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PARASITE-HOST FITNESS TRADE-OFFS CHANGE WITH PARASITE IDENTITY: GENOTYPE-SPECIFIC INTERACTIONS IN A PLANT-PATHOGEN SYSTEM

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Abstract.—Simultaneous effects of host and parasite in determining quantitative traits of infection have long been neglected in theoretical and experimental investigations of host-parasite coevolution with the notable exception of gene-for-gene resistance studies. A cross-infection experiment, using five lines of the plant *Arabidopsis thaliana* and two strains of its oomycete pathogen *Hyaloperonospora parasitica*, revealed that three traits traditionally considered those of the parasite (number of infected leaves, transmission success, and time until 50% transmission), differed among specific combinations of host and parasite lines, being determined by the two protagonists of the infection. However, the two parasite strains did not differ significantly for most measured phenotypic traits of the infection. Globally, transmission increased with increasing virulence among the different host-parasite combinations, as assumed by most models of evolution of virulence. Surprisingly, however, there was no general relationship between parasite and host fitness, estimated respectively as transmission and seed production. Only one of the two strains showed the expected significant negative genetic correlation between these two variables. Our results thus highlight the importance of taking into account both host and parasite genetic variation because their interaction can lead to unexpected evolutionary outcomes.

Key words.—*Arabidopsis thaliana*, *Hyaloperonospora parasitica*, oomycete, transmission, virulence.

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How parasites and hosts coevolve is a major question for human health and agriculture. Indeed, understanding and controlling the evolution of parasite virulence (reduction of host fitness due to parasitic infection) and host defenses could help control human, animal, and plant diseases. Many theoretical studies have investigated this field but surprisingly, until recently, most have studied the evolution of host defenses or parasite virulence separately. Even now, models exploring host-parasite coevolution, except one (Restif and Koella 2003), consider that traits are determined either by the host (resistance or recovery) or by the parasite (virulence, infectivity, transmission, etc.). Models of gene-for-gene resistance, in which infection success depends on host and pathogen identity, are a notable exception to this rule (Thompson and Burdon 1992). The same compartmentalization can be observed in experimental studies. Variation in host resistance, parasite virulence, and infectivity, which are necessary for coevolutionary dynamics, have been documented in several studies (Alexander et al. 1993; Sorci et al. 1997; Koskela et al. 2002), but usually separately for hosts and parasites. Where both have been examined simultaneously, however, host and parasite phenotypes relating to resistance, infectivity, and virulence depend on the interaction of particular host and parasite genotypes (Peever et al. 2000; Carius et al. 2001; Kaltz and Shykoff 2002; Webster et al. 2004; Lambrechts et al. 2005). In other words, these traits are controlled by both the host and the parasite.

That both host and parasite determine virulence and transmission phenotypes is particularly relevant for the trade-off theory of optimal virulence. Most models of parasite evolution assume a trade-off between virulence and parasite reproductive capacity (Bull 1994). Virulence is considered an unavoidable consequence of the parasite using host resources to produce its own transmission stages. However, high virulence can also reduce host survival and therefore the duration of transmission; thus, theoretical models predict an optimal intermediate virulence that maximizes transmission while taking this trade-off into account. Transmission and virulence are not linked in all diseases (Lipsitch and Moxon 1997), but most, though not all, experimental studies (Zhan et al. 2002; reviewed in Ebert and Bull 2003) have found evidence for a trade-off between transmission and longevity as a function of increasing virulence. In general, such studies deal with microparasites and report positive phenotypic or genetic correlations between virulence and traits linked to parasite fitness. However, just as for studies of trait variation mentioned above, these studies consider parasite strains or descendents of one strain that evolved under different selection pressures infecting a single host genotype and therefore do not test for possible interactions between host and parasite genotypes for phenotypic expression. Phenotypic traits of host-parasite interactions such as the relationship between virulence and transmission or between host fitness and resistance may often depend on genotype-specific interactions. For example, different shapes of the cost-of-resistance function generate different evolutionary outcomes (Bowers and Hodgkinson 2001; Boots and Bowers 2003), and these may vary across combinations of host and parasite. Thus, when new host and parasite combinations arise this can change the selection regime on host and parasite life-history traits. It is therefore extremely important to access the nature of the relationship of parasite and host fitness trade-offs across a range of host and parasite genotype combinations.

