Polymorphism of attack and defense

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Coevolution of attack and defense occurs in host–parasite systems and various forms of genomic conflict. Attackers benefit when their specific molecules allow entry past host defenses. Defenders gain when their matching biochemical specificities aid recognition. Selection continually favors new attack specificities that avoid matching defense and, in turn, new defense specificities that match novel attackers. The introduction of novel specificities strongly influences the spatial and temporal dynamics of conflict. Lack of reciprocally matching diversity in a particular system suggests biochemical constraints that prevent diversification. New work on cytoplasmic male sterility, B chromosomes and meiotic drive suggests that varying biochemical constraints on recognition cause varying patterns of diversity and spatiotemporal dynamics

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'To put the matter rather figuratively, it is much easier for a mouse to get a set of genes which enable it to resist *Bacillus typhimurium* than a set which enable it to resist a cat'[1].

Haldane[1] foresaw the great molecular specificity that has become the hallmark of modern biology. Small biochemical changes in pathogens allow escape from immune surveillance. Escape mutants are tracked by hosts that regain specific recognition. Pathogens and hosts are just one form of attack and defense. With each passing decade biologists have uncovered new arenas of conflict mediated by biochemical specificity[2,3] (Box 1).

The biochemical specificity of attack and defense determines the potential for genetic diversity. Limited specificity constrains polymorphism to relatively few types, with little chance of novel evasion by attackers or recognition by defenders. Mutation or immigration rarely perturbs populations because the potential for new specificities is low.

By contrast, strong biochemical specificity and high potential diversity mean that populations occasionally will be perturbed by locally novel attack and defense genes[4–6]. New attack genes may create epidemics when invading a population that lacks sufficient defense. Matching defense specificities may, in turn, sweep through the population of defenders, causing a radical turnover in the local distribution of genetic variants.

Here I focus on new studies that provide clues about the level of potential diversity in natural populations. These studies are particularly important because they implicate potential diversity as a crucial factor driving the spatiotemporal processes of demography and selection.

After I summarize studies with high potential diversity, I turn to the opposite case. Why do some systems, with apparent potential for molecular specificity of attack and defense, fail to show polymorphisms? Conflict mediated by molecular interactions seemingly compels specificity and diversity. The lack of specificity in particular cases demands an explanation more strongly than does the existence of polymorphism.

Cytoplasmic male sterility

I summarize recent work on cytoplasmic male sterility (CMS), a form of attack and defense between mitochondrial and nuclear genes. This new work reveals greater specificity and polymorphism than found in previous studies. I emphasize how the degree of specificity influences the conceptual framework in which further studies must be developed. Before turning to the new work, I first introduce the problem (Box 2).

The mitochondria of some hermaphroditic plants inhibit pollen development and simultaneously enhance the production of seeds[7,8]. Selection of genetic variants in the mitochondria favors reduced allocation to pollen, in exchange for an increase in seed production, because the mitochondrial genes are transmitted only through seeds[9].

Reallocation of resources from pollen to seeds reduces the transmission of nuclear genes because biparental transmission depends on success through both seeds and pollen. Thus there is a conflict of interest between the mitochondrial (cytoplasmic) and nuclear genes over the allocation of resources to male (pollen) and female (ovule) reproduction[4,10]. Consistent with this idea of conflict, nuclear genes often restore male fertility by overcoming the male-sterility effects of the cytoplasm.

Wild populations of CMS plants maintain several distinct cytoplasmic genotypes (cytotypes). Each cytotype is capable of causing male sterility by an apparently different mechanism, because each is susceptible to a particular subset of nuclear restorer alleles. Nuclear restorer alleles are typically polymorphic at several loci, with each allele specialized for restoring pollen fertility when associated with particular cytotypes[4,11–13].

The biochemistry of cytonuclear interactions sets the potential number of matching cytoplasmic and nuclear specificities. This potential diversity profoundly affects evolutionary dynamics[4]. When there are only a few matching types, each population will contain most of the possible genotypes and the dynamics will be driven by local interactions. When there are many matching types, some populations are likely to lose particular alleles. In this case, dynamics will be driven by genetic extinctions and colonizations over time and space[4,10].

