THE ORIGIN OF SPECIFICITY BY MEANS OF NATURAL SELECTION: EVOLVED AND NONHOST RESISTANCE IN HOST–PATHOGEN INTERACTIONS

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Most species seem to be completely resistant to most pathogens and parasites. This resistance has been called "nonhost resistance" because it is exhibited by species that are considered not to be part of the normal host range of the pathogen. A conceptual model is presented suggesting that failure of infection on nonhosts may be an incidental by-product of pathogen evolution leading to specialization on their source hosts. This model is contrasted with resistance that results from hosts evolving to resist challenge by their pathogens, either as a result of coevolution with a persistent pathogen or as the result of one-sided evolution by the host against pathogens that are not self-sustaining on those hosts. Distinguishing evolved from nonevolved resistance leads to contrasting predictions regarding the relationship between resistance and genetic distance. An analysis of cross-inoculation experiments suggests that the resistance is often the product of pathogen specialization. Understanding the contrasting evolutionary origins of resistance is critical for studies on the genetics and evolution of host–pathogen interactions in human, agricultural, and natural populations. Research on human infectious disease using animal models may often study resistances that have quite contrasting evolutionary origins, and therefore very different underlying genetic mechanisms.

KEY WORDS: Coevolution, parasitism.

Most pathogens that organisms encounter in nature fail to establish infection, and a pathogen infecting one host species (the source host) is less likely to infect potentially novel hosts that are distantly related (Perlman and Jaenicke 2003; Sorenson et al. 2004; Streicker et al. 2010; Longdon et al. 2011). A similar phenomenon is observed within host species, where pathogens are more infectious on hosts from their native population than on hosts from other, novel populations, and are said to show "local adaptation" (Lively 1989; Ward 1992; Ebert 1994; Ebert and Hamilton 1996; Sapp and Loker 2000a; Greischar and Koskella 2007; Hoeksema and Forde 2008). Are these two phenomena related to each other? Can microevolutionary adaptive processes acting at the within-species level explain macroevolutionary patterns across host and pathogen taxa? This question is not new, but has been asked previously in the context of "nonhost resistance," a term used by Heath (1981) to describe resistance

shown by species not considered to be hosts for the pathogen in question and by which they are not normally infected. For example, even though farmers are repeatedly exposed to spores of wheat rust pathogens, they do not get infected by them; humans therefore have nonhost resistance against wheat rust pathogens.

Infection is a property of an interaction between the host and the pathogen, and it is therefore presumptuous to ascribe a failure of infection as being a host property without considering it also a feature of the pathogen. Here, we argue that the failure to infect nonhost species may be the result of pathogen evolution leading to specialization on its own source host species and not the result of host evolution for resistance. We then discuss the implications of this for genetic and evolutionary studies of host resistance.

Because of the extremely diverse contexts and meanings of the words resistance and specificity, we first delimit our use of these terms. We define host specificity as variation among host species or genotypes in their performance (or reaction) following exposure to a pathogen; similarly, we define pathogen specificity as variation among pathogen species or genotypes in their performance on a host. We focus primarily on the phenotypic traits of resistance in the host and infectivity of the pathogen at the among-species level, and use the term specificity in a descriptive context, independently of the evolutionary processes leading to it. Specificity in resistance is evidenced from infection experiments where the host species or genotypes differ in the degree to which they can be infected by a pathogen that they are tested against. The inverse of resistance is susceptibility. Similarly, specificity in infectivity is evidenced by differences among the pathogen species or genotypes in their ability to infect a given host. Specificity is often studied as a matrix showing the infection success in different host and pathogen species or genotype combinations. By virtue of its statistical nature, specificity can only be evaluated within the panel of host and pathogen species included in the study, and different panels may reveal different levels of specificity.

We use the term "resistance" to mean the ability of a host to prevent infection or reduce the likelihood of infection, and "infectivity" as the ability of a pathogen to infect and grow or multiply in a host, regardless of the severity of the resulting disease. Note that in plant pathology infectivity is usually termed "virulence." Although the words resistance and infectivity have acquired a wide range of meanings, we use them here as complementary concepts that are operationally measurable by the proportion of hosts that are infected following challenge by a pathogen; given our use of the word, for a specific host–pathogen combination, resistance is the inverse of infectivity.