In this study we experimentally investigate how infection phenotypes are controlled by each protagonist and how trade-offs between host and parasite fitness are expressed. We used the plant-oomycete pathosystem *Arabidopsis thaliana–Hyaloperonospora parasitica* to simultaneously compare host and parasite traits in cross-infections between five genotypes of the host and two genotypes of the parasite.

Materials and Methods

Materials

The oomycete *H. parasitica* causes nonlethal systemic infection on its specific host *A. thaliana* (Slusarenko and Schlaich 2003). This parasite reproduces both asexually, via conidiospores produced on the surface of infected leaves, and sexually, via oospores that remain within leaves until host death, then reinfect seedlings' roots the next season. We used two strains of *H. parasitica*, Noco and Emwa, obtained from the Sainsbury laboratory (John Innes Center, Norwich, U.K.). The isolates are routinely maintained as asexual cultures on fresh seedlings of a specific *A. thaliana* line (Columbia [Col] for Noco, and Wassilewskija [Ws] for Emwa). Furthermore, each culture host is resistant to the other isolate, which precludes contamination during culture maintenance (Holub et al. 1994).

Five additional host lines that were susceptible to both strains were used in the experiments. Host lines were generated from one generation of selfing of plants issued from seeds collected on one mother plant in wild populations across Europe: Pyrenees (Pyr), Sweden (Sue), Germany (Ger), Czech Republic (Tch), and England (Gb).

Methods

Each of the five host lines (Pyr, Sue, Ger, Tch, and Gb) was subjected to three treatments: inoculation with Noco spores (10 replicates), inoculation with Emwa spores (10 replicates), and control (mock inoculation without spores, five replicates). Five control plants of the Col and Ws lines and 10 plants of these two lines inoculated respectively with Noco and Emwa spores were added to the experiment as controls for infection success with this inoculation protocol, and kept in the same conditions as the other plants. All the plants used in this experiment were sown the same day in 5 cm $\times$ 5 cm $\times$ 5 cm pots, placed in the dark at 5°C for six days to synchronize germination and then grown in the greenhouse. We inoculated seedlings with four to six leaves 15 to 16 days after germination by putting a 4-μL drop of spores suspension (between 5×10^4 and 1×10^5 spores per mL) on each leaf of the plant (Dangl et al. 1992). Control plants were inoculated with water.

The time between inoculation and the appearance of the first symptoms (latency) was on average one day longer for Noco than for Emwa on these host lines. Therefore we inoculated with Noco on day 1 (with two control replicates) and with Emwa on day 2 (with three control replicates) to ensure that the first symptoms would appear on about the same day. After inoculation each plant was placed in its own transparent plastic cylinder to maintain high humidity and avoid contamination, and its position was randomized in a growth chamber at 13.35°C $\pm$ 2°C average temperature, 10: 14 light:dark photoperiod, and 98% average hygrometry. Position of each plant within the growth chamber was subsequently changed regularly.

From day 7 to day 30 we recorded the number of leaves bearing conidiospores on each inoculated plant and the transmission ability of the parasite in three of the 10 inoculated replicates on each of the host lines from wild populations and five of 10 for lines Col and Ws at three- or four-day intervals as follows. On each observation day we sprayed water on the inoculated plant from above while holding it 10 cm above another pot containing three test plants of the same host line at the four- to six-leaf stage. New test plants were used for each transmission test. Transmission success was estimated as the total number of infected leaves on the three test plants after eight or nine days. Plants not used to measure transmission were similarly misted with water. We measured transmission success nine times over the life span of the infection. Total transmission over the 30-day period was estimated as the asymptote of the sigmoid curve fitted to the transmission data, and the time until 50% of total transmission was estimated using the same sigmoid curve. After 30 days no more infected leaves appeared.

