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Coevolutionary interactions between host and parasite genotypes

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More than 20 years after Dawkins introduced the concept of 'extended phenotype' (i.e. phenotypes of hosts and parasites result from interactions between the two genomes) and although this idea has now reached contemporary textbooks of evolutionary biology, most studies of the evolution of host–parasite systems still focus solely on either the host or the parasite, neglecting the role of the other partner. It is important to consider that host and parasite genotypes share control of the epidemiological parameters of their relationship. Moreover, not only the traits of the infection but also the genetic correlations among these and other traits that determine fitness might be controlled by interactions between host and parasite genotypes.

The 'extended phenotype'

The concept of 'extended phenotype' [1] is now widely used to describe that phenotypes of hosts and parasites result from not only their own genotype but also the genotype of their partner. The potential importance of this concept was shown in a recent theoretical model of host–parasite coevolution that considered that epidemiological traits are controlled by the interaction between the two partners [2]. However, most other theoretical studies of the evolution of host–parasite systems still consider that traits of infection such as host resistance or parasite virulence (see Glossary) are determined by the genotype of either the host or the parasite, but not both. In this article, we review the epidemiological and evolutionary importance of some of the extended phenotypes, review some experimental data supporting the concept and, in particular, argue that not only the epidemiological parameters of a host–parasite relationship but also the genetic correlations of these parameters with host and parasite life-history traits might be controlled by interactions between the two genomes.

Evolutionary models of host–parasite interactions

Most models of the evolutionary processes in host–parasite systems assume that the evolution of attack or defense strategies is governed by the balance of their evolutionary costs and benefits from the point of view of either the parasite or the host and, thus, hold the other partner constant. In other words, they consider that the traits of the relationship are determined by the genotype either of the host or of the parasite. For example, many theoretical studies have modeled the evolution of virulence, a trait that is usually assumed to be controlled exclusively by the parasite [3–7]. Reciprocally, other theoretical studies have focused on the evolution of host defenses [8–12] such as qualitative resistance (reduction of the probability of infection) and tolerance (reduction of detrimental effects of the parasite), ignoring the evolution of the parasite. Recently, more attention has been paid to coevolutionary processes, in which both the host and the parasite are considered to evolve [13–17]. This can lead to an epidemiological feedback, whereby the response to the evolutionary pressure changes the epidemiological situation that is responsible for the evolutionary pressure. But, again, most of these coevolutionary models assume that each trait of the relationship is controlled either by the host or by the parasite.

Exceptions are gene-for-gene and matching-allele models (Box 1), in which the outcome of infection is determined by the specific combination of the host and the parasite genotypes. These models are supported by empirical studies showing that the compatibility of host–parasite systems is often based on genotype-by-genotype interactions (Box 2). In such systems, some hosts are compatible with a subset of parasite genotypes, whereas other hosts are compatible with another subset. However, gene-for-gene or matching-allele models, and experimental studies of genotype-by-genotype interactions usually focus on host–parasite compatibility (i.e. host qualitative resistance or parasite infectivity) and, thus,

Glossary

Gene-for-gene model: genetic model of infection assuming that, for each gene conferring resistance to the host, there is a corresponding gene in the parasite. Only a single combination of one allele of the host and one allele of the corresponding parasite gene prevents the infection (see Box 1).

Genotype-by-genotype interaction: in a host–parasite system, describes the effect of the interaction of host and parasite genotypes on the outcome of infection (i.e. when the infection phenotype comprises a component that is specific to the particular combination of host and parasite genotypes) (see Box 2).

Matching-allele model: genetic model of infection assuming that, for each gene conferring resistance to the host, there is a corresponding gene in the parasite with an equal number of alleles. For each allele of the host gene, only one 'matching' allele of the corresponding parasite gene enables infection to occur (see Box 1).

Virulence: in evolutionary ecology, corresponds to the detrimental effects of parasite infection on host fitness, such as increased mortality rates or reduction in fecundity.