In the context of this article, we make no conceptual distinction between pathogens and parasites, and these terms could be used interchangeably. However, for consistency we use the term "pathogen" throughout the text.

THE EVOLUTION OF PATHOGEN SPECIFICITY IN INFECTION

We begin by presenting a phenomenological scenario of a host population being initially exposed to a pathogen it has not previously encountered in the past and we call the host that is challenged by the pathogen the "novel" host. Two evolutionary forces will act when pathogens successfully infect a novel host. First, there will be selection on the pathogen for increased performance on the novel host. This includes both the ability to infect, grow, and reproduce in this host as well as the ability to transmit and reproduce on other members of the host population. Second, there will be selection for the host to minimize or avoid the negative effects of the pathogen, including selection for resistance. The pathogen in turn may then adapt to overcome these new resistance mechanisms; this is the beginning of a coevolutionary process that is likely to lead to the host and the pathogen becoming more and more specific to each other's genetic make-up. The mechanisms of specialization have been extensively discussed not only for pathogens (Kawecki 1998; Johnson et al. 2009), but also in the context of plant herbivores (Fox and Morrow 1981; Bernays and Graham 1988; Jaenike 1990). The evolution of pathogen specialization may include adaptation to the biochemical features of the new host that are effective in defense, to the host's life-history features, to the external abiotic and biotic environment of the host, and to the host's symbiont community.

During continuing host–pathogen coevolution, there will be selection for increased resistance in the host, and this in turn will likely select for specific responses by the pathogen. If there are trade-offs between pathogen performance on the new host and performance on the source host, these processes may lead to further specialization. Even in the absence of an evolutionary response of the host (e.g., in the case of low virulence), the pathogen is likely to adapt more and more to specific features of the new host, thereby diminishing its performance on other potential hosts. This has been repeatedly shown to occur in passaging experiments where pathogen adaptation on a new host leads to a loss of infectivity in the former host (Ebert 1998), although the magnitude of the effects can be variable (Ciota and Kramer 2010). As a consequence of this process, pathogens will be able to infect fewer and fewer of those species with which they do not interact, that is, allopatric species as well as former source host species. Host shifts are predicted to occur mainly between closely related host species (Davies and Pedersen 2008); when host shifts are noticed that occur across kingdoms (Van Baalen et al. 2007), they often result in headline news. At a practical level, assessment of the safety of biological-control agents involves "'relatedness procedures" that test if phylogenetically related nontarget species are likely to be attacked by the control agent (McEvoy 1996). Thus, we hypothesize that the macroevolutionary pattern of widespread nonhost resistance may be explained by microevolutionary events

of the pathogen rather than by host evolution of resistance toward that pathogen. This idea follows Heath's (1981) conjecture that mechanisms of resistance for source hosts and nonhosts represent fundamentally different phenomena and are therefore based on different genetic mechanisms.

A corollary to the above is that, if a pathogen is currently able to infect a host, it may do so in part by having genes that are specific to this host population (Thordal-Christensen 2003). We would therefore expect that if the infectivity of a set of pathogens is tested on a particular source host, there will be on average a decline of infectivity with decreasing phylogenetic relatedness among the pathogens. We say "on average" because clearly quite unrelated pathogens (e.g., protozoa and helminths) can sometimes infect the same host. The infectivity of parasitic nematodes on various *Drosophila* species is consistent with this prediction (Perlman and Jaenike 2003). Additionally, studies of cross-species transmission or host-shifts show that similar pathogens are more likely to occur on related host species (Charleston and Robertson 2002; Davies and Pedersen 2008; Streicker et al. 2010; Kitchen et al. 2011; but see Roy 2001; Ronquist and Liljeblad 2001). Thus, the predictions made for the effect of phylogenetic distance of different pathogens tested on one host are similar to those for the effect of phylogenetic distance of different hosts challenged with one pathogen. However, there is obviously variation in these patterns. Two pathogens with distant but equal relatedness to the focal pathogen may still differ strongly with respect to the genes responsible for their interaction with the host. Over short phylogenetic distances this can lead to patterns where other factors such as biogeography, ecology, or physiology explain specificity better than relatedness. For example, in *Bursera* the presence or absence of secondary plant compounds (Beccera and Venable 1999) explained specificity of feeding by the beetle *Blepharida* better than relatedness. In RNA sigma viruses, in addition to phylogenetic distance from the source host, relatedness among the *Drosophila* hosts was also a factor in the success of cross-species infections (Longdon et al. 2011).