On day 37 all plants were moved to warmer conditions at a longer photoperiod and kept until their death. For each plant we then counted the number of fruits and the number of seeds in the three lowest fruits of the primary inflorescence. Total seed production was estimated as the product of average seeds per fruit and fruit number. For each host line and parasite strain combination, we estimated parasite virulence as the difference between average seed number of control plants of the same host line and of the inoculated plants.

Statistical analyses were performed with the SAS statistical package (ver. 9.1, SAS Institute, Cary, NC), testing for host line, parasite strain, and interaction effects with analysis of variance tests (procedure GLM) for parasite transmission and time until 50% transmission (with three replicates of each combination), and for the number of infected leaves (with 10 replicates for each combination). We compared seed production among host lines and among the three inoculation treatments (two parasite strains and controls) and their interaction using 10 replicates for each combination with parasite treatment and five replicates for control plants of each host line. Transmission and time until 50% transmission were log-transformed to obtain normally distributed residuals.

To test the relationship between parasite transmission and virulence, and between host and parasite fitness (seed production and transmission respectively) we employed analyses of covariance (ANCOVA; procedure GLM), using the centering option for the covariable in the interaction term. This option centers the means to zero by subtracting the mean for its parasite strain from each datum. This procedure therefore compares means rather than intercepts for the main effects as well as testing whether the slopes of these relationships differ between parasite strains. For both relationships we used the means for each host and parasite combination, thereby calculating genetic correlations. Furthermore, we included the data for Noco infecting Col and Emwa infecting Ws, even though the reciprocal combination was not available, because we did not test for host line effects.

Results

Phenotypic Traits of the Infection

Of the 120 plants inoculated with one of the parasite strains, 84.2% showed disease symptoms, that is, bore conidiophores. None of the 10 plants of the host line Ger in-

