Intragenomic Conflict as an Evolutionary Force

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SUMMARY

Ultra-selfish genes increase in frequency in a population despite the harm they inflict on their host. The spread of both ultra-selfish genes and their suppressors is evidence of conflicts between genes within an individual for transmission into the next generation. Here I synthesize a body of past work, and argue that intragenomic conflict might be an important evolutionary force. I discuss the evolutionary history of cytoplasmic genes as an illustration. I first consider the evolution of sex. Recent evidence suggests that the initial evolution of sex might have been driven by an ultra-selfish gene. The existence of sex in turn creates a series of new conflicts which may explain the existence of sexes and uniparental inheritance of cytoplasmic genes. Uniparental inheritance of cytoplasmic genes sets up a new set of conflicts over the sex ratio, which in turn may influence the evolution of sex determining systems, sex allocation systems and post-zygotic isolating mechanisms.

1. INTRODUCTION

Ultra-selfish genes (Crow 1988) are characterized by their ability to spread in a population despite the harm they inflict on their host (reviewed in Werren *et al.* (1988)). The invasion and spread of both ultra-selfish genes and their suppressors is evidence of a conflict of interest between components of the genome. For instance, cytoplasmic genes are not transferred to the next generation through sperm, and hence can gain an advantage if they distort the sex ratio in favour of females. Autosomes, however, can be selectively favoured if they can return the population to a 1:1 sex ratio. Thus there exists a conflict of interests between cytoplasm and autosomes over the control of the sex ratio.

Since the introduction of the notion of the selfish gene (Hamilton 1963; Dawkins 1976), ultra-selfish genes have been used as key examples to show that the fundamental unit of selection is the linkage group (Dawkins 1982, 1990). In this context, the organism is understood not as unit of selection but rather as a vehicle for genes, each with more-or-less the same probability of future transmission. The organism is a level of selection because the interests of the various genes are similar. The existence of ultra-selfish genes show that these interests, although similar, are not identical. Is this resolution of the 'paradox of the organism' the limit to the interest an evolutionary biologist might have in intragenomic conflict? Here I expand on a suggestion of Werren *et al.* (1988) that intragenomic conflict might be a fundamental driving force in evolution. I support this view by discussing the evolutionary interests of cytoplasmic genes and how they might relate to the evolution of sex, sexes, sex ratio, sex allocation systems, sex determining systems, and post-zygotic isolation. Alternative explanations for the phenomena considered will not be presented.

2. THE INITIAL EVOLUTION OF SEX

Hickey & Rose (1988; also Hickey (1982) and Rose (1983)) have presented the elegant idea that sex might initially have evolved as a means by which an ultraselfish gene might have increased its transmission frequency at a cost to the host genome. A gene without such a means of transfer, or any parallel one, is stuck in the vertical lineage that descends from the original parent cell. A gene with horizontal transmission capability has the potential to infect numerous other lineages. How might a gene achieve such a transfer? The construction of a conjugatory pilus through which the gene may pass is one possible means. The genes responsible for construction of *E. coli*'s pilus are on the F plasmid, and duly it is this plasmid which is transferred through the pilus to a new host while leaving a copy of itself in the original host (Willetts & Skurray 1980). Hurst (1991*a*) has drawn attention to a plasmid that inhabits the mitochondria of the slime mould *Physarum polycephalum* (Kawano *et al.* 1991). Zygotes are formed by the fusion of two isogamous gametes, each of which has its own mitochondria. If one set of mitochondria has the plasmid but the other does not then the mitochondria fuse, recombine and then split apart. The plasmid is then found in all the mitochondrial products. In the absence of the plasmid, fusion is not witnessed. Kawano *et al.*'s (1991) finding is significant in that it reveals that plasmids are capable of complex manipulations of their hosts: they can force the fusion of two otherwise asexual lineages. Mitochondria are, however, transformed prokaryotes, and it is unclear that the Hickey & Rose model for the evolution of sex has any relevance to the evolution of eukaryotic sex (but see Hurst 1991*a*).