Suppose, for example, that a population lacks a cytotype and its matching restorers. Immigration of that cytotype leads to its rapid increase because it will cause male sterility and increased seed fertility. A high frequency of male-sterile plants favors the introduction and increase of the matching nuclear restorer alleles.

The spread of one cytotype drives down the frequency of other cytotypes, possibly causing local loss of genotypes. Nuclear restorers that match locally extinct cytotypes no longer provide any benefit. Unmatched restorers will be driven from the local population if they carry any negative fitness costs because such costs are no longer offset by the benefits of restoration. The local extinction of a cytotype and matching restorers eventually leads to another round of colonization. This process of genetic extinctions and colonizations maintains spatial variation among populations[4,6].

The details of different species vary in important ways. But, in general, greater potential diversity means more opportunity for dynamics to be driven by local extinction and colonization processes of particular alleles[4,5].

How many matching specificities occur? This question is not easily answered[2,4]. A new cytotype is defined by a different segregation pattern of male sterile and hermaphrodite progeny. This difference must be measured relative to other, known cytotypes across a set of nuclear backgrounds with different restorer genotypes. To establish such differences for a candidate cytotype requires extensive analysis of progeny phenotypes in a large number of crosses. The task is even more difficult if one searches for a

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Box 1. Examples of attack and defense

Humans and other vertebrates deploy a complex array of defenses against parasites[35]. For example, host surveillance molecules may recognize the protein coat of a parasite, allowing the host to kill the parasite. But, a few amino acid substitutions in a parasite's coat can sometimes allow the parasite to avoid these defenses until the host can generate new recognition molecules[36,37]. This highly specific recognition causes rapid evolution of the nucleotide sequences that encode the parasites' surface molecules[38].

In some parasites, each individual carries many variant copies of the gene that encodes a surface molecule[39], but expresses only one genetic copy. An individual occasionally switches which gene is expressed. Such programmed variation allows parasites to escape recognition by host defenses for a longer period of time. In this case, coevolutionary interactions with hosts may affect the diversification of parasite sequences among the individual genes in the family of alternatives and also the rates of switching among the alternatives[40].

Host molecules that recognize attackers may be produced directly by a single gene. If small changes in the matching parasite molecule can evade recognition, then one expects rapid evolution of the hosts' DNA sequence. Host molecules may serve as a site of attachment by parasites, but small biochemical changes allow the host to evade attachment. Parasites must track these changes in the host by matching attachment specificities[41,42].

Many defense molecules are created by splicing pieces of different genes together in various combinations[35]. This allows the host to create a large array of different recognition specificities. With multigene splicing, coevolutionary interactions may influence the rate of sequence evolution of the individual components and the regulatory mechanisms that control which spliced sequences are amplified and expressed.

A different coevolutionary system occurs among bacterial attackers and bacterial defenders[43]. The attackers produce toxins that kill competing neighbors unless those neighbors have the necessary defense. Many bacterial populations produce a diverse set of toxins. Each toxin is neutralized only by a specific matching set of antitoxins. A defender may also avoid attack by altering its external receptor through which the toxin binds and enters the cell. There appears to be some diversity at such receptors, although perhaps less than in the matching sets of toxins and antitoxins. Preliminary evidence suggests reciprocal selective pressures and sequence evolution of some toxins and antitoxins[43].

The examples I use in the text focus on genomic conflict, in which the attack and defense genes occur in the same genome. I chose those examples because they clearly illustrate the problems of biochemical constraint and spatial and temporal processes. Many details differ between those examples of genomic conflict and, for example, vertebrate immunity. But, in all cases, the biochemical nature of specificity sets the constraints and influences the spatial and temporal scales by which one may understand observable diversity.

new cytotype without prior information about likely candidates.

Plantago lanceolata is perhaps the best analyzed case of CMS in natural populations. van Damme *et al.*[14,15] conducted a series of extensive crossing experiments over many populations and several years. They established the identity of two cytotypes, for each of which they found matching nuclear restorer genotypes.

