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Short Review

Selfish genetic elements and speciation

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This review concerns the importance of selfish genetic elements (SGEs) in speciation. We assess the importance of medea genes, meiotic drive elements, transposable elements and the bacterium *Wolbachia* in the creation of postzygotic isolation. Although all of these elements can contribute to postzygotic isolation, their contribution will often disappear if there is gene flow between the populations. Further, there is the possibility that incompatibilities produced by SGEs may lessen over time. We conclude that although some of the case studies are tantalizing, particularly those associated with *Wolbachia*, the role of selfish genetic elements in speciation remains unproven.

Keywords: medea, meiotic drive, postzygotic isolation, speciation, transposable element, *Wolbachia*.

Introduction

Selfish genetic elements (SGEs) spread through populations by distorting the patterns of transmission away from Mendelian segregation. The discovery of SGEs has often been accidental, deriving from observation of unusual patterns of mortality, sex ratio or mutation rates in hybridization experiments performed for other reasons. Within the literature on cytoplasmic male sterility (cms), for instance, 20 per cent of records derive from studies where interpopulation crosses were performed, and 30 per cent derive from interspecies hybridizations (Frank, 1989). In natural populations, the cms phenotype is not observed. Similarly, the discovery of new transposable elements and of cytoplasmic incompatibility-inducing *Wolbachia* has also commonly been fortuitous, the phenotypes of these SGEs again being exhibited in interpopulation crosses. The observations of these phenotypes in hybrids has given two major insights. First, they suggest SGEs may be more common than at first believed (they are there, but not easily detected). Secondly, the fact that the deleterious phenotypes of SGEs appear in hybrids has led many workers to make a connection between selfish genetic elements, the formation of reproductive isolation, and speciation.

The question we seek to answer is whether divergence of SGEs in allopatry is important in speciation. It is not the purpose of this review to discuss whether selfish genetic elements are the sole or even the most important cause of inviability and sterility. It is clear from studies of speciation genetics that there are many cases where SGEs are not important. Our aim is to evaluate critically the potential for SGEs to produce reproductive isolation, in the knowledge that they are one of many factors.

We therefore examine four SGEs (medea genes, meiotic drive genes, transposable elements, and cytoplasmic incompatibility-inducing *Wolbachia*) and address two main questions. First, what is the empirical evidence that a particular SGE reduces hybrid fitness? Secondly, will any reductions of hybrid fitness caused by SGEs be maintained over significant periods of evolutionary time following secondary contact? In the discussion, we will take the advice of our spell-checker, which throughout the composition of this piece has shown an unusually dry sense of humour, relentlessly suggesting we replace the word 'speciation' with 'speculation'. We will place ourselves in the intellectually precarious position of attempting to assess the importance of the different classes of selfish genetic elements in producing reproductive isolation.

Medea genes

Medea (Maternal effect dominant embryonic arrest) genes were first recorded in *Tribolium castaneum*, and were suggested as a potential cause of postzygotic isolation (Beeman *et al.*, 1992). Singapore and U.S. strains were crossed, creating a fully viable F_1 hybrid. F_1 hybrid females were found to produce half the usual number of viable progeny in backcrosses to males from the U.S. population, due to elevated embryonic mortality. Genetic analysis showed that the trait occurred because F_1 females were heterozygous for a particular gene (termed medea) and their backcross partner lacked it. Medea is a combination of a maternal effect trait (putatively, the

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presence of medea in the mother dictates the presence of a toxin in the embryo), with an embryonic rescue trait. Progeny are rescued by the presence of what is either the 'maternal effect toxin' gene itself, or a gene closely linked gene to it, inherited from either parent. The observation of Beeman *et al.* (1992) is consistent with the medea complex (toxin and antidote) arising and spreading to fixation in the Singapore population, but being absent in U.S. beetles (hence F_1 incompatibility). Similar elements have since been recorded in both wild and laboratory mice (Hurst, 1993; Peters & Barker, 1993; Weichenhan *et al.*, 1996).