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Box 1. Gene-for-gene and matching-allele models

The gene-for-gene hypothesis, originally formulated by Flor [29], was inspired by patterns of compatibility in plant–pathogen systems [30]. In a simple haploid single-locus gene-for-gene model (Table I), parasites harboring a 'virulence' (V) allele can infect all hosts, whereas parasites harboring an 'avirulence' (A) allele can infect 'susceptible' (S) hosts but not 'resistant' (R) hosts. In this interaction, some parasites can infect a wider range of host genotypes than can their competitors, and some hosts can resist infection by a wider range of parasite genotypes than can other hosts. Note that, in gene-for-gene models, virulence refers to the infectivity of the parasite and, thus, differs from the evolutionary ecology definition of virulence (which is provided in the Glossary).

In matching-allele models, which were inspired by the self–non-self recognition mechanisms that underlie animal immune systems [31], infection occurs when the alleles of the parasite match the corresponding alleles of the host [32]. In a simple haploid single-locus matching-allele model (Table II), parasites harboring a P1 allele can infect only hosts with the matching H1 allele, whereas parasites harboring a P2 allele can infect only hosts with the matching H2 allele. In this interaction, individual hosts are resistant to only a portion of the parasite genotypes and, reciprocally, individual parasites can infect only particular host genotypes. No parasite is best at infecting all hosts, and no host is best at resisting all parasites.

Table I. Host–parasite compatibility in a haploid single-locus gene-for-gene model

Parasite genotype	Host genotype	
	R	S
A	Incompatible	Compatible
V	Compatible	Compatible

Table II. Host–parasite compatibility in a haploid single-locus matching-allele model

Parasite genotype	Host genotype	
	H1	H2
P1	Compatible	Incompatible
P2	Incompatible	Compatible

Box 2. Host genotype by parasite genotype interactions

Assuming no environmental influence, the phenotype of infection traits in a host–parasite interaction (such as host resistance or parasite virulence) is expected to be determined by the host and the parasite genotypes. Host genotype by parasite genotype interactions are measured as the interaction effect in a statistical analysis of the infection phenotype as a function of host genotype and parasite genotype [21,33,34].

Such genotype-by-genotype interactions have been found to underlie the resistance of hosts to their parasites in many host–parasite associations, including plants to their fungal pathogens [30], snails to their schistosome parasites [35], bumble-bees to their trypanosome parasites [36], *Daphnia* to its bacterial parasite *Pasteuria ramosa* [33] and *Anopheles gambiae* mosquitoes to the human malaria parasite *Plasmodium falciparum* [21].

Genotype-by-genotype interactions can be visualized in a graphic representation of the infection phenotype as a function of host genotype (or parasite genotype), with each parasite genotype (or host genotype) being identified by a different line. To facilitate the visualization of interactions, the genotypes indicated on the *x*-axis should be ranked according to the mean value of their infection phenotype. In this type of graphic representation, parallel lines indicate the absence of genotype-by-genotype interactions, whereas non-parallel lines indicate these interactions.

Figure I shows the infection phenotype (e.g. resistance or virulence) in a hypothetical host–parasite association that consists of two host genotypes (A and B) and two parasite genotypes (1 and 2). Figure II shows the graphic representation of genotype-by-genotype interactions underlying the qualitative resistance of mosquitoes to malaria parasites.