The transfer of a plasmid probably inflicts a cost on the host. The process is, for instance, time consuming. However, if for a time the plasmid can have 'power',

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i.e. it is not suppressed by the host genome, then the initial cost of establishing the sexual process may be overcome and the trait can spread. Once established, the transfer can be adapted to the advantage of the host genome. When an F plasmid does not exist in its independent state, but rather as an integral part of the host's circular DNA, the host DNA is transferred to the recipient cell. Recombination is much more frequent when the plasmid is included in the host DNA than when it is independent, and the first DNA to be transferred is that of the host DNA with the plasmid going last (Willetts & Skurray 1980). This balance of power is indicative of the host taking control of a parasitic selfish gene.

3. THE EVOLUTION OF SEXES

After the evolution of cytoplasmic fusion of gametes, a new conflict arises, namely one between maternally and paternally derived cytoplasmic genes for control of the zygote: a tragedy of the common cytoplasm (Eberhard 1980; Cosmides & Tooby 1981; Hurst 1990). Cytoplasmic genes from one parent may attempt to annihilate their competitors from the other parent. It has been suggested that this sort of aggressive behaviour might lead to the evolution of sexes (Hoekstra 1987; Hurst & Hamilton 1992).

Consider an isogamous population with no sexes, i.e. any gamete can mate with any other in the same population. The evolution of sexes occurs in three stages, as follows (Hoekstra 1987; Hurst & Hamilton 1992).

1. A cytoplasmic gene from parent 1 which attempts to destroy the similar cytoplasmic gene from parent 2 goes to fixation if it can invade.

2. A nuclear control gene acting in a haploid which leaves its associated cytoplasmic gene vulnerable to destruction invades because it prevents potentially costly cytoplasmic gene war. If there is a cost relative to the heterozygous condition for two bearers of the suppressor gene to fuse then the suppressor gene reaches a heterotic stable polymorphism.

3. A gene which prefers its haploid cell to fuse with only one of the opposite suppressor type, but which has declining preference with time, invades the polymorphic population provided the costs of choice do not outweigh the advantages of non-like mating. If such a gene can enter it goes to stable fixation, so establishing binary mating types.

The model proposes that the essential asymmetry between sexes is an asymmetry in the nuclear genes to prevent transmission of cytoplasmic genes, and hence prevent cytoplasmic gene conflict. This is supported by empirical observation. The mating types of Chlamydomonads are associated with an exact system in which nuclear genes have specific effects on particular endosymbionts such that mitochondria are inherited from − type parent but chloroplasts are inherited from the + type, despite the fact that the zygote inherits both types (Bennoun *et al.* 1991). In several species, the mechanism has been investigated and supports the view that cytoplasmic gene conflict is central to the

process. Chiang (1976) has shown that in *Chlamydomonas* the chloroplasts from + and − type parents fuse, and chl DNA from both types attempt to destroy each other by means of digestion by restriction endonucleases. In some cases, up to 95% of all DNA is destroyed. Typically, however, the + type DNA is destroyed more slowly than the − type DNA, and hence + type chl DNA constitutes the cytotype. Other reports claim a unilateral disarmament of the chloroplast genes by nuclear genes in the − type gamete (Sager 1977).

