin–antidote systems that could be eliminated without fitness effects on the host genomes, centromeric DNA and kinetochore proteins are completely essential for every cell division. Therefore, genetic conflicts shape not only rogue selfish genes but also essential components of the chromosome segregation machinery.

These battles during male and female meiosis can profoundly affect fertility and potentially drive reproductive isolation and speciation among recently diverged populations. Two influential papers suggested that a battle of the sex chromosomes, via repeated cycles of meiotic drive and suppression, could lead to reproductive isolation of hybrid species (Frank, 1991; Hurst and Pomiankowski, 1991). In its simplest configuration, hybrid males inherit meiotic drivers but not unlinked suppressors, resulting in hybrid male sterility. This model may also explain the pattern of postzygotic reproductive isolation in animal species, wherein the hybrid of the heterogametic sex (i.e. XY males in mammals and *Drosophila*, ZW females in birds and butterflies) is more likely to be sterile or inviable compared with its homogametic sibling. This near-universal pattern in animal speciation was described by J. B. S. Haldane and referred to as Haldane's rule (Laurie, 1997). Despite its explanatory power, the idea that speciation patterns could result from genetic conflicts during meiosis was initially met with skepticism. However, recent work mapping hybrid incompatibility genes (so called 'speciation genes') whose mutation can reverse hybrid sterility or inviability (Barbash et al., 2003; Brideau et al., 2006; Phadnis and Orr, 2009), supports the idea that genetic conflicts during meiosis may underlie a significant proportion of postzygotic isolation between animal species (Johnson, 2010; Maheshwari and Barbash, 2011; Presgraves, 2010).

Cytoplasmically inherited genomes: 'mother's curse'

In plants and animals, whereas the nuclear genome is inherited from both male and female parents, the cytoplasm and other cytoplasmic entities are almost universally inherited maternally, via the egg. Cytoplasmic entities include mitochondria in both plants and animals, chloroplasts in plants, and cytoplasmically inherited bacteria (e.g. *Wolbachia*, *Spiroplasma*) (Fig. 4A). From the perspective of these cytoplasmic genomes, males are an 'evolutionary dead-end' as they will not transmit these entities to the next generation. This asymmetry creates an evolutionary incentive for cytoplasmically inherited genomes to maximize female fitness (thereby increasing their own transmission), sometimes at the expense of male fitness. Perhaps the most dramatic examples of such manipulation come from the intracellular bacteria of insects, which elicit a range of male-harming phenotypes that serve to enhance their own propagation (Fig. 4B–E) (Moran et al., 2008). In some instances, the bacteria can be female-beneficial, for example by increasing female fecundity (Weeks et al., 2007).

In some respects, it is easier to 'rationalize' such behavior by intracellular bacteria, which range from symbiotic (to female fitness) to parasitic (to males). However, the same evolutionary principles apply to all cytoplasmic entities including mitochondria and chloroplasts, textbook examples of symbiosis. Indeed, in plants, both mitochondrial and chloroplast genomes can acquire 'male-harming' mutations that result in male sterility (Budar et al., 2003; Chase, 2007). In outcrossing hermaphroditic plants, so-called *cytoplasmic male sterile* (*cms*) mutations subvert resources to ovule production that would otherwise be used for pollen production. This action increases the transmission probability of mitochondria and chloroplasts harboring *cms* mutations. These mutations result in the production of a novel chimeric protein that is 'toxic' to male fertility (Schnable and Wise, 1998). Over time, as male fertility wanes within populations, the fitness of the nuclear genomes decreases. Thus, as the Red Queen paradigm predicts, nuclear suppressors of

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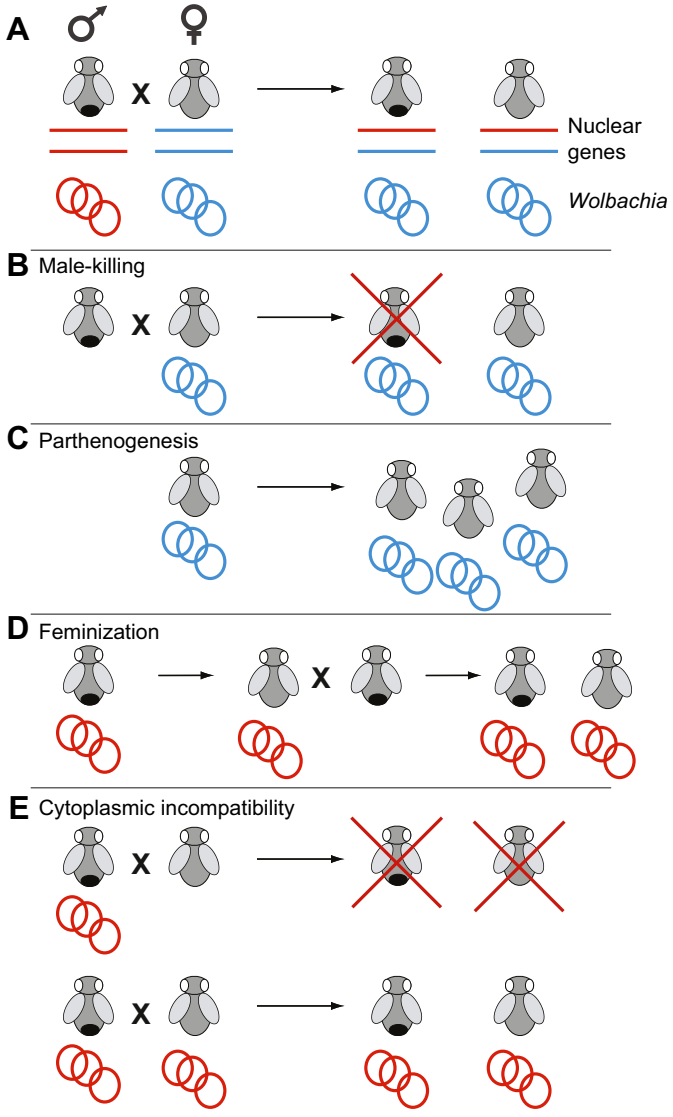