The population genetics of such elements is straightforward. They are self-selecting, in that they kill individuals that do not bear them. This advantage is frequency dependent. As medea climbs in frequency, the probability of a medea-free individual dying increases. The medea elements invade deterministically once they drift beyond a threshold frequency at which the fitness of the non-medea allele (diminished because of medea action) is less than the cost imposed by the medea element on its host (we assume there is some metabolic cost of toxin production, Wade & Beeman, 1994). Alternatively, medea elements deterministically invade if the death of medea-free embryos reduces the intensity of antagonistic interactions between siblings (e. g. sibling–sibling competition for resources) or if killed embryos are consumed by their siblings (Bull *et al.*, 1992; Wade & Beeman, 1994). Under these conditions, the medea gene can spread whatever its initial frequency.

Given that individual medea genes only produce a 50 per cent unidirectional reduction in hybrid fitness, they are unlikely to produce full reproductive isolation on their own. This would require allopatric populations to have been invaded by a range of different medea genes, such that each population was at fixation for more than two medea genes unique to it. The scarcity of reports of medea genes suggests that they are rather rare, and thus we consider multiple invasion unlikely.

In terms of the contribution of individual genes to the creation of isolation, a gene causing 50 per cent embryonic mortality is a gene of major effect (Coyne, 1992). Thus on first examination, medea genes appear to be important speciation genes. However, if postzygotic isolation is not complete, the medea gene will be introduced into the population which did not bear it. It is likely to spread in this population, removing any contribution it might have made to the isolation of the populations.

Perhaps the most realistic scenario in which medea genes can represent important elements in reproductive isolation is where introgression of medea genes is prevented because the gene is closely linked to other loci that contribute to postzygotic isolation. This would increase the effective cost of medea invading a new population, and thus might prevent invasion. Invasion into the new population will be most difficult where the medea gene must reach a threshold frequency to invade (i.e. where there are no antagonistic interactions between siblings). The spread of such genes into the naive population may then be severely limited, and in such cases, medea genes may make a continued contribution to reproductive isolation.

The loss of meiotic drive suppressors

Meiotic drive occurs when one chromosome haplotype is inherited by more than half the progeny because of the disruption of gametes bearing the homologous chromosome. Meiotic drive genes will be over-represented in progeny whenever there is competition between gametes from the same individual for fertilization. If the driving chromosome is a sex chromosome then drive causes sex ratio distortion. The spread of the driving chromosome is frequently followed by the spread of suppressor genes, both on the driven chromosome and through the rest of the genome. This can result in the complete suppression of drive within a population, with drive being confined to hybrids. This pattern has been observed in *Drosophila simulans*, where crosses between female Seychelles flies mated to males from mainland Africa give rise to F_1 male progeny which show X chromosome drive (Merçot *et al.*, 1995).

Hurst & Pomiankowski (1991) extended this argument to explain how drive could cause F_1 sterility of the heterogametic sex. Consider a pair of allopatric populations where the male is heterogametic. In one of these, an X driver has spread and been suppressed; in the other, a Y driver has spread and been suppressed. Male hybrids that inherit the driving Y from their father, and the driving X from their mother, will show both X and Y drive, and will thus fail to produce any viable sperm. If both populations bear suppressed X and Y drive, then all male hybrids will be affected. Although this scheme is clearly plausible (both X and Y drive are known), there is as yet no empirical study confirming simultaneous sex chromosome drive in a hybrid. Empirical studies point to a general rarity of Y chromosome drive in natural populations, making the probability of getting X drive in one population and Y drive in the other rather low. Thus, although this explanation for F_1 heterogametic sex sterility is viable, it is unlikely to be very common.