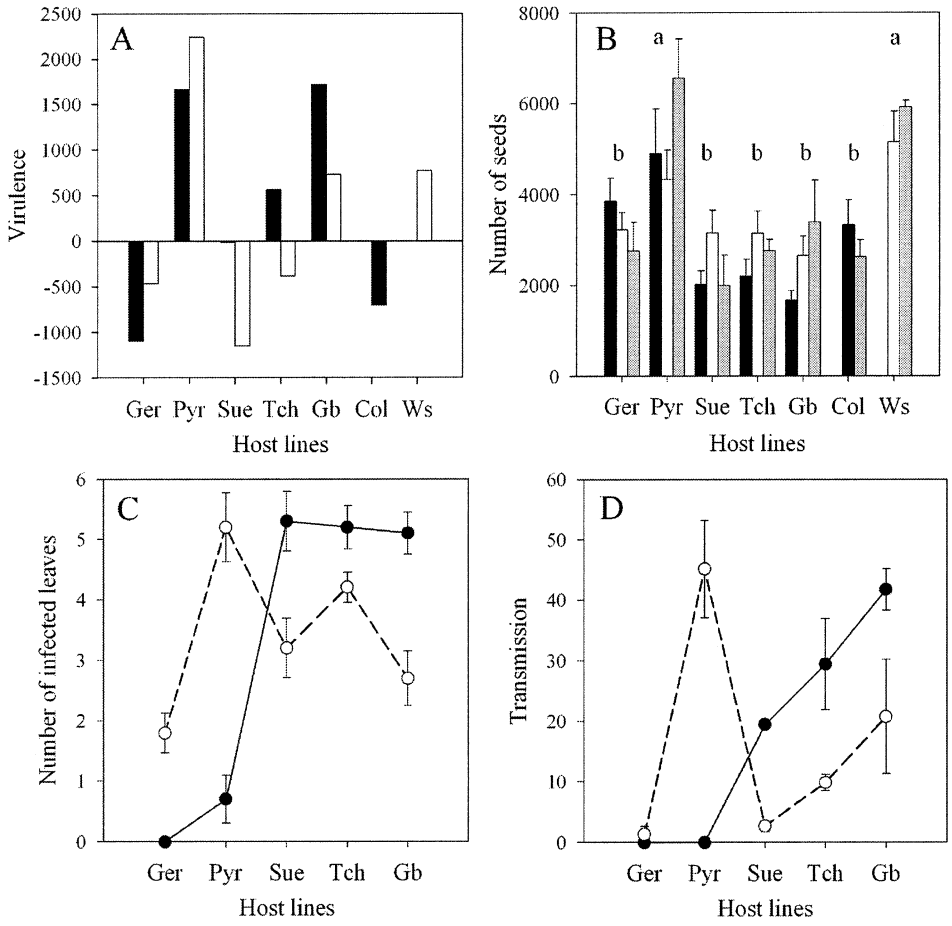

FIG. 1. Phenotypic traits of infection across host and parasite lines: (A) Virulence measured as the difference between the mean seed production of control and inoculated host plants; (B) mean (±SE) seed production of inoculated host plants (hosts lines with the same letter did not differ significantly); (C) mean (±SE) damage in number of sporulating leaves on the inoculated host plants; (D) mean (±SE) transmission: number of sporulating leaves on secondary infected test plants. Black bars or symbols, Noco; white bars or symbols, Emwa; gray bars, controls.

oculated with Noco produced symptoms of the infection. No plants died during the experiment.

We found negative values for virulence in some cases (Fig. 1A). Indeed, the mean difference between uninfected and infected plants was negative for the Ger host line, for Sue and Tch lines infected by Emwa, and for Col lines (infected by Noco). Thus, in these combinations hosts had on average an increased seed production when infected.

Host lines varied significantly for every other phenotypic trait of the infection (Figs. 1B, 1C, and 1D; Tables 1, 2, and 3), and host lines changed in their ranking across traits, with no globally inferior or superior host lines.

Only the time until 50% transmission differed between parasites strains, with Noco performing its transmission faster than Emwa.

All characters except the number of seeds varied as a function of the host and parasite combination as revealed by significant interaction terms (Tables 1, 2, and 3). Figure 1 (C and D) shows reaction norms of the two *H. parasitica* strains

TABLE 1. Analyses of variance testing the effect of host line, parasite strain, and interaction on transmission and time until 50% transmission (using a logarithmic transformation).

		Transmission		Time until 50% transmission	
Source	df	Type III SS	*F*	Type III SS	*F*
Host line	4	31.07	23.53***	16.86	25.90***
Parasite strain	1	0.07	0.21^{ns}	2.85	17.52***
Host × parasite	4	30.07	22.77***	4.87	7.48***
Error	20	6.60		3.26	

ns, $P > 0.05$; *** $P < 0.001$.

TABLE 2. Analyses of variance testing the effect of host line, parasite strain, and interaction on the number of sporulating leaves (10 replicates).

		Number of sporulating leaves	
Source	df	Type III SS	*F*
Host line	4	181.94	28.59***
Parasite strain	1	0.64	0.40^{ns}
Host × parasite	4	172.66	27.13***
Error	90	143.20	

ns, $P > 0.05$; *** $P < 0.001$.

TABLE 3. Analyses of variance testing for the effect of host line, parasite strain (Emwa, Noco, or control), and interaction on the variable number of seeds (10 replicates).

Source	df	Number of seeds	
		Type III SS	*F*
Host line	4	124804745	11.59***
Inoculation type	2	6355759	1.18^{ns}
Host × parasite	8	38156166	1.77^{ns}
Error	110	296066422	

ns, $P > 0.05$; *** $P < 0.001$.

across the five host lines. Emwa transmission and number of sporulating leaves were higher than those of Noco on Pyr and Ger lines but lower on the other host lines. These three variables—transmission, number of sporulating leaves, and time until 50% transmission—generally considered as phenotypic traits of the parasite, were in this case determined by the genotype-specific interaction between host and parasite. In contrast, parasite virulence and host fitness (number of seeds) depended only on host identity.

Transmission-Virulence Correlation

Parasite fitness, estimated as transmission, increased with increasing virulence when considering all combinations of infections (ANCOVA on transmission, virulence effect: $F_{1,8} = 6.24$, $P = 0.037$), revealing a positive genetic correlation between these two variables (Fig 2A). There was no difference in transmission between the parasite strains (parasite strain effect: $F_{1,8} = 0.07$, $P = 0.79$), nor was there a significant difference in the slope of this relationship for the two parasite strains (parasite × virulence interaction: $F_{1,8} = 1.80$, $P = 0.22$).