The model makes three key predictions (Hurst & Hamilton 1992). First, when zygotes are formed by the fusion of gametes, a system with more than two sexes is unstable. This instability will be caused by the spread of a cytoplasmic variant which refuses to be eliminated or shut down. Hurst & Hamilton (1992) have thus argued that the plasmid of *Physarum polycephalum*, discussed above and by Hurst (1991 *a*), is significant in that it is found in one of the very few organisms which has both fusion of gametes and more than two sexes. Second, in heavily inbred isogamous organisms with fusing gametes, cytoplasmic genes can regulate their own conflict. Hence these organisms could stably maintain biparental inheritance of cytoplasmic genes, and thus need not be differentiated into sexes. Significantly, there is no evidence that cytoplasmic genes are not biparentally inherited during fusion between genetically identical plasmodia of slime moulds (M. Carlile, personal communication). (For an analogous situation in which ultra-selfish genes evolve to suppress their own activity, see Brookfield (1991).) Third, those systems in which sex does not involve gametic fusion (or alternative means of mixing cytoplasmic genes) need not have exclusively binary mating types, and those systems in which fusion and some outbreeding is witnessed should have exclusively binary mating types. With the two exceptions discussed above, fusion is nearly always associated with binary mating types (Grell 1973; Hurst & Hamilton 1992). In contrast, both basidiomycetes (Day 1978) and ciliates (Kudo 1977; Grell 1973), which have sex without fusion, have a number of incompatibility types which is both high and very variable.

In parallel with the above argument, it has been argued that the evolution of anisogamy (small sperm) might have as a key component the prevention of the transmission of cytoplasmic genes (Grun 1976; Cosmides & Tooby 1981; Hurst 1990; Hastings 1992; Law & Hutson 1992). In contrast to isogamy, in which specific nuclear–cytoplasmic relations are required to control the inheritance of cytoplasmic genes, the small size of sperm acts as a general anti-symbiont technique, excluding even potentially dangerous parasites such as bacteria and possibly viruses. From this viewpoint, a species ought to be anisogamous unless ecological constraints force otherwise. The small size of sperm also probably has a variety of energetic advantages as well as symbiont removal.

This model makes no strong predictions about the existence of isogamy against anisogamy above and beyond the usual ecological ones and pointing out a perpetual tension which isogamy entails. Rather, the

central theme of these ideas is the essential asymmetry of the sexes, and how this affects an understanding of nucleus–cytoplasm relations in anisogamous and isogamous species, and how these in turn permit an understanding of, for example, sperm anatomy (Hurst 1990) and unilateral gene disarmament in isogamous species. For instance, many species of land plants have cytoplasmically rich spermatozoids. However, the entrance to the chamber containing the oocyte is narrow, and these cytoplasmically rich spermatozoids can only pass through the archegonial constriction after they have shed their cytoplasm (Whatley 1982). This stripping off of cytoplasm is understandable in terms of intragenomic conflict.

4. CYTOPLASMIC SEX RATIO DISTORTERS

Because cytoplasmic genes are not transferred from the father to the zygote, cytoplasmic genes are in conflict with the nucleus for control of the sex ratio (Lewis 1941; Howard 1942; Hamilton 1967, 1979). Cytoplasmic genes can, and do, increase their propagation by biasing the sex ratio in favour of females. The means by which this is achieved include feminizing the host (Legrand *et al.* 1987), killing male hosts (see Hurst (1991*b*) for review), inducing females to produce all-female broods parthenogenetically (Stouthamer *et al.* 1990*a,b*; Zchori-Fein *et al.* 1992; Hurst *et al.* 1990) or in haplodiploids forcing an increase in the frequency of fertilization (Skinner 1982). All of these instances are evidence for an evolutionary conflict over the sex ratio.

In the case of feminizing factors in crustaceans, the conflict takes the form of a wrestle for control of sex determination, which in turn leads to the evolution of a new sex-determining mechanism (Juchault & Legrand 1989). For instance, the isopod *Armadillidium vulgare* has as its native sex-determining system XY females and XX males. Some populations are infected with a cytoplasmic feminizing factor which renders would-be males female. This feminizing factor spreads through the population, and the XY females can be entirely replaced by feminized males. In these populations, the sex-determining system is no longer female heterogamety but rather one in which nuclear genes masculinize and the presence of the feminizing cytoplasmic genes forces the host to be female (Juchault & Legrand 1989). The sex ratio evolves to be controlled, not by the segregation of X and Y, but rather by a set of nuclear genes which control the transmission from mother to progeny of the cytoplasmic factor. Similarly, the evolution of haplodiploidy in bark beetles might be the result of meiotic drive forced by cytoplasmic genes (Hamilton 1993).