THE EVOLUTION OF RESISTANCE IN HOSTS

Hosts are expected to evolve resistance when they regularly encounter a pathogen that impairs their fitness. We distinguish two scenarios for host evolution of resistance. The first scenario occurs when the pathogen has a self-sustaining and evolving population on the host. In this case, we expect not only adaptation of the pathogen to the host, but also adaptation of the host to the pathogen. In this microevolutionary scenario, host populations closely related to the source host population may possess the gene variants necessary for such resistance, but these variants have not been subject to selection and their frequency is likely to be low. Because gene variants are less likely to be shared by more distantly related hosts of the same species, we expect a
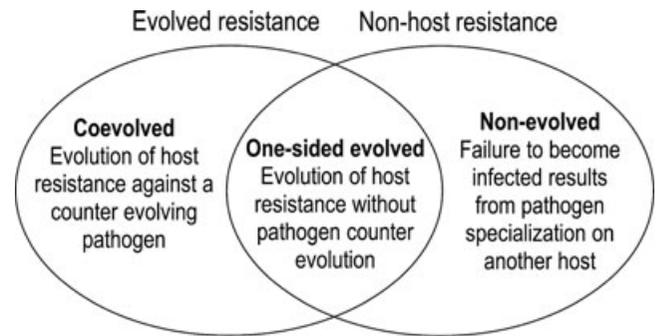

Figure 1. Types of resistance discussed in the text, classified according to the selective forces that result in their evolution.

genetic-distance component to be also present, with more distantly related host populations being less resistant to the pathogen of the source host population. Resistance to human malaria provides a good example for evolved resistance. The high frequency of the sickle-cell alleles in central Africa is the result of evolved resistance of humans against the malaria pathogen *Plasmodium falciparum*; similarly, the high frequency of Duffy-negative blood group antigens in sub-Saharan Africa is likely to be a consequence of selection for resistance against *P. vivax* (Hedrick 2011).

A second scenario for the evolution of resistance occurs when the host is a dead-end for the pathogen, such that infection produces no or too few transmission stages to maintain the pathogen population without an alternative host. In this case, the host may be expected to evolve resistance because of the negative effects of the infection, but there would be no or negligible counter adaptation of the pathogen to the novel host because its evolutionary trajectory is determined by the source host on which the pathogen is sustained (Holt and Gomulkiewicz 1997). There is then a one-sided evolutionary dynamic of host resistance rather than a coevolutionary process, and possibly an appearance of "pathogen maladaptation" (Kniskern et al. 2011). In contrast to the coevolutionary scenario where the host and pathogen effects are expected to become more and more specific, during one-sided evolution of host resistance, any variant with increased resistance will spread regardless of whether it has a highly generalized or specific defense. Thus, one-sided evolution of host resistance can be highly variable and on average we expect it to be less specific and act generally toward different pathogen genotypes in contrast to resistance arising from a coevolutionary scenario. If more than one pathogen genotype or species attacks the host, then we expect that selection will lead to general resistance mechanisms that can protect the host against multiple pathogens. Thus, nonhost resistance may be of two kinds (Fig. 1). First, it may be the result of pathogen specialization on the source host, and therefore "nonevolved" (in that the inability to infect a novel host is a property of the pathogen, not an evolved trait of that host). Second, it may be the consequence of "one-sided evolution" on the part of the host to infrequent,

nonself sustaining but repeated challenges by the pathogen, where the pathogen does not counter evolve.