Fig. 4. Uniparentally inherited cytoplasmic bacteria distort transmission in their own favor. (A) The two parents equally contribute to the nuclear genomes of their male and female progeny (sex chromosomes are an obvious exception). In contrast, cytoplasmically inherited bacteria such as *Wolbachia* and *Spiroplasma* (as well as mitochondria and chloroplasts in plants) are maternally inherited. As a result, males represent an 'evolutionary dead-end' for any cytoplasmically inherited bacteria, and they adopt a number of insidious strategies to avoid this fate (B–E). (B) Because male fitness is inconsequential (and may even be harmful) to *Wolbachia*, it can eliminate male larvae via lethal interaction between the male genotype and the cytoplasmically inherited *Wolbachia* (Fukui et al., 2015; Hurst and Jiggins, 2000). This maximizes resources available to the female larvae, which can transmit *Wolbachia* to future generations. (C) If males are a dead-end, it is not in *Wolbachia*'s genetic interests to have any males at all. By converting sexual females into parthenogenetic females (Adachi-Hagimori et al., 2008), it can ensure it is passed on productively to all of the progeny of the parthenogenetic females. (D) One means by which *Wolbachia* 'trapped' in males can skirt their inevitable elimination is to convert genetic males into reproductive females (Kageyama et al., 2002), thereby ensuring they can be passed on to its offspring. (E) Another means by which *Wolbachia* can quickly spread in the population is by reducing the reproductive fitness of uninfected females relative to infected ones. For instance, under cytoplasmic incompatibility, all progeny resulting from a cross between an infected male and an uninfected female are inviable (Bordenstein and Werren, 1998). In contrast, crosses between infected males and infected females are viable and, thus, successfully increase the proportion of *Wolbachia*-infected individuals (especially females) in the next generation.

cms mutants arise, restore male fertility, and arrest the selfish behavior of mitochondria and chloroplasts. These 'fertility-restorer' alleles usually encode proteins with pentatricopeptide repeats (PPRs) that prevent the production of the toxic *cms*-associated protein (Wang et al., 2006). Reflecting the history of these genetic conflicts between nuclear and mitochondrial genomes in plants, most plants harbor hundreds of PPRs, many of which demonstrate signatures of positive selection (Fujii et al., 2011). Thus, one can draw parallels between the molecular signature of genetic conflicts seen in nuclear suppressors of mitochondrial selfishness and the KRAB-ZNF proteins that adapt to recurrent threats of novel transposable element families (Thomas and Schneider, 2011). This also suggests that there must exist a 'tit-for-tat' dynamic in *cms*-restorer conflicts that has yet to be fully explored mechanistically.

Although this behavior has been primarily studied in plants, there is growing evidence that such male-harming 'mother's curse' mitochondrial mutations may also be present in animals (Camus et al., 2015; Patel et al., 2016). However, much less is known about how these mitochondrial DNA mutations manifest their male-harming behavior, and even less about how they are suppressed by nuclear genomes. It is quite possible that the larger mitochondrial genomes and the hermaphroditic nature of plants make male-harming mitochondrial mutations more likely to occur.

The genetic conflict between nuclear and mitochondrial genomes can not only affect male fertility within species but also dramatically affect fertility in crosses between closely related species (Leppälä and Savolainen, 2011; Simon et al., 2016). If the genetic conflict between *cms*-restorer alleles is rapid, crosses between closely related species could result in inheritance of *cms* mutations but not the appropriate restorer alleles, producing male sterility (Rieseberg and Blackman, 2010). Indeed, some hybrid incompatibility loci in plants have been mapped to putative restorer genes that likely function to rescue the effect of hidden *cms* mutations or their restorer alleles (Barr and Fishman, 2010; Case and Willis, 2008). The parallels between the speciation patterns that emerge from two distinct genetic conflicts – cytonuclear versus meiotic – are striking and reflect the same underlying principles behind the two types of interactions.