Cytoplasmic sex ratio distorters might also have a role in the evolution of dioecy from hermaphroditism (Cosmides & Tooby 1981). In a hermaphrodite, a cytoplasmic gene which forces the destruction of male tissue can, by so doing, both prevent inbreeding and force an increase in investment into female tissue. Such cytoplasmic genes can thus be kin selected and increase in frequency, forcing the population to become gynodioecious (Charlesworth & Ganders 1979; Couvet

et al. 1986). The imbalance in the sex ratio which results can be rectified either by the hermaphroditic organisms decreasing investment into female tissue or by the purely female organisms suppressing the selfish cytoplasmic gene. The former possibility results in dioecy, the latter in a return to hermaphroditism (e.g. *Thymus vulgaris* (Couvet *et al.* 1986)).

From this standpoint, dioecy can be viewed as a relatively stable way to deal with cytoplasmic sex ratio distorters for, unlike the case of the hermaphrodite, male killing or sterility in a dioecious population will only advantage the cytoplasmic gene responsible if the kin selective advantage due to the male's death is preferentially directed to that male's relatives (and hence the cytoplasmic gene's clonal relatives) (Hurst 1991*b*). In the hermaphrodite, the increased supply of resources to the organism's female tissue is all but guaranteed to go preferentially to clonal relatives of the male-killing cytoplasmic genes: the beneficiaries need be no further away than in carpellary tissue of the same flower. This model of the evolution of dioecy is consistent with one which views dioecy as a trap which species can be drawn into but find hard to leave. Cytoplasmically induced sterility is frequently reported in hermaphroditic plants (Frank 1989) but, possibly because of a lack of intense study, has yet to be reported in hermaphroditic animals.

5. POST-ZYGOTIC INCOMPATIBILITY

The costs to the host of cytoplasmic sex ratio distorters ensures that repressors of such genes can be selectively favoured. The specificity between distorter and repressor ensures that any given repressor can work only in a given context. This notion underlies the idea that male-specific sterility in species hybrids could be caused by an incompatibility between suppressors and cytoplasmic sex ratio distorters (Hurst & Pomiankowski 1991*a*; Levy 1991). Of all known incidences of cytoplasmic male sterility in plants, 20% have been discovered in a hybrid context (Frank 1989). Hurst & Pomiankowski (1991*a,b*) and Frank (1991) have conjectured that sex ratio-distorting meiotic drive systems might also be involved in speciation.

Not all incidences of hybrid disruption involve sex-specific effects. One class of such disruption is known to be mediated by cytoplasmic genes which increase in frequency because of their ultra-selfish nature (Laven 1967; Yen & Barr 1974; Rousset & Raymond 1991; Hurst 1991*c*). Within any given population of *Culex pipiens*, there are two sorts of individuals: those which harbour cytoplasmic symbionts of the genus *Wolbachia*, and those which do not. *Wolbachia* is a gram negative prokaryote sometimes referred to as a rickettsid. These symbionts are vertically transmitted within eggs but not in sperm. The symbionts are responsible for a system of reproductive compatibility known as cytoplasmic incompatibility. A female mosquito with the symbionts is compatible with males regardless of whether the male is infected. Similarly, an uninfected female is compatible with uninfected males. However,

an uninfected female is incompatible with infected males (the female lays eggs which do not hatch) (Laven 1967; Yen & Barr 1974). Cytoplasmic incompatibility is not restricted to mosquitos, and has been reported in several insect groups and isopod crustaceans. Genetic analysis (O'Neill *et al.* 1992) suggests that it might be much more common than previously considered.