Hurst & Pomiankowski (1991) and Frank (1991) envisaged also that loss of suppression of a meiotic drive gene in a novel population might give rise to complete sterility of the F_1 heterogametic hybrid. As such, loss of suppression of meiotic drive genes was seen as underlying Haldane's rule (Haldane, 1922), a thesis that provoked much controversy (Coyne *et al.*, 1991; Charlesworth *et al.*, 1993). It is clear, through counterexample (e. g. Johnson & Wu, 1992), that it is not *the* explanation for *the* rule. The question that must be asked therefore is whether it is ever a cause of hybrid sterility, and thus ever important in speciation (Pomiankowski & Hurst, 1993). Opposition to the idea that meiotic drive can cause hybrid sterility derives mainly from the fact that it is not intuitively obvious why unrepressed meiotic drive should have any

phenotype other than drive. This criticism must be addressed empirically.

Hurst & Pomiankowski (1992) and Pomiankowski & Hurst (1993) point to examples that might represent unsuppressed drive producing sterility. The most compelling is the case of the *t* complex in mice. The *t* complex on *Mus musculus* chromosome 17 contains a meiotic driver. Hybrid males from *M. spretus* × *M. musculus* hybridizations are sterile, and the genes causing this sterility also map to the *t* complex. A causal link between sterility and drive has been shown by the findings of Braidotti & Barlow (1997), who observed that both phenotypes were associated with the *Tcte2* gene.

Evidence that unsuppressed meiotic drive can produce sterility has also been derived from the study of the *Stellate* gene family on the X chromosome of *D. melanogaster* (Hurst, 1992). The product of the *Stellate* gene causes the accumulation of crystals in the testes of XO males. This production is inhibited in XY individuals by a gene family on the Y chromosome, *Suppressor of Stellate*, *Su (Ste)*. Both *Stellate* and *Su (Ste)* are multicopy repeats. *Stellate* appears to have no function in spermatogenesis itself (many species of *Drosophila* do not have it, Livak, 1984, 1990), and it is this appearance of redundancy that led to it being proposed as a meiotic drive gene-suppressor system, where loss of suppression is associated with hybrid sterility (Hurst, 1992).

For this case to stand up as an example of an unsuppressed meiotic drive gene producing sterility, it is necessary to provide some evidence that there is X chromosome meiotic drive when *Su (Ste)* is in low copy number or absent, and that the intensity of drive is related to *Stellate* copy number. Analysis of data of Palumbo *et al.* (1994) did find a positive correlation between the number of *Stellate* elements and the rate of transmission of the X-chromosome to progeny (Hurst, 1996). Although the case is not yet proven (see Hurst, 1996; Robbins *et al.*, 1996), the data obtained so far are consistent with *Stellate* being a meiotic driver creating hybrid male sterility.

We conclude that meiotic drive genes can play some role in the generation of postzygotic isolation, through the production of hybrid sterility. Even if we exclude the cases of *Tcte2* and *Stellate*, one day there will be a case of mutually repressed drive. We must therefore ask whether this source of isolation will remain after secondary contact. The answer appears to be yes, sometimes. Consider the case where a single driving element causes F_1 heterogametic sterility when its suppressor is lost (*Tcte2*, *Stellate*-type elements). Here, the selfish phenotype (meiotic drive) that caused the spread of the SGE initially is not present in the naive population (we see sterility, not drive), and the SGE will not spread in this population. However, if we consider the case of mutual drive causing hybrid male infertility, the case is less clear. Recombination in hybrid females will allow the formation of hybrid-X chromosomes, which possess various combinations of drivers and suppressors. X chromosomes will be created that possess insensitivity to all Y drivers, and these will spread through the population in which they are not suppressed. Following such spread, we expect the invasion of modifiers that suppress drive, for example a Y chromosome resistant to both driving X chromosomes. Thus, full hybrid male fertility will be restored.

Transposable elements

The movement of transposable elements (TEs) during germ-line divisions has a variety of effects. Most obviously, they produce mutations, which are typically deletions of function and recessive, caused by the insertion of a TE into a functional gene, or its regulatory region. Further, TE activity is also associated with an elevated rate of chromosomal rearrangements, especially inversions. The most dramatic phenotype observed is gonadal dysgenesis, which is associated with the *P* and *I* transposable elements. When a female without TEs mates with a male which bears multiple copies, the F_1 hybrids have decreased fertility because of malformation of the gonads. The degree of fertility loss varies with temperature (greater at high temperature for *P*, greater at low temperature for *I*) (see Kidwell & Lisch, 1997 for review of case studies of these phenomena).