In plant pathology, there has been the view that nonhost resistance is "highly effective and durable" and therefore of especial interest to plant breeders attempting to generate varieties whose resistance cannot be overcome by pathogen evolution (Thordal-Christensen 2003). However, when nonhost resistance is the result of pathogen specialization, it is likely to be a phantom that does not represent any particular host traits; correspondingly predictions about its durability may depend more on features of the pathogen than those of the host. When nonhost resistance is the result of one-sided evolution, studies of nonhosts are likely to identify generalized features of resistance, effective against a broad range of pathogen challenges. However, it would seem that few predictions could be made about the durability of such resistance with respect to pathogens that are already present and evolving on the crop host.

Nonself sustaining infections are common in humans. The potential of such infections to act as a continuous, but one-sided, selective force on the human immune system is evidenced by the large number of opportunistic infections in immunocompromised patients, as well as by the fact that of the 1400 or more organisms known to cause disease in humans, the majority are considered to be zoonoses and less than a quarter are epidemiologically self-sustaining (Taylor et al. 2001). Similar processes are likely to be equally common but to go unobserved in natural populations. We know of no studies that have directly tested for evidence of such "one-sided" evolution leading to resistance in natural populations, although it has been demonstrated in phage-bacteria experimental systems (Paterson et al. 2010).

In summary, evolved resistance, regardless of whether it is a result of coevolution or one-sided evolution, results from selection of the host as a result of infection by pathogens. It requires prolonged contact (sympatry) of hosts and pathogens and typically cannot explain resistance to allopatric pathogens.

COMBINING NONHOST AND EVOLVED RESISTANCE INTO ONE PICTURE

The previous sections posited two fundamentally different evolutionary mechanisms that can lead to the failure of infection, indicating that the term resistance is being used to describe very different phenomena. First, pathogen specialization to the source host may account for the failure of infection in hosts that are ecologically or phylogenetically distant from the source host. Second, exposure of hosts to a pathogen will lead to the evolution of resistance, but the level of specificity is likely to differ depending on whether the pathogen is or is not coevolving with the host. Both models make a prediction about the change of resistance across a gradient of genetic distance but, importantly, the predictions are in opposite directions.

There is no unambiguous term for the first kind of host resistance where failure to become infected results from the evolution of pathogen specialization. This resulted in extensive discussions among us as authors as well as with reviewers. We will call this type of host resistance "nonevolved resistance" to distinguish it as a type of nonhost resistance. We present a Venn diagram to clarify this terminology (Fig. 1).

For any specific host–pathogen combination, it is difficult to say if any resistance that is observed is the result of evolution of the host (coevolution or one-sided evolution) or if it is nonevolved and the result of pathogen specialization. Ideally (as in testing many evolutionary hypotheses) one would like to be able to rewind the past and have knowledge of antecedent states and ecologies; for example, it would be hard to determine if resistance has evolved to a pathogen that is recently extinct. It is, nevertheless, possible to make some general a priori inferences based on present-day patterns. Nonevolved resistance of a host is expected to increase with increasing genetic distance from the source host (Fig. 2A). On the other hand, evolved resistance (whether by one-sided host evolution or coevolution) is expected to decrease with genetic distance (Fig. 2B) because potential hosts that are less closely related to the source host or which are allopatric would not be expected to have evolved resistance. A simple example is the frequency of the sickle-cell allele in Africa; it is high where malaria occurs, but low in Europe where malaria is rare or absent, and more distantly related hosts (e.g., Europeans) are on average more susceptible. However, a relationship like the one in Figure 2B may not be visible because it is confounded with nonhost resistance. This is illustrated in Figure 2C that combines the patterns produced by the two models, assuming the two types of resistance act additively.

Variation around the mean close to the source population is likely to be high, because there may be polymorphisms for resistance in the source host, or some intermediate level of resistance depending on the shape of the resistance-fitness trade-off curve (Best et al. 2009). Therefore, in Figure 2B we have for illustration arbitrarily set the origin at approximately 0.5, but any value below 1 is possible.