Correlation between Host and Parasite Fitness Estimates

Host fitness, estimated as seed production, varied neither with parasite fitness overall (ANCOVA on seed production, transmission effect: $F_{1,8} = 1.45$, $P = 0.26$) nor between parasite strains (parasite strain effect: $F_{1,8} = 2.78$, $P = 0.13$), but the slope of the relationship between host and parasite fitness differed between the two parasite strains (parasite × transmission: $F_{1,8} = 19.83$, $P = 0.0021$). Host fitness decreased with increasing parasite fitness when infected with the strain Noco but increased, though not significantly, when infected with Emwa (Fig. 2B).

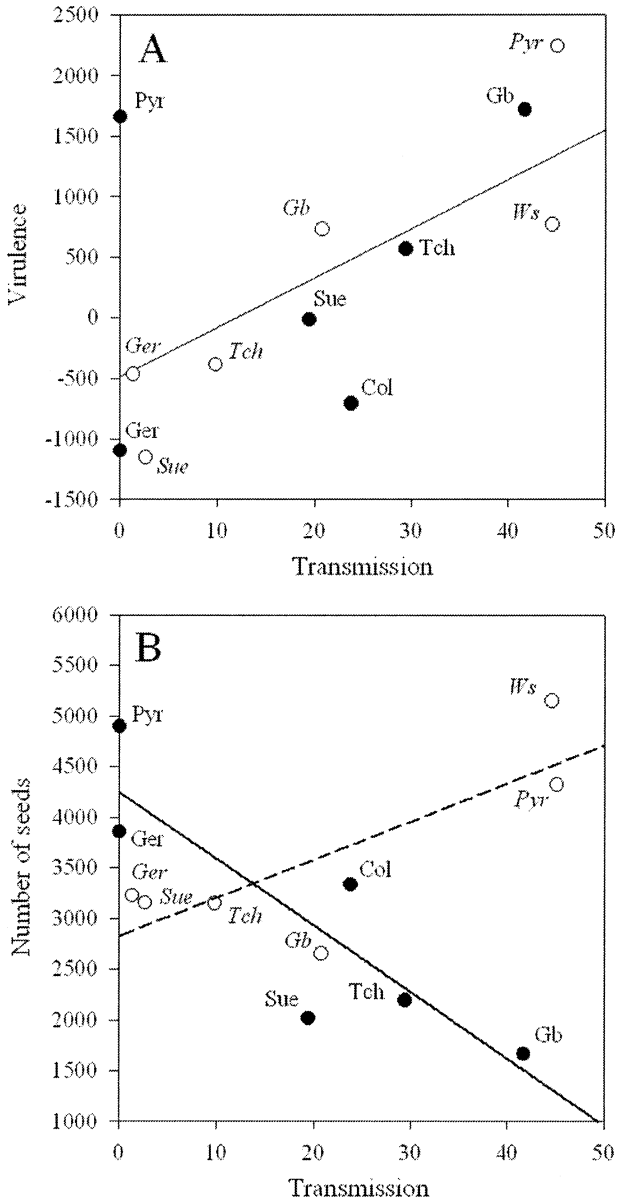

FIG. 2. Genetic correlations between (A) parasite transmission and virulence: regression line $y = 40.868x - 491.66$ ($r^2 = 0.39$), the slope is significantly positive ($P = 0.029$), and (B) parasite transmission and host seed production: regression line for Noco infections (solid line) $y = -65.594x + 4245.7$ ($r^2 = 0.75$) the regression is significantly negative ($P = 0.025$); regression line for Emwa (dashed line) $y = 37.657x + 2828.1$ ($r^2 = 0.65$), the regression is not significantly positive ($P = 0.054$). Each symbol represents a unique combination of host and parasite lines. Black symbols, combinations with the parasite strain Noco; white symbols, combinations with the parasite strain Emwa.