Transposable element activity, and thus phenotype, is most profound in hybridizations; TEs are relatively benign within the population in which they have spread. The presence of the gonadal dysgenesis phenotype in the hybrid context led to TEs being proposed as a potential source of reproductive isolation (Bingham *et al.*, 1982; Rose & Doolittle, 1983; Ginzburg *et al.*, 1984). In most formulations of TE-mediated speciation, allopatric populations are invaded by a range of different TEs whose collective effect is such that all hybrids are sterile. Such collective action of TEs has been observed in *D. virilis*, where certain crosses show evidence for multiple TE mobilization (Petrov *et al.*, 1995).

How important could TE-mediated dysgenesis be in speciation? Empirically, studies on drosophilids have failed to produce evidence for TE involvement in hybrid inviability and sterility, despite the presence of TEs in these species (Coyne, 1985, 1986, 1989). However, lack of a role for TEs in the production of isolation in one group does not prove that they never play a role. Further, it is hard to rule out the existence of TEs producing complete sterility, as these would be very hard to detect empirically (we infer TE presence only when they have incomplete effects, through their mutagenic activities).

We may perhaps gain more insight from theory. For TEs to contribute to isolation over prolonged periods requires an absence of gene flow through hybrids. If any gene flow occurs, each TE would quickly invade and spread through the naive population. The case for the spread of TEs into the previously naive population is even stronger here than for medea genes, because the TE can potentially escape linkage with other genetic causes of incompatibility through transposition. It is also notable that transmission of the TE between the two populations,

with concomitant loss of TE-mediated isolation, could occur even if there were no gene flow through hybrids, via a horizontal transmission event. Horizontal transmission is known to be common in the *mariner* element, and has also been observed for *P* (Daniels *et al.*, 1990; Robertson, 1993).

Could the elevation of mutation rates associated with TE activity potentially speed the rate at which hybrid inviability and sterility develop? Consider allopatric populations, in one (or both of which) a TE has arisen, producing elevated mutation rates. Would this elevation in mutation rate convert into an elevation in the rate at which sterility and inviability develop? Although it may be hard to see the production of individual mutations as being a limiting factor in the evolution of sterility and inviability, the production of chromosomal rearrangements by transposable elements could perhaps contribute to isolation. Transposable elements are often observed to be associated with inversions: within natural populations of *Drosophila willistoni*, 10 of 24 *P* element insertions examined mapped to sites of inversions (Regner *et al.*, 1996). Given that the rate of production of new chromosomal arrangements in natural populations is generally very low, and that they are generally underdominant, the rate of fixation of new chromosome arrangements is likely to be a function of the rate of production of new types. Given it is also true that chromosomal rearrangements can be associated with decreased hybrid viability and hybrid sterility, there is a case that transposable element activity may enhance the rate of production of hybrid incompatibility. However, the precise effect of TE-induced karyotype changes on the rate of production of hybrid incompatibilities is uncertain.

Wolbachia and cytoplasmic incompatibility: infectious speciation?

Cytoplasmic incompatibility, or CI, is a common phenomenon in insects, caused by the bacterial symbiont *Wolbachia*. When a *Wolbachia*-infected male mates with an uninfected female, the eggs or embryos die. The net effect is a decrease of the fitness of uninfected females, which over time results in the infected cytotype becoming fixed in the population. This type of CI is known as unidirectional CI. Bidirectional CI has also been observed. It occurs when the individuals from two populations are infected by different strains of *Wolbachia*, such that crosses in both directions are incompatible. The isolation that can be achieved through possession of different strains of *Wolbachia* led Coyne (1992) to dub this infectious speciation.