Sexual conflict: the battle of the sexes

Genetic conflict can also emerge from divergent interests between the two sexes (Rice and Holland, 1997). Sexual conflict arises when a trait that is favorable to one sex (e.g. frequent mating in males) is detrimental to the other. If such a dimorphic (male-beneficial, female-detrimental) trait evolves that confers a selective advantage to certain males over others (whether in courtship, mating, parental care or fertilization), this fitness advantage may increase the frequency of the trait. However, the success of this trait would result in an increasing cost to females, and thus solicit a counter-adaptation to protect females from this male-beneficial, female-detrimental trait. In this way, antagonistic interactions stemming from sexual conflict fit the dynamics of Red Queen interactions. Present-day genomes could be thought of as a détente between female and male interests. If this dynamic were true, then arresting the ability of one sex to adapt might break the truce and reveal the intermediate states of the sexual conflict. Indeed, experimental manipulations arresting female-specific selection in *Drosophila melanogaster* found increased male fitness and decreased female fitness (Prasad et al., 2007; Rice, 1998).

One category of genes that show molecular signatures of sexual conflict is genes encoding fertilization proteins; specifically, the binding interaction between sperm and eggs. Most plant and animal species produce orders of magnitude more sperm than eggs; the latter require considerably more investment. Sperm are under intense competition to improve their ability to bind and fertilize the egg, and any allele that enables a sperm to do so faster would be favored. However, in most instances, this increased binding affinity and the numerosity of sperm leads to an increased risk of polyspermy – multiple sperm fertilizing the same egg. Polyspermy is frequently catastrophic, producing inviable, multiply fertilized eggs. This means that increased binding affinity of sperm proteins to maximize their chances of fertilization may be at odds with the fitness of the egg. Egg proteins are thus predicted to counter-evolve to reduce binding affinity and polyspermy. Thus, even though fertilization is beneficial to both egg and sperm genomes (i.e. to both females and males), they paradoxically have different fitness optima for the binding affinity of their gametes. As sperm competition will inevitably select for 'faster binding', this divergent interest results in perpetual cycles of adaptation and counter-adaptation. Indeed, sperm and egg proteins have been shown to be among the most rapidly evolving in plant and animal genomes (Swanson and Vacquier, 2002; Vacquier and Swanson, 2011), consistent with the sperm–egg interface representing a Red Queen interaction.

Separating the genetic location of male-beneficial and female-beneficial traits may be one way to help resolve this conflict. For instance, female-beneficial traits may be more likely to be retained on the X chromosome (which spends two-thirds of its existence in females), whereas male-beneficial traits are more likely to accumulate on the Y chromosome. Under this scenario, akin to the 'toxin–antidote' model, one might expect sex chromosomes to exhibit selfish behaviors to reduce the fitness of offspring that do not inherit them (e.g. X chromosomes harm male offspring whereas Y chromosomes harm female offspring), in what has been referred to as the 'sexually antagonistic zygotic drive' model (Friberg and Rice, 2015; Rice et al., 2008). Although there is tantalizing evidence in favor of this model (Friberg et al., 2011), its molecular basis is still unclear.

Sexual conflict can also occur in parental care or development of offspring. In viviparous animals, the fertilized zygote develops within the body of the mother until it is capable of independent existence. This sets up a potential genetic conflict where the paternal genome is at odds with the maternal genome over allocation of resources (Haig, 2004). Specifically, the paternal component of the offspring genome would benefit from acquiring as many resources for the offspring as possible (even at the expense of maternal fitness and prospects of future offspring), whereas the maternal genome would be selected to offer resources more equitably to her present and future offspring (including those sired by other males). This maternal–paternal conflict can result in differential genome imprinting, in which paternal alleles (of growth factor genes, for example) may be expressed to manifest their 'selfish' resource demands whereas maternal alleles that may 'dampen' such demands are not expressed. It is also possible that imprinting represents cooperation between maternal and paternal genomes (Haig, 2014). In mammals, genomic imprinting is most obvious in the placenta, the location of the biological negotiations for resource allocations to the developing fetus (Frost and Moore, 2010). This influential model has considerable intuitive appeal, but it is unclear to us what molecular signatures would uniquely attest to this unusual conflict (Wolf and Hager, 2006). For instance, parent-of-origin DNA methylation can also be attributed to genome defense against transposable elements (Bestor, 2003). Furthermore, unless there were an active dynamic of methylation and de-methylation, it remains unclear whether maternal–offspring conflict would spur the perpetual cycles of adaptation and counter-adaptation we associate with Red Queen interactions.

Concluding comments

In this overview, we attempt to highlight the common principles (e.g. over-replication, asymmetric inheritance) that shape diverse genetic conflicts (Burt and Trivers, 2006; Dawkins, 1976; Hurst and Werren, 2001; Hurst et al., 1996; Werren, 2011), driving perpetual cycles of 'tit-for-tat' evolution. This diversity, only some of which we represent in this article, attests to the fact that genes and genomes have been remarkably opportunistic and inventive to exploit every possible advantage in the Darwinian struggle for survival.

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Competing interests

The authors declare no competing or financial interests.

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