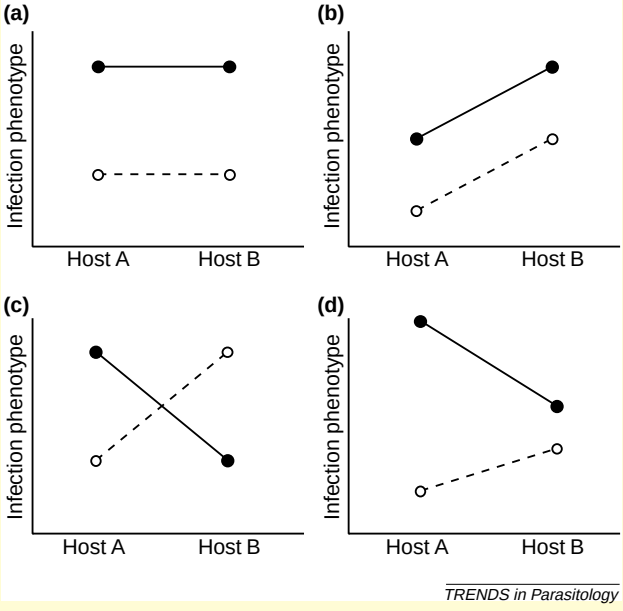

Figure I. Infection phenotype of different hypothetical combinations of two host genotypes and two parasites genotypes. The two host genotypes (A and B) are arranged along the *x*-axis and each line represents one parasite genotype (parasite 1 genotype, black circles; parasite 2 genotype, white circles). **(a)** A main effect of parasite genotype is visualized by the vertical spacing between the two lines. **(b)** A main effect of host genotype is indicated by the positive slope of the lines, in addition to a vertical main effect of parasite genotype. **(c,d)** Host genotype by parasite genotype interactions are suggested by non-parallel lines. In (d), note that main-effect components can cumulate with an interaction.

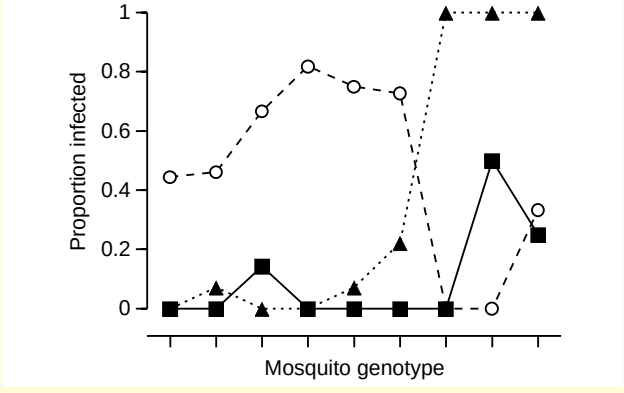

Figure II. Infection prevalence of three genetically different isolates of malaria parasites in nine mosquito genotypes. Nine genetic backgrounds of mosquito (ranked on the *x*-axis) were challenged with three genetically different isolates of *Plasmodium falciparum* (isolate 1, squares; isolate 2, circles; isolate 3, triangles). Although neither the mosquito genotype ($P > 0.5$) nor the parasite isolate ($P > 0.5$) had a main effect on the proportion of infected mosquitoes, the effect of the interaction between mosquito genotype and parasite isolate was highly significant ($P < 0.001$), suggesting a strong genotype-by-genotype interaction (indicated by crossing lines). Figure adapted, with permission, from Ref. [21].

ignore other important epidemiological traits such as transmission or virulence.

Shared control of epidemiological traits

Epidemiological traits were considered in a recent theoretical study of host–parasite coevolution that highlighted the importance of considering that each trait of the relationship is affected by both participants [2]. This model, in which the host and the parasite shared the control of several epidemiological traits (e.g. transmission, virulence and recovery), led to several novel predictions about the evolution of host defense and parasite virulence. In contrast to classical predictions [2], increasing the background mortality rate of the host, for example, can decrease parasite virulence. In addition to this model, there are several experimental studies supporting the idea that host and parasite genotypes share the control of not only compatibility but also every trait of infection.

For example, virulence is a trait of infection that is usually assumed to be determined by the parasite. By definition, virulence includes all effects of the parasite on host life-history traits that are related to host fitness. But, reciprocally, one might expect that some of the host life-history traits are involved in its ability to reduce parasite virulence (i.e. host tolerance to infection). This has been investigated by testing the correlated response of the virulence of the microsporidian parasite *Edhazardia aedis* to the genetic selection on age at pupation of its mosquito host *Aedes aegypti* [18]. In this study, the rate of parasite-induced mortality of the host was higher in mosquito lines selected for late pupation than in lines selected for early pupation (Figure 1). In other words, the level of parasite virulence was determined partly by the genetic basis of mosquito age at pupation. This finding indicates that virulence is not a simple trait controlled by parasite genes alone. Rather, virulence is expressed in several traits due to subtle interactions between the genomes of the host and the parasite. One might, therefore, also expect virulence to