Box 2. CMS: phenotypic effects and generation of new variants

Hundreds of cases are known in which mitochondria or other matrilineally inherited genes cause male sterility of normally hermaphroditic plants[7]. The evolutionary logic for this association follows from the fact that matrilineally inherited genes do not transmit through pollen. Thus, a mitochondrion increases its fitness by aborting pollen and, by reallocation of resources, causing an increase in the number or success of seeds.

How do mitochondria cause hermaphrodites to become male sterile? The best known example comes from studies of *Petunia*[8]. Pollen normally develop from a bundle of pollen mother cells in the anther. The pollen mother cells are surrounded by a layer of tissue called the tapetum. The tapetal layer has a high density of mitochondria, presumably to deliver the high level of energy needed to fuel differentiation of pollen mother cells into pollen grains. In male-sterile *Petunia*, the mitochondria in the tapetum deteriorate during pollen development, aborting the process and preventing the development of mature pollen grains.

Nuclear genes can counteract the effects of male-sterile mitochondria and restore pollen fertility[44]. The nuclear restorer genes typically are specific for particular mitochondria. Apparently, each mitochondrial type causes male sterility by a different nucleotide sequence or by altered molecules, because each mitochondrial type can be counteracted by a specifically matching subset of nuclear restorer loci.

One interesting problem concerns the generation of new male-sterile mitochondria. Suppose we could identify the particular mitochondrial DNA sequence that caused male sterility. Do new male-sterile variants arise by small modifications of the existing male-sterile sequence? Or do new variants arise *de novo* by rare, large sequence changes, either in existing male-sterility loci or at other locations in the mitochondrial genome? In the first case, we might expect relatively rapid sequence evolution of mitochondrial genes and matching restorers. In the second case, we might expect an ancient and relatively stable polymorphic array of mitochondrial male-sterility types and matching restorers, with slow sequence evolution at each locus.

Based on this limited number of specificities, they favored a model in which local interactions dominate evolutionary dynamics[16].

de Haan *et al.*[17] used molecular tools to study the diversity of *P. lanceolata* mitochondria. They sampled 528 plants from 12 populations in The Netherlands and 13 plants from seven European and North American populations. Their tools did not directly identify genes involved in CMS. Instead, they established characteristic RFLP (restriction fragment length polymorphism) patterns for over 20 mitochondrial types, of which nine were relatively common.

They used the nine common RFLP types as candidates for new CMS specificities, tested by classic segregation analysis[17]. They established two new mitochondrial CMS specificities and matching nuclear restorer sets – a total of four types now have been identified. Other candidates within their sample may be new CMS types, but the segregation analyses were not sufficient to identify them unambiguously. This study demonstrates the specificity that had gone undetected in previous, extensive analyses. Given the limited sampling in this first major molecular study of *P. lanceolata*, perhaps more diversity remains to be discovered.

Two studies suggest that CMS dynamics of *P. lanceolata* occur over short distances within a field. de Haan (PhD thesis, University of Utrecht, 1996) measured the spatial distribution of phenotypes in several populations. She found that blocks of length 10–20 meters maximized the variation among spatial units, suggesting that differentiation occurred on a relatively short spatial scale within large aggregations of plants.

van Damme[18] analyzed a particular field (225 m $\times$ 350 m). He found that one cytotype (*P*) had an overall frequency of 0.94. The restorers for this cytotype were also common, thus most plants were hermaphrodites. The other cytotype (*R*) in the field, at a frequency of 0.06, had associated restorer alleles with low frequencies between 0.02 and 0.08. Genotypic composition was different in four small areas (7–25 m^2) with high frequencies of male-sterile plants. The *R* cytotype, rare in the population as a whole, had frequencies ranging between 0.26 and 0.39 in these small patches. The *R*-specific restorers, also rare in the whole field, were more frequent in these male-sterile clusters, although the exact frequencies were difficult to estimate.

van Damme's[18] interpretation agrees with the colonization model outlined above. Initially, most of the field was dominated by *P* cytotypes and *P*-specific restorers. *R*-bearing colonists founded

new male-sterile clusters and, because the *R*-specific restorers were initially rare, the male-sterile phenotype spread from a central focus. Male-sterile plants produce more seeds that are larger and survive better than seeds from hermaphrodites[19], thus the male-sterile phenotype has a competitive advantage locally. Seeds disperse slowly[20] (8 cm per year) and pollen flow also occurs over short distances, thus well-defined patches can form. As the frequency of unrestored *R* cytotypes rises in an area, selection favors an increase in *R*-specific restorers. In an area with a high concentration of *R* cytotypes, the main pollen donors will be *R*-restored hermaphrodites.