In killing only uninfected eggs, the symbiont can spread through the population. Spite is successful in this system because all of the costs of being spiteful are inflicted on the host and not on the symbionts. However, it is only in the interests of a cytoplasmic bacterium in a male to kill uninfected eggs if it cannot receive transmission from male to egg. Thus uniparental inheritance of cytoplasmic genes lies at the heart of cytoplasmic incompatibility.

In a cross between two different populations, the bacteria in the eggs are mutually incompatible and the eggs are killed by the symbiont's toxic action. Hence these instances of incompatibility between 'species' can also be viewed as a side product of the spread of ultra-selfish genes within species.

6. DISCUSSION: INTRAGENOMIC CONFLICT AS AN EVOLUTIONARY FORCE

I have argued above that the initial evolution of sex might have been facilitated by intragenomic conflict but that the ensuing fusion of cells in turn presents a new suite of conflicts. Conflict between cytoplasmic genes forces the evolution of sexes and the uniparental inheritance of cytoplasmic genes, which in turn presents a new conflict, namely between cytoplasmic genes and the non-transmitting host. This conflict is expressed in instances of cytoplasmic sex ratio distortion. Cytoplasmic sex ratio distorters can force the evolution of new sex-determining systems and new forms of sex allocation. Suppression of these conflicts, and those between nuclear genes, is probably going to be species specific and hence, in the novel context of the hybrid, sex ratio distorters might attempt to express, and in turn cause, disruption and speciation. Similarly, cytoplasmic incompatibility agents spread only because symbionts in a male cannot colonize an egg, and hence are better off killing eggs which do not contain their clonal relatives.

The tendency for the prevention of one form of conflict simply to give rise to a new conflict is analogous to Red Queen type explanations of evolution. *In toto* intragenomic conflict can be seen as a perpetual driving force to evolutionary change. Hence, in opposition to more conventional views in which evolution is seen as adaptation to local environment, the view advocated here is that much of the evolution of genetical systems is internally driven and would continue without ecological and environmental variation.

Although this paper takes as its start position the evolution of sex, there is no reason to suppose that conflict was not important as an evolutionary force long before such a process, and indeed might well be important both in the early evolution of life and the evolution of very basic genetic structures from the simplest genes to circular DNA loops to chromosomes (see Szathmáry (1991) and references therein). Equally, the pressure of conflict at higher levels, for instance within colonies of eusocial insects, might be an important force in the evolution of various aspects of colony design (Leigh 1991).

Many of the suggestions presented in this paper are hypothetical, contentious and require experimental verification. However, the case for intragenomic conflict as an evolutionary force can be strengthened by considering conflicts between nuclear genes, as well as the cytoplasmic genes discussed in this article. Nuclear gene conflict is possibly important in the evolution of meiotic mechanisms (Haig & Grafen 1991; Crow 1991; Hurst & Pomiankowski 1991*b*) as well as numerous sex-determining systems. For instance, the elimination of the paternal chromosome set in male coccids might be evidence of a past history of meiotic drive (Haig 1992). In a seminal paper, Haig & Grafen (1991) show that crossing over could have evolved as a mechanism against meiotic drive.

Conflicts between nuclear genes need not be expressed only in terms of meiotic drive. In species with parental investment to offspring, conflict between maternal and paternal genes for the extraction of resources from parents can exist. The differential action of maternal and paternal genes (genomic imprinting), probably for control of resource extraction from a parent (Moore & Haig 1991), precludes the possibility of parthenogenesis (Moore & Haig 1991). The relevance of the conflict between other selfish genes, notably transposons and B chromosomes, and the host genome and its consequences for the evolution of genome size (C value), has been much discussed (Cavalier-Smith 1985), as has the importance of mobile elements as mutation generators. The full importance of intragenomic conflict has yet to be determined, but it is clear that such conflict deserves serious consideration as a central force driving evolutionary change.

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