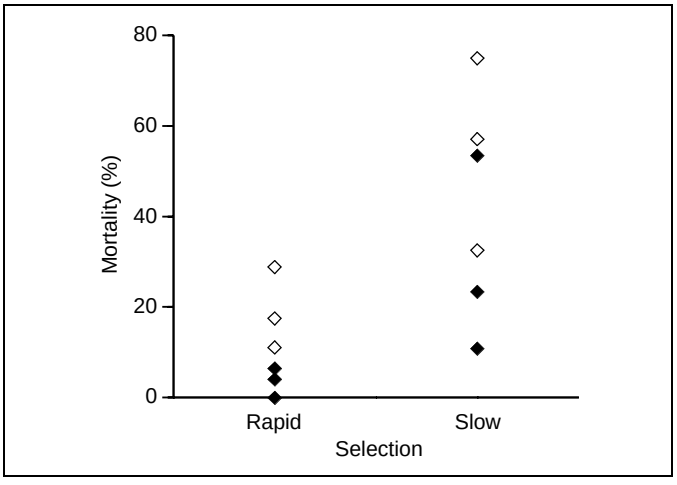

Figure 1. Parasite-induced mortality (percentage dying before emergence) of three lines of mosquitoes selected for early (rapid) pupation (mean 6.9 days) and three lines selected for late (slow) pupation (mean 7.9 days) after four generations of selection. Larvae were exposed to 500 spores mL^{-1} (black diamonds) or 2000 spores mL^{-1} (white diamonds) of the parasite. Modified, with permission, from Ref. [18].

be governed by genotype-by-genotype interactions. However, in the one study in which the weight loss and anemia of two lines of rodent malaria parasites were compared in three genotypes of mice, no evidence of genotype-by-genotype interactions was found [19]. By contrast, other epidemiological traits – particularly resistance – are often governed by genotype-by-genotype interactions (Box 2).

Overall, it is likely that most epidemiological traits of host–parasite relationships (including transmission and recovery) are neither traits of the parasite nor traits of the host, but are controlled by complex interactions between the two genotypes. This should not be fundamentally different if the host is simultaneously infected by several parasite genotypes. Because mixed-genotype infections are not equivalent to the sum of single-genotype infections [20], a mix of parasite genotypes can be considered as a particular genetic entity [21].

Shared control of genetic correlations

A genetic correlation associates negatively or positively two traits that vary together among genotypes. Consequently, the evolutionary response of a trait is likely to be associated with changes in all the traits to which it is genetically correlated. In particular, if two traits that are positively related to fitness are negatively genetically correlated (an evolutionary trade-off), an increase in one trait is linked to a decrease in the other, so fitness cannot be maximized for both traits. Because of their crucial role in the coevolution of host–parasite relationships, genetic correlations are at the center of the theoretical framework of evolutionary epidemiology.

It is worth mentioning again that evolutionary forces operate not only on epidemiological traits but also on every other fitness-related trait. Indeed, genetic correlations between epidemiological traits and life-history traits have been identified. For example, it is possible to select fruit flies genetically for an increased melanization rate of parasitoid eggs, and this correlates with a decrease in larval competitive ability [22]. It has been suggested that a resource trade-off links the higher hemocyte load underlying the higher qualitative resistance to parasitoids and the lower competitive ability [23]. Models that include an evolutionary cost of resistance assume such an evolutionary trade-off between resistance and any other fitness-related life-history trait.

However, such trade-offs need not be constant but can be influenced, in particular, by parasite presence. For example, infection by the microsporidian parasite *E. aedis* influenced the genetic correlations among life-history traits in the mosquito *Ae. Aegypti* [24]. Indeed, there was a positive relationship in some cases between adult size and fecundity in uninfected mosquitoes, whereas infected mosquitoes showed the opposite trend. Genetic correlations between epidemiological and host life-history traits might also be influenced by parasite genotype.