The situation where there is coevolution, as opposed to one-sided evolution, needs further qualification as the expectations depend on whether, in the populations of interest, host or pathogen are currently the "winners" in the situation. Where hosts evolve resistance more quickly than pathogens evolve infectivity, resistance should decline with increasing genetic distance (as in Fig. 1B); however, where pathogens are winners (there is pathogen local adaptation), resistance may increase with increasing genetic distance, at least initially.

To distinguish the consequences of coevolved from one-sided evolution would require careful choice of comparisons; for example, patterns in dead-end hosts could be compared with patterns from hosts where the same or related pathogen can be
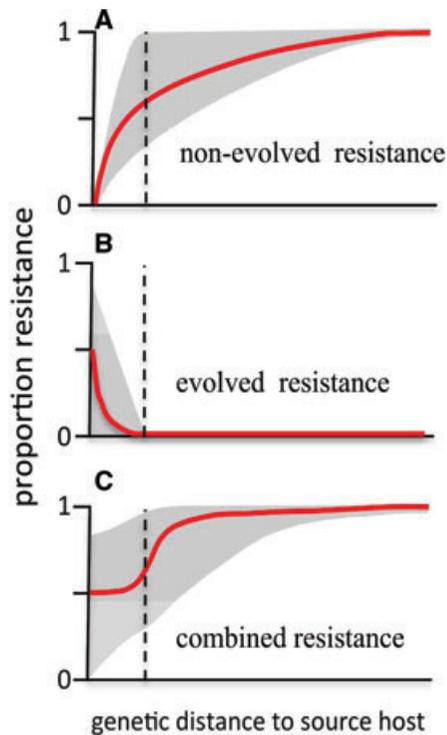
Figure 2. Predicted patterns of resistance to a pathogen or parasite from the source population as tested on the source host (the very left side of the *x*-axis) and on hosts with decreasing degrees of genetic relatedness to the source host toward the right side of the *x*-axis. The stippled vertical line demarcates the point on the *x*-axis separating within species (to the left) from between-species comparisons. (A) Predictions for nonhost resistance. Resistance of the source host is scaled to zero, with complete resistance set to 1. (B) Predictions for coevolved resistance. (C) Predictions for combined additive effects of nonhost and coevolved resistance. The red lines show the mean resistance and the gray areas show approximate envelopes into which the majority of the data might be expected to fall.

self-sustaining. We might predict that with one-sided evolution, and depending on the diversity of pathogens to which the host is exposed, the relationship with genetic distance is likely to be much flatter than with coevolution.

The patterns at this intraspecific level are likely to be complex. For example, theoretical work on local adaptation in host–pathogen interactions has stressed the role of gene flow (Gandon 2002). At an intraspecific level, genetic distance is likely to correlate with geographical distance, so the impact of gene flow from a source host population to any novel host population would decline. Crossing the species boundary would render such gene flow effectively zero, and correspondingly, if the pathogen was largely host-specific, the effect of coevolution on resistance of nonhost populations would be expected also to be absent.

How do these overall predictions compare to real data? We reviewed the data from 21 cross-infection studies involving source
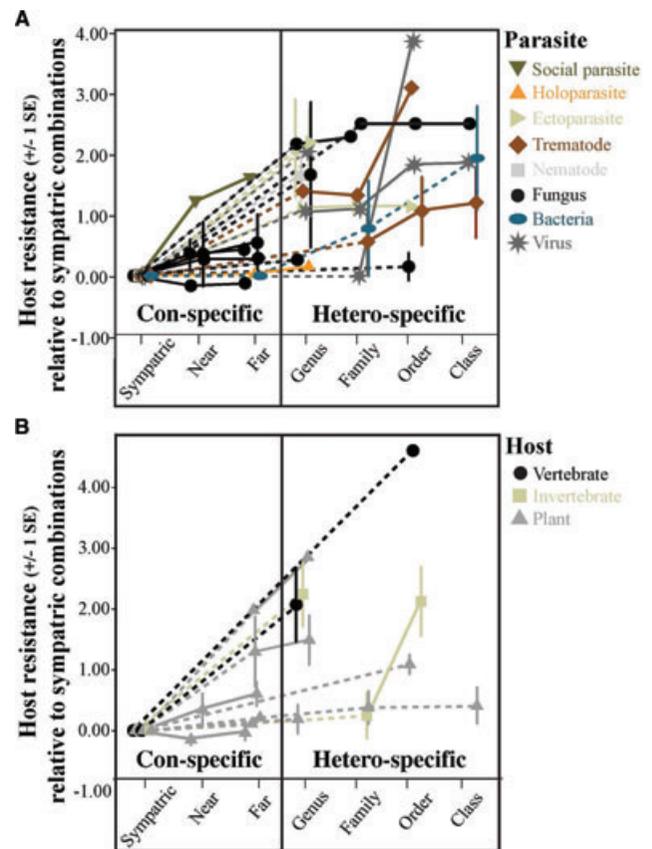