Bidirectional incompatibility was first recorded in the mosquito *Culex pipiens*. Individuals from different populations were found to be incompatible, but the incompatibility could be removed by treatment of males with antibiotics (Laven, 1951; Yen & Barr, 1971, 1973). Bidirectional incompatibility has also been recorded in *Drosophila simulans* (see Clancy & Hoffmann, 1996 for review), and between the sympatric species *Nasonia vitripennis* and *N. giraulti* (Breeuwer & Werren, 1990, 1993). Incompatibility has always been observed to be associated with infection by bacteria from the *Wolbachia* clade.

Can *Wolbachia* alone produce speciation? This awaits a definitive answer, and the reader is referred to Werren (in press) for a fuller analysis. In the case of *D. simulans* the bacterium is not perfectly transmitted between generations (Hoffmann *et al.*, 1990). Thus, some uninfected males arise each generation, and some gene flow occurs. Gene flow is also observed in the case of *C. pipiens*. Despite the existence of CI crossing types, studies of resistance to organophosphate (OP) pesticides reveal the worldwide spread of a particular OP resistance mutation from a point source (Raymond *et al.*, 1991). In the case of the *N. vitripennis*/*N. giraulti* system, incompatibility appears to be complete and gene flow negligible. However, the two populations are also reproductively isolated by virtue of autosomal genes, such that even when the strains are cured of *Wolbachia*, F_2 hybrid breakdown is complete (Breeuwer & Werren, 1995). It is thus unclear whether *Wolbachia* was the primary agent causing reproductive isolation (with autosomal incompatibilities evolving later), or whether the bidirectional incompatibility was secondary (evolving after autosomal incompatibilities).

Thus it would be premature to state that we have evidence that CI induced by *Wolbachia* has caused speciation. Although it seems likely that an example will be found where complete isolation between populations derives solely from the presence of different *Wolbachia* strains, there are perhaps three reasons to suspect that it might not be common. The first is the presence of inefficient transmission from female to progeny and incomplete penetrance of the CI condition between infected males and uninfected females in natural populations. Perfect transmission and complete penetrance are perhaps the exception and not the rule. Secondly, models predict that selection on both host and *Wolbachia* favour a lowering of the penetrance of the incompatibility phenotype (Turelli, 1994), and hence the loss of *Wolbachia* (Hurst & McVean, 1996). Thus systems may evolve from high penetrance to low to none, that is, from a case of no gene flow to some gene flow. Finally, there is the possibility that one of the *Wolbachia* strains will be transmitted horizontally between the populations. This would create a dually infected lineage compatible with all other types, whose spread creates a single panmictic population. The frequency of dual infections in nature suggests that this process occurs at a fairly high rate on an evolutionary timescale (Werren *et al.*, 1995). Thus, *Wolbachia* alone is perhaps unlikely to keep populations distinct over long periods of evolutionary time.

Perhaps therefore the most likely role of CI in speciation will involve selection for assortative mating by crossing type. The scenario envisaged is the spread of different *Wolbachia* strains through allopatric populations to fixation, secondary contact of these populations (where

hybrids are not viable, and hybrid matings costly), and lastly the spread of genes producing assortative mating by crossing type.

If incompatibility is complete, the spread of assortative mating genes is trivial. This will mean isolation will continue (through prezygotic isolation) even if *Wolbachia*-induced incompatibility later disappears. Where incompatibility is incomplete or maternal inheritance imperfect, the conditions for the spread of genes for assortative mating is more restrictive, and the situation falls into the class of speciation models referred to as reinforcement (Butlin, 1987). Genes promoting assortative mating must spread in spite of gene flow between the populations. Recent models have suggested that reinforcement can evolve under some circumstances (Liou & Price, 1994; Kelly & Noor, 1996). So it is possible that cytoplasmic incompatibility can promote speciation even when incompatibility is incomplete.

It is also possible that, in line with the rationale for medea genes and transposable elements, *Wolbachia* plays a role in speciation in conjunction with other sources of isolation. The case of the *Drosophila recens*/*D. subquinaria* species pair appears to be one case in which *Wolbachia* plays a partial role (Shoemaker, Katju & Jaenike, cited in Werren, in press). Here, reproductive isolation appears to be mediated in part by *Wolbachia* in one direction (crosses between *recens* males and *subquinaria* females), but not in the other. There is no reason why such situations should not commonly arise. They suggest that unidirectional incompatibility (infection of just one of a species pair) and partial bidirectional incompatibility may act to enhance speciation rates by acting in conjunction with other forces of isolation.