We suggest that not only individual epidemiological traits but also genetic correlations among the traits are under the shared control of the host and the parasite. This means that the genetic correlation between two traits observed within a host (or a parasite) population when

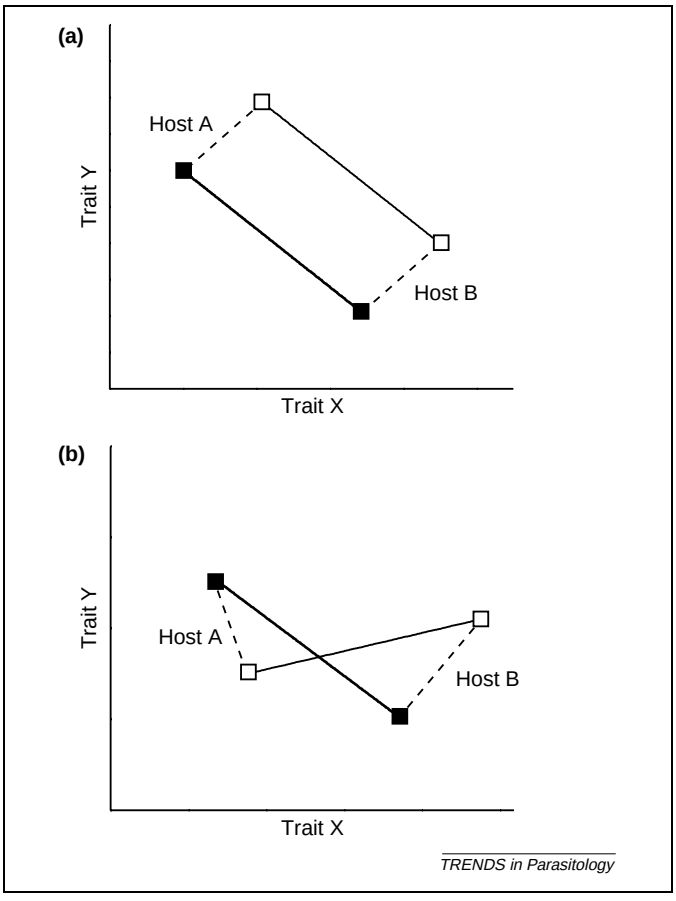

Figure 2. Relationships between two hypothetical traits of two parasite genotypes infecting two host genotypes. The hypothetical traits are assigned arbitrary phenotypic values X and Y; parasite 1 is represented by black squares and parasite 2 is represented by white squares; the host genotypes are referred to as either A or B. Unbroken lines represent the genetic correlations between traits X and Y among hosts infected by parasite 1 (thick line) and parasite 2 (thin line). Broken lines show genetic correlations between parasites. **(a)** X and Y are negatively genetically correlated between hosts, and the slope of the correlation is the same for both parasites. **(b)** X and Y are negatively genetically correlated between hosts infected by parasite 1 and are positively genetically correlated between hosts infected by parasite 2.

interacting with a particular parasite (or host) genotype might be different when interacting with another parasite (or host) genotype (Figure 2). In a moderate case, the value of the slope might vary slightly, whereas in more-extreme cases the slope might switch from positive to negative values (or vice versa). Such a shared control of correlations and trade-offs by host and parasite genotypes has been suggested by a recent study of several populations of *Arabidopsis thaliana* that were infected by two strains of the fungal parasite *Hyaloperonospora parasitica* [25]. In this system, the correlation between host and parasite fitness (seed production and transmission, respectively) depends on the specific combination of host and parasite genotypes. Although host fitness and parasite fitness are negatively correlated when the host genotypes are challenged by one of the two pathogen strains, the correlation is positive (although not in a way that is statistically significant) when the same genotypes of the host are challenged by the other pathogen strain. To our knowledge, these data are the first to suggest that a genetic correlation depends on the interaction between host and parasite genotypes.