The low frequency of the *R*-specific restorers in the overall population suggests that these alleles are at a selective disadvantage when the *R* cytotype is absent. If so, then a population dominated by the *P* cytotype is likely to lack the *R* restorers, as apparently occurred. A population dominated by *P* cytotypes is susceptible to invasion by *R* cytotypes, followed by a subsequent change in genotypic composition.

In summary, the specificity of CMS in *P. lanceolata* is greater than previously believed, and further study may reveal even more potential diversity. The greater the potential diversity, the more likely it is that allelic colonizations and extinctions influence evolutionary dynamics[4–6].

B chromosomes

B chromosomes are large pieces of nuclear DNA other than the standard chromosomes[21]. The B chromosomes often increase in number during transmission – successful gametes have on average more than one-half the number of B chromosomes in the parent genome. This drive-accumulation during transmission tends to increase the number of B chromosomes in a lineage. Transmission is, however, stochastic. Some progeny have fewer B chromosomes than their parents, others have more.

Those individuals without any B chromosomes often have a higher fitness than those individuals carrying B chromosomes[21]. Thus, selection may oppose drive-accumulation, leading to a balance that stabilizes the distribution of the number of B chromosomes per individual. In this scenario, driving B chromosomes are parasites against which the standard genomic components would gain by defending themselves. Defense would reduce the number of B chromosomes by whatever molecular processes could prevent drive-accumulation.

Until a recent study on Spanish grasshoppers[22,23], there has been no evidence of specificity in interactions between B chromosomes and their hosts. This new study demonstrated only a limited degree of specificity. But the spatial distribution of polymorphism and the processes inferred from this study suggest that locally novel specificities may drive the spatiotemporal dynamics of the system[22].

The grasshopper *Eyprepocnemis plorans* carries B chromosomes in most natural populations throughout the Iberian Peninsula[23]. These B chromosomes have differentiated into more than 40 types based on cytological characters. The most widespread variant, B_1, is considered the ancestor of all other types[24], including B_2 and B_5, which are locally dominant in particular regions. These three types do not show drive-accumulation when crossed within local populations[25]. For example, females with B_2 crossed to local males with no B chromosomes do not exhibit drive. But when those same females are crossed to males from a population with no B chromosomes, the B_2 chromosome does show drive. Apparently, the B_2 drive is suppressed by the genome of the population in which it occurs[26].

A new driving variant would replace a suppressed B type, causing local turnover and selection for suppression of the new type[22]. Zurita *et al.*[23] have observed this process of invasion and replacement. In 1984, a sample from Torrox (Spain) was dominated by B_{24}, a derivative of the B_2 type that dominated all surrounding regions. This 1984 Torrox sample contained approximately 70% B_{24} and 30% B_2. Samples in 1992 and 1994 found only B_{24} at this location, suggesting local replacement of B_2 by B_{24}.

The B_2 chromosomes did not drive or harm the host in local crosses. By contrast, the B_{24} chromosomes did accumulate during transmission and also reduced egg fertility. Thus B_{24} apparently had increased toward a drive-selection balance and, in the process, had pushed the B_2 type to local extinction.

Such local replacements could explain the spatial mosaic of B types[22]. Replacements followed by eventual host suppression of B drive could also explain the observation that most crosses within populations show no drive, whereas crosses between populations sometimes do have drive.

How many matching drive-suppression specificities exist among Iberian populations? Do novel B specificities enter local populations only by new mutations, or does migration play a role? The data do not, at present, provide answers to these questions (Box 3).