Figure 3. Host resistance across increasing physical distance (left panel) and taxonomic distance (right panel). Data were taken from 21 studies examining pathogen and/or parasite specificity, and presented as (A) how well a pathogen performs on hosts of increasing distance and (B) how well a host resists pathogens from other hosts of increasing distance. In both cases, data were standardized against the sympatric host–pathogen combination as: host resistance = ln (resistance of allopatric combination/resistance of sympatric combination). Thus, sympatric combinations were given a value of 0 to represent the given level of resistance for each host to its own pathogen. Error bars are one standard error of the mean. Data are from Akimoto (1990); Barber et al. (1993); Biere and Honders (1996); Bolin et al. (2009); Briese et al. (2005); Capelle and Neema (2005); Dennehy et al. (2006); Doggett and Porter (1995); Elmes et al. (1999); Giorgi et al. (2004); Huang et al. (2007); Kaltz et al. (1999); Kaupp et al. (2011); Kearn (1967); Konno et al. (2011); Laine (2005); Perlman and Jaenike (2003); Sapp et al. (2000b); Sicard et al. (2007); Thrall et al. (2002); and Wood et al. (1985).

and nonsource hosts spanning within- and among-species relationships. We compared the resistance of a host when a source pathogen was tested on its own host and on a range of nonsource hosts (Fig. 3A), and when the source host was tested against its own pathogen and a range of nonsource pathogens (Fig. 3B). In these graphs, the data have been standardized relative to the resistance of the source host tested against the source

pathogen. Whenever the inoculations involved comparisons above the species level, resistance increased rapidly with increasing taxonomic and presumably phylogenetic distance of both the host (tested with a source pathogen) as well as the pathogen (tested against the source host). This has often been found in other comparative cross-species studies (Perlman and Jaenike 2003; Gilbert and Webb 2007). This is congruent with our theoretical expectations in Figure 2A and strongly argues that much of the observed pattern is due to nonevolved resistance. The pattern at the infraspecific level is less clear-cut, and there is little overall change in resistance as hosts or pathogens become presumably more genetically divergent with distance. So the pattern in Figure 2B is not evident; in only one case, does resistance decrease in allopatry. The results are therefore qualitatively more congruent with our theoretical expectations (Fig. 2C) where the signal of nonevolved resistance overwhelms the signals of coevolved and host-evolved resistances. Most empirical studies do not include very distantly related hosts in such experiments, knowing (or assuming) that they are totally resistant. Thus, with truly random sampling of taxa and with a further extension to higher taxonomic orders, the increase in resistance may be even steeper.

Unfortunately, it is difficult to make a statistical comparison between the observed data and any explicit theoretical expectation because of high variability in taxon sampling, different resistance test procedures, and correlated errors when a host–pathogen combination is used for several comparisons. Clearly, to test our predictions explicitly, more complete cross-inoculation studies that span intraspecific as well as a wide range of taxonomic levels (and quantified in terms of phylogenetic distances) would be desirable.