In addition to potential genotype-by-environment interactions [26], or even genotype-by-genotype-by-environment interactions [27], a shared control of genetic correlations by host and parasite genotypes might make the evolution of host–parasite interactions much more complex than was previously thought. Nevertheless, it could help to explain some puzzling issues of the evolutionary biology of host–parasite systems. For example, a classical hypothesis underlying theoretical studies of host–parasite relationships is the so-called trade-off model for the evolution of virulence [3]. According to this hypothesis, an increase in the rate of parasite growth is associated not only with an increase in the rate of parasite transmission but also with a decrease in host lifespan (i.e. increased virulence). Because reducing the lifespan of the host is usually detrimental to the parasite, an increase in the rate of parasite transmission is traded off with a minimization of virulence, leading to an optimal level of virulence at intermediate values. Numerous studies have investigated this trade-off experimentally and, although some of them succeeded in identifying the expected correlation, many failed [28]. A possible explanation for this inconsistency of empirical data could be that this trade-off varies according to the combination of host and parasite genotypes.

Future prospects

Following the work of Restif and Koella [2], we emphasize that every epidemiological component of a host–parasite relationship can be controlled by the two interacting genomes. Furthermore, we suggest that genetic correlations such as trade-offs between epidemiological and life-history traits could be controlled by the interactions between host and parasite genotypes. This would have considerable evolutionary consequences for host–parasite coevolution. Indeed, hosts and parasites would reciprocally change the potential for an adaptive response of their partner by modifying the matrix of genetic covariances between life-history and epidemiological traits, leading to complex coevolutionary processes. We hope to encourage future theoretical and experimental studies to explore such interactions and their role in the evolutionary ecology and epidemiology of host–parasite associations.

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References

1 Dawkins, R. (1982) *The Extended Phenotype*, Oxford University Press
2 Restif, O. and Koella, J.C. (2003) Shared control of epidemiological traits in a coevolutionary model of host–parasite interactions. *Am. Nat.* 161, 827–836
3 Anderson, R.M. and May, R.M. (1982) Coevolution of hosts and parasites. *Parasitology* 85, 411–426
4 Van Baalen, M. and Sabelis, M.W. (1995) The dynamics of multiple infection and the evolution of virulence. *Am. Nat.* 146, 881–910
5 Frank, S.A. (1996) Models of parasite virulence. *Q. Rev. Biol.* 71, 37–78