If it turns out that specificity is limited, what processes prevent diversification? The next section suggests how the molecular mechanisms that mediate attack and defense can limit potential diversity.

Box 3. Molecular basis of B chromosome drive

New work on the Spanish and related Moroccan populations of the grasshopper *Eyprepocnemis plorans* provides the first clues about the molecular basis of drive. Cabrero *et al.* studied three populations in which the widespread B_1 chromosome was replaced locally by a variant B – the newly successful B type differing at each location[45]. All of the B chromosomes carry a 180 bp repeat sequence rich in AT nucleotides. Interestingly, the three newly successful variants all contain more of the 180 bp repeat than does B_1. It is too soon to draw firm conclusions, but these data suggest some interesting possibilities[45].

For example, expansion of the repeat may lead to enhanced drive and spread of the B type. The autosomes may then counter by neutralizing the drive associated with the expanded repeat. Once neutralized, the expanded repeat may lose in competition with a smaller B type when both are neutralized because the smaller chromosome may be a superior competitor. This may lead to cycles in which there is expansion of the repeat, drive of the expanded type, neutralization by the autosomes and loss of the expanded type. Such cycles could explain many of the observations by a simple quantitative model of drive and neutralization, without any specificity of interaction. In addition, the repeats may differ in sequence among populations, with some specificity in autosomal neutralization based on sequence. This may lead to a combination of both quantitative and specific effects, with selection acting both on the number of repeats and on the sequence composition. In any case, it is clear that the molecular basis of the interaction determines the degree to which variants act quantitatively or specifically, which, in turn, controls key aspects of molecular evolution and the dynamics of variant types over space and time.

Lack of specificity – segregation distorter

Attack and defense invariably favor diversification[1]. A new attack specificity evades defense and spreads quickly. If matching defense specificities arise, they in turn spread to check the novel attack. The biochemical mechanisms that mediate attack and defense determine the limits to diversification[6].

High molecular specificity means that an increase in the effectiveness of defense against one particular attack allele leads to a decline in the effectiveness against other attack specificities. By contrast, low molecular specificity means that an increase in the effectiveness of defense against one attack variant implies an increase against most or all other attack variants. The interaction under low specificity is quantitative, whereas under high specificity the interaction is qualitative.

Box 4. Alternative models of segregation distorter

Current evidence suggests that segregation distorter (SD) lacks specificity in attack and defense (see text). Further studies may or may not uncover some specificity. To understand what studies should be done and how they could be interpreted, it is useful to consider four alternative models. No evidence supports the last three models. However, it is helpful to consider these possibilities, if only to understand why they do not occur.

(1) Attack may be a simple presence or absence polymorphism as implied by the *Sd*/*Sd*$^+$ notation for alternative alleles at a single locus. Defense may, in turn, be a simple quantitative effect of the number of *Rsp* repeats. This model of attack and defense matches the currently available data, but there is certainly more to the story. For example, linked enhancers of *Sd* are needed to produce the full effect of biased transmission of gametes[31]. On the defense side, suppressors of *Sd* can arise quickly by *de novo* mutations throughout the genome[46]. Hiraizumi[47] has observed negative distortion in some crosses, in which an insensitive responder is less successful than a paired chromosome bearing a sensitive responder.

(2) There may be some specificity in the effect of suppressors on *Sd*. If there is high specificity, with small biochemical changes of suppressors causing qualitatively different effects on various *Sd* sequences, then sequence evolution may be rapid. If only a few alternative specificities are possible, then there may be stable polymorphisms of suppressors and *Sd* with relatively slow sequence evolution.

(3) The linkage relations between *Sd* and *Rsp* create interesting interactions. A successful chromosome that can win in competition against other chromosomes must have both the attack allele, *Sd*, and the insensitive defense allele, Rsp^i. If, by contrast, the attack component *Sd* is linked to a sensitive responder, Rsp^s, the attack component will kill its own chromosome. This linkage constrains the ways in which new specificities can arise. A new *Sd* specificity that could overcome the standard insensitive defense, Rsp^i, would kill itself. However, if the linked Rsp^i was a rare, specific variant that could resist the new *Sd* variant, then the linked pair would kill competing chromosomes and spread through the population – this scenario is unlikely because it requires two rare variants to occur on a single chromosome. One possibility is that an Rsp^i with a broader spectrum of specific resistance may arise first, followed by a new *Sd* variant within this broader spectrum of resistance. Although this seems unlikely, a similar, plausible scenario has been suggested for the coevolution of bacteriocin toxins and antitoxins[43] (see Box 1).