Although we have considered host resistance and pathogen infectivity in relation to phylogenetic distance separately, for any host–pathogen system graphs such as in Figures 2 and 3 can be visualized as really having three dimensions. In addition to one axis for a range of hosts tested against the source pathogen, a second axis could be drawn for a range of pathogens tested against the source host (with increasing distance from the source pathogen). We predict that a landscape would emerge with a pattern being dominated by evolved-resistance processes close to the origin and patterns dominated by nonevolved resistance further away from the origin. Such an approach could be combined with other dimensions, such as geographic and ecological similarity, in efforts to understand the origins of specificity and to better predict the likelihood of cross-species transmission leading to new diseases on new hosts, an issue of importance for disease emergence and biological control.

CONTRASTING FEATURES OF EVOLVED RESISTANCE AND NONEVOLVED RESISTANCE

There are several fundamental differences between evolved and nonevolved resistance. Nonhost resistance itself can be of two kinds, either the fortuitous result of pathogen specialization or the result of one-sided evolution. These contrasts provide a series of testable hypotheses (Table 1). Moreover, given uncertainty about the evolutionary and geographical history of host–pathogen relationships, these contrasting features suggest ways in which the types of resistance can be distinguished.

Evolved resistance is expected to be a derived trait, whereas nonevolved resistance is expected to be an ancestral trait. Genes determining coevolved resistance (and conversely those determining infectivity in a coevolved pathogen) are expected to show signals of recent selection. Methods for detecting signals of selection in DNA sequences would be hard to apply in any predictive manner to genes determining nonevolved resistance because this phenomenon is not based on selection on host genes.

The stepwise components of the infection process might be used as means to differentiate the different forms of resistance; mechanistic approaches to distinguishing host and nonhost resistance have been posited in recent studies of plant–pathogen systems (Thordal-Christensen 2003; Schultze-Lefert and Panstruga 2011). We speculate that with increasing genetic distance between a nonevolved and the source host, an increasing number of rather ad hoc mechanisms might be present that would block pathogen infection. This is because distantly related hosts would differ in many aspects from the host on which the pathogen had specialized (just as different species will show increased genetic incompatibility with increasing phylogenetic distance when crosses are made between them). In contrast, one-sided host-evolved resistances would be effective against a broad range of pathogens. Coevolved resistances would consist of avoidance or inactivation of these blocking steps, combined with mechanisms that are specific to the particular host–pathogen interaction in question.

Much research effort is devoted to identifying the genetic basis of resistance. For coevolved resistance, it is possible to do this by contrasting susceptible and resistant host genotypes using the sophisticated tool boxes of genetic analysis, such as quantitative trait locus identification, gene expression based methods, reverse genetics, or comparative genomics. Nonhost resistance is more difficult to investigate in this way, because usually no "complementary" susceptible genotypes are likely to exist. Thus, to produce infected individuals one has to force the pathogen to infect the host (for example, by inoculation that by-passes normal routes of pathogen entry or by looking for susceptible mutants) and this may miss steps that otherwise normally block infection. When the nonhost resistance is a fortuitous by-product of pathogen specialization, insights into host resistance may be best obtained by manipulation of pathways in the pathogen and not in the host!

The likely difference in genetic architecture between coevolved resistance and nonhost resistance is also important when using model systems to study mechanisms of resistance (or

Table 1. Contrasting features of evolved, nonevolved, and nonhost resistance.

	Host resistance		Nonhost resistance
	Evolved resistance		
	Coevolved	One-sided evolved	Nonevolved resistance
Microevolutionary process	Evolves as a consequence of pathogen adaptation on the host	Evolves as a consequence of host being challenged with pathogens that cannot evolve on the host	Is a by-product of pathogen adaptation to other host species
Macroevolutionary pattern	Resistance to sympatric pathogens	Resistance to sympatric (or formerly sympatric) pathogens	Resistance increases with phylogenetic distance from the source host
Level of resistance	Incomplete resistance, but high level of variation	High resistance to sympatric pathogens	High resistance to allopatric pathogens
Biogeography	Arises within a local host population	Arises within a local host population	No spatial pattern
Impact on pathogen	As hosts evolve resistance, pathogens likely to evolve counter adaptations	No impact expected, because pathogens cannot establish on nonhosts	No impact expected, because pathogens cannot establish on nonhosts
Phylogenetic pattern	Resistance