6 Lipsitch, M. *et al*. (1996) The evolution of virulence in pathogens with vertical and horizontal transmission. *Evolution Int. J. Org. Evolution* 50, 1729–1741
7 Day, T. (2004) A general theory for the evolutionary dynamics of virulence. *Am. Nat.* 163, E40–E63
8 Antonovics, J. and Thrall, P.H. (1994) The cost of resistance and the maintenance of genetic polymorphism in host–pathogen systems. *Proc. R. Soc. London Ser. B. Biol. Sci.* 257, 105–110
9 Boots, M. and Haraguchi, Y. (1999) The evolution of costly resistance in host–parasite systems. *Am. Nat.* 153, 359–370
10 Roy, B.A. and Kirchner, J.W. (2000) Evolutionary dynamics of pathogen resistance and tolerance. *Evolution Int. J. Org. Evolution* 54, 51–63
11 Bowers, R.G. (2001) The basic depression ratio of the host: the evolution of host resistance to microparasites. *Proc. Biol. Sci.* 268, 243–250
12 Brown, D.H. and Hastings, A. (2003) Resistance may be futile: dispersal scales and selection for disease resistance in competing plants. *J. Theor. Biol.* 222, 373–388
13 Van Baalen, M. (1998) Coevolution of recovery ability and virulence. *Proc. Biol. Sci.* 265, 317–325
14 Restif, O. *et al*. (2001) Virulence and age at reproduction: new insights into host–parasite coevolution. *J. Evol. Biol.* 14, 967–979
15 Gandon, S. *et al*. (2002) The evolution of parasite virulence, superinfection, and host resistance. *Am. Nat.* 159, 658–669
16 Nuismer, S.L. *et al*. (2003) Coevolution in temporally variable environments. *Am. Nat.* 162, 195–204
17 Koella, J.C. and Boëte, C. (2003) A model for the coevolution of immunity and immune evasion in vector-borne diseases with implications for the epidemiology of malaria. *Am. Nat.* 161, 698–707
18 Koella, J.C. and Agnew, P. (1999) A correlated response of a parasite's virulence and life cycle to selection on its host's life history. *J. Evol. Biol.* 12, 70–79
19 Mackinnon, M.J. *et al*. (2002) Virulence in rodent malaria: host genotype by parasite genotype interactions. *Infect. Genet. Evol.* 1, 287–296
20 Taylor, L.H. *et al*. (1997) Mixed-genotype infections of the rodent malaria *Plasmodium chabaudi* are more infectious to mosquitoes than single-genotype infections. *Parasitology* 115, 121–132
21 Lambrechts, L. *et al*. (2005) Host genotype by parasite genotype interactions underlying the resistance of anopheline mosquitoes to *Plasmodium falciparum*. *Malar. J.* 4, 3
22 Kraaijeveld, A.R. and Godfray, H.C. (1997) Trade-off between parasitoid resistance and larval competitive ability in *Drosophila melanogaster*. *Nature* 389, 278–280
23 Kraaijeveld, A.R. *et al*. (2001) Basis of the trade-off between parasitoid resistance and larval competitive ability in *Drosophila melanogaster*. *Proc. Biol. Sci.* 268, 259–261
24 Koella, J.C. and Offenberg, J. (1999) Food availability and parasite infection influence the correlated responses of life history traits to selection for age at pupation in the mosquito *Aedes aegypti*. *J. Evol. Biol.* 12, 760–769
25 Salvaudon, L. *et al*. Parasite–host fitness trade-offs change with parasite identity: genotype-specific interactions in a plant–pathogen system. *Evolution Int. J. Org. Evolution* (in press)
26 Mitchell, S.E. *et al*. (2005) Host–parasite and genotype-by-environment interactions: temperature modifies potential for selection by a sterilizing pathogen. *Evolution Int. J. Org. Evolution* 59, 70–80
27 Thomas, M.B. and Blanford, S. (2003) Thermal biology in insect–parasite interactions. *Trends Ecol. Evol.* 18, 344–350
28 Ebert, D. and Bull, J.J. (2003) Challenging the trade-off model for the evolution of virulence: is virulence management feasible? *Trends Microbiol.* 11, 15–20
29 Flor, H.H. (1956) The complementary genetic systems in flax and flax rust. *Adv. Genet.* 8, 29–54
30 Thompson, J.N. and Burdon, J.J. (1992) Gene-for-gene coevolution between plants and parasites. *Nature* 360, 121–126
31 Grosberg, R.K. and Hart, M.W. (2000) Mate selection and the evolution of highly polymorphic self/nonself recognition genes. *Science* 289, 2111–2114
32 Agrawal, A. and Lively, C.M. (2002) Infection genetics: gene-for-gene versus matching-alleles models and all points in between. *Evol. Ecol. Res.* 4, 79–90
33 Carius, H.J. *et al*. (2001) Genetic variation in a host–parasite association: potential for coevolution and frequency-dependent selection. *Evolution Int. J. Org. Evolution* 55, 1136–1145
34 Kaltz, O. and Shykoff, J.A. (2002) Within- and among-population variation in infectivity, latency and spore production in a host–pathogen system. *J. Evol. Biol.* 15, 850–860
35 Webster, J.P. and Woolhouse, M.E.J. (1998) Selection and strain specificity of compatibility between snail intermediate hosts and their parasitic schistosomes. *Evolution Int. J. Org. Evolution* 52, 1627–1634
36 Schmid-Hempel, P. *et al*. (1999) Dynamic and genetic consequences of variation in horizontal transmission for a microparasitic infection. *Evolution Int. J. Org. Evolution* 53, 426–434