(4) The specificities may be of a matching type. Suppose that the responders exist as a series of n types with labels $j = 1,2 \ldots n$. The n different *Sd* attack alleles have matching specificities $k = 1,2 \ldots n$. Here, an Sd_k only kills chromosomes with a matching responder specificity, Rsp_k. Thus an attack allele Sd_k does no harm to its own chromosome if it is linked to a responder of any type except Rsp_k. This allows freedom of the matching *Sd* and *Rsp* specificities to mutate without the linkage constraint of model (3). This sort of matching specificity may occur in several attack–defense systems[2]. If SD lacks such specificity, it will be important to understand why the biochemical details prevent such diversification.

Limited specificity of attack and defense is often observed in spite of the fact that selection invariably favors diversification[27]. In some cases, the low observed diversity simply reflects limited study. Further analysis will uncover additional diversity, as in the case of cytoplasmic male sterility discussed earlier. But, in many cases, systems do seem to lack qualitative diversity – high specificity may in fact be the exception.

The segregation distorter (SD) system of *Drosophila melanogaster* provides a good example of quantitative interactions at the molecular level (see also Box 3 and Ref. 28). SD is a system of autosomal meiotic drive[29]. Two major loci influence gametic success. At the distorter (attack) locus, the *Sd* allele can destroy sperm and the *Sd*$^+$ allele lacks attack capability[30]. At the responder (defense) locus, the *Rsp* allele determines sensitivity to attack: *Sd* kills sperm with sensitive responder alleles, Rsp^s, but does not affect sperm with insensitive responder alleles, Rsp^i (Ref. 31).

A chromosome that has both *Sd* and Rsp^i increases in frequency because it destroys competing sperm that carry sensitive responder alleles. The sensitivity of the *Rsp* locus is a quantitative trait. This locus, in the heterochromatic region of the chromosome, has alleles with varying numbers of 120 bp repeats[32,33]. The greater the number of repeats, the more sensitive the chromosome. Sensitivity is measured by the probability of transmission when paired with a driving (Sd/Rsp^i) chromosome. Insensitive responder alleles are transmitted at the normal mendelian probability of 0.5. The transmission probability of responder alleles declines toward zero as the number of repeats increases.

Defense is a quantitative trait determined by the number of repeats at the *Rsp* locus. There does not appear to be specific interaction of *Rsp* with different attack alleles at *Sd*. The presently available data suggest that this system lacks specificity and consequent diversification (Box 4).

Conclusions

Selection favors diversification of matching attack and defense[34]. Some systems do indeed have widespread, specific polymorphisms[2]. But many cases lack matching specificities[27,31]. Such cases focus attention on how the molecular interactions between attack and defense limit specificity. For example, defense in SD varies quantitatively rather than by qualitative changes of specificity[31].

The degree of specificity and polymorphism in each case is an empirical problem. The conceptual issues outlined here call attention to five points as guides for future work.

First, one should test a system carefully before declaring that it lacks specificity. Detection of matching polymorphism can be difficult[2]. The example of CMS shows how, over time, better tools reveal more detail about the reciprocal interactions of attack and defense.

Second, lack of specificity suggests biochemical or physical limits to diversification.

Third, mechanisms governing the generation of new attack and defense specificities determine whether molecular sequence evolution is fast or slow (Boxes 1–4).

Fourth, the potential for specific diversity strongly influences spatiotemporal dynamics. A rise in the number of matching specificities increases the tendency for genetic turnover across space and time[4–6].

Finally, strong biochemical specificity implies a high potential for genetic diversity. The observed diversity can, however, be high or low, depending on the dynamics and the spatial and temporal scales of observation[6].

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