Discussion

Although selfish genetic elements often cause decreased hybrid fitness, they are less likely to be important in speciation than first examination of their phenotypes would suggest. Although medea genes and transposable elements clearly reduce hybrid fitness, neither is likely to produce full reproductive isolation. Thus, unless reproductive isolation is completed by other factors, gene flow will carry them into the other population. They will then spread and the hybrid incompatibility will be lost. Thus, the hybrid dysfunction caused by these elements may in fact be of little importance in speciation. The same is true to some extent for *Wolbachia*, through horizontal transmission, and in certain circumstances for meiotic drive genes.

The other feature of selfish genetic elements that limits their role in speciation is the possibility that their phenotype may wane over evolutionary time. In relation to *Wolbachia*, the penetrance of the incompatibility phenotype is expected to decrease, and indeed *Wolbachia* may be lost over time. Under some circumstances, the same is true of medea genes (Smith, in press). If the assumptions underlying these models are correct, then the contribution made by *Wolbachia* and medea genes to reproductive isolation will decrease with time, and their invasion will need to be followed by other factors producing pre or postzygotic isolation if speciation is to be permanent.

Putting aside consideration of possible constraints, the potential contribution of *Wolbachia* to speciation can be assessed empirically. There are two main questions. First, are there any patterns to the taxa in which CI-induced speciation will be important? Secondly, within these taxa, how commonly will it be responsible for speciation?

There are some empirical data upon which we can base an answer to the first question. On the grossest level, inherited bacteria such as *Wolbachia* are only really common in invertebrates. Within invertebrates, a survey of molluscs failed to find any case of *Wolbachia* infection (Schilthuizen & Gittenberger, 1998). Apart from the records in insects so far discussed, *Wolbachia* has been recorded in mites (Johanowicz & Hoy, 1996), isopod Crustacea (Rousset *et al.*, 1992) and nematodes (Sironi *et al.*, 1995). *Wolbachia*-induced cytoplasmic incompatibility has been found in mites (Breeuwer, 1997) and postulated in isopods (Rigaud & Rousset, 1996) as well as insects. Thus, we can state that *Wolbachia*-induced speciation is potentially important in the two most speciose of animal groups (insects and mites), and we believe it could also play a role in speciation in a range of other invertebrate groups, though (apart from isopods) precisely which groups is hard to ascertain.

The second question, regarding the importance of *Wolbachia*-induced speciation relative to more classical modes, is more difficult to answer. In a survey of tropical insects, *Wolbachia* was found in 16 per cent of the species surveyed (Werren *et al.*, 1995). However, it is not known what proportion of these infections cause cytoplasmic incompatibility. If we estimate that 10 per cent of species are infected with CI-causing *Wolbachia*, then around 1 per cent of species-pairs will show bidirectional incompatibility. This leaves us with the impression, on *ad hoc* calculation, that cytoplasmic incompatibility will turn out to be a motive force in somewhere between 0.025 per cent and 0.5 per cent of all speciation events within the Insecta.

The last selfish elements to be discussed have meiotic drive genes. We have argued that the case for suppressed meiotic drive causing heterogametic F_1 hybrid sterility is yet to be proved. How important such effects are in causing speciation is another issue. On one hand, meiotic drive of sex chromosomes can be quite common. In a random survey of drosophilids, Jaenike (1996) reports five of nine species to be polymorphic for X chromosome drive. However, it is not known what proportion of suppressed meiotic drive elements cause hybrid sterility. Workers on *Drosophila* speciation genetics argue that, despite drive being common in this group, meiotic drive has not been found in semisterile hybrids, and it is thus unlikely to be an important cause of hybrid sterility. In this matter, despite the encouragement of our spell-checker, we will resist the temptation to speculate. Rather, we await future empirical studies.

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