DISCUSSION

Variability and Interaction on Phenotypic Traits

We found variability among host lines for all the phenotypic traits we measured. Such variability in hosts has already been documented in many studies, most often for traits such as resistance, susceptibility, or tolerance (reviewed in Carius et al. 2001; Webster et al. 2004). Indeed, in this particular pathosystem, variability of susceptibility in *A. thaliana* and of infectivity in *Peronospora* (=*Hyaloperonospora*) *parasitica* has already been demonstrated (Holub et al. 1994). Here we used only host lines already known to be susceptible to the two strains of *H. parasitica* employed. However, although variation in susceptibility and infectivity was not expected, one combination of infection, Ger plants inoculated with Noco, failed to produce any conidiospore. Nonetheless the percentage of successfully infected plants in all the other combinations was close to 100%, and exclusion of the Ger line did not qualitatively change the results, with all interactions remaining significant.

None of the traits usually considered ''parasite traits,''

except the time until 50% transmission, varied between parasite strains, but this is probably due to the small number of strains tested. We employed laboratory strains in this study that have been maintained through serial inoculation of young *A. thaliana* plants for hundreds of asexual generations. One could imagine that selection under such conditions could have homogenized the different parasite strains for important life-history traits. However, this was clearly not the case, because three important life-history traits—transmission, number of sporulating leaves, and time until 50% transmission—varied significantly among specific combinations of host and parasite. These results are particularly noteworthy in the context of many theoretical models of host parasite coevolution. Indeed, in many such models, transmission and virulence are fixed for a particular parasite, whereas resistance or tolerance are fixed for a particular host regardless of the host and parasite combination. Such lack of plasticity of host and parasite phenotype across a range of antagonists clearly is not the case in our system, and we wonder about the generality of these model assumptions for hosts and parasites in general (see also Carius et al. 2001; Kaltz and Shykoff 2002).

Such genotype-specific interactions are encountered in theoretical models of coevolution under a gene-for-gene resistance mechanism. In these models, infection success depends on both host and parasite genotypes, requiring the combination of particular susceptible alleles in the host and virulence allele in the parasite. Many studies have found genes implicated in this mechanism of resistance in the pathosystem *A. thaliana–H. parasitica*, and to date 28 loci of *A. thaliana* involved in *H. parasitica* recognition are reported (Slusarenko and Schlaich 2003). Our results demonstrate that not only the success of infection but also quantitative traits of parasite transmission and host damage depend on genotypic combinations in this parasitic interaction.

Negative Virulence

We unexpectedly found that five of 10 infection combinations expressed negative virulence, with infected plants producing on average more seeds than did uninfected controls of the same host line in the same growing conditions. Infected plants bear a down of conidiophores on the surface of infected leaves (imparting the parasite's common name ''downy mildew''). These leaves necrose (Holub et al. 1994) and are lost to the host more rapidly than are uninfected leaves. Furthermore, this parasite is systemic, and unseen hyphae inside host tissues might cause other damage. Thus, it is unexpected that infected plants attain higher fitness than controls despite all infection damage. Both parasite strains in our experiment imparted higher host fitness on infection of some host lines. Host lines, however, appeared to vary in their ability to profit from parasite infection, with some enjoying positive effects of infection regardless of the parasite strain, others always suffering from infection, and one host line (Tch) experiencing positive or negative effects depending on the infecting parasite strain.

One hypothesis to explain these results is that under low infection intensity hosts overcompensated for damage caused by the parasite. Overcompensation is well known in some plant-herbivore interactions, and increased fruit production after apical meristem damage has already been described in some lines of *A. thaliana* (Weinig et al. 2003a). Fitness increase following herbivore damage may be due to modified plant architecture and resource allocation patterns, but this remains unclear (Stowe et al. 2000). In host-parasite associations, mechanisms for tolerance and overcompensation are poorly understood, but an increase in fitness by infected plants, explained as a cost of tolerance, is known (Simms and Triplett 1994). More generally, interactions between plants and certain parasites, such as endophytic fungi, may range from parasite to mutualist (Saikkonen et al. 1998).

It is also possible that resistance mechanisms such as systematic acquired resistance, demonstrated to protect *A. thaliana* against *H. parasitica* (Slusarenko and Schlaich 2003) if induced by *H. parasitica* in young plants, might confer increased resistance against other enemies or stresses, thereby reducing later fitness losses during flowering and seed production.

The evolutionary consequences of negative virulence in our system are intriguing. Although some hosts benefited from some infections, implying that selection would not necessarily favor resistance, both parasite strains performed better when they induced higher costs to their host. Parasites are thus selected to increase rather than decrease their virulence, and negative virulence may be transitory.

Genetic Correlations between Hosts and Parasites

The trade-off hypothesis is a key assumption of every model of parasite evolution. Virulence is considered a consequence of the production of transmission stages, so experimental tests have examined traits linked to transmission among parasite strains that differ in virulence or virulence among strains differing in transmission ability. To date, these genetic correlations have been tested only across parasite strains infecting the same host or parasite species on their specific hosts (Ebert and Mangin 1997; Lipsitch and Moxon 1997; Taylor et al. 1998; Turner et al. 1998; Mackinnon and Read 1999; Messenger et al. 1999; Davies et al. 2001; Elena 2001; Jakel et al. 2001), thereby ignoring the potential interaction effects on parasite phenotypic expression. Here, each of our five host lines, taken independently, showed the expected trade-off—albeit with only two observations corresponding to the two parasite strains. In all five cases, host seed production was lower when the host was infected with the parasite with higher transmission than with the parasite with lower transmission success (see Fig. 2B). However, parasites changed their performance ranking across host lines. On the host lines Sue, Tch, and Gb the parasite strain Noco transmitted better than Emwa, whereas the opposite occurred on the hosts Pyr and Ger. This interaction had no consequence on the correlation between virulence and transmission, which was positive regardless of the parasite strain and thus supported the trade-off hypothesis, but led to a differential trade-off between host fitness and parasite transmission for Emwa and Noco.

These results therefore may give new insights into the evolution of host-parasite interactions, with different points of view depending on which protagonist is considered. For

an infected *A. thaliana*, whatever its genotype, there was always a negative correlation between host and parasite fitness and a positive correlation between virulence and transmission. Indeed, it was always better for the host to be infected with the pathogen strain that transmitted less successfully because this host produced more seeds and suffered less from the infection. The host's point of view was then consistent with the trade-off hypothesis, and any reduction of parasite transmission benefited the host.

In contrast, for both strains of *H. parasitica* considered, parasite fitness always increased with increasing virulence. However, the two strains studied in this experiment differed in the relationship between their transmission and host fitness. For Noco, higher virulence implied higher transmission success and lower seed production by infected hosts. This strain behaved as expected by the trade-off hypothesis, with parasite transmission imparting a real cost to its host. For Emwa, higher virulence was similarly associated with higher transmission success but not with an absolute decrease in host fitness. Host lines on which Emwa was the most successful suffered higher virulence but were globally extremely fecund (Fig 1B); thus, even when their seed production was greatly reduced by parasite infection they still produced more seeds than did other lines. This effect of fecundity variation among host lines resulted in the absence of a relationship between host fitness and parasite fitness for Emwa.

Relevance for the Real World

In this experiment we confronted parasite strains with host lines that they were unlikely to have encountered before, from distinct geographic regions. The phenotypes of these untried combinations of host lines and parasite strains reflect parasite strategies when they are confronted with novel host genotypes. However, encounters with such novel host genotypes may not be such an uncommon situation for a parasite, especially in the pathosystem of this study. *Arabidopsis thaliana* populations are patchy, probably ephemeral, and highly differentiated genetically for both neutral and selected loci (Weinig et al. 2003b). Genetic similarity is poorly explained by geographical proximity (Jorgensen and Mauricio 2004; Stenoien et al. 2005); thus, immigrants or new colonizers may be genetically quite distinct from resident plants, and parasites may regularly be confronted with genetic novelty.

In conclusion, our results generally support the trade-off hypothesis, but different strategies among parasite strains in interaction with particular genotypes exist. Recent studies have also highlighted the importance of genotype-by-environment interactions (Thomas and Blanford 2003; Mitchell et al. 2005) on the evolutionary outcome of host-parasite associations. Such complex interactions could explain why indirect selection for changes in virulence often fail to obey the expected response even when trade-offs are evident (Ebert and Bull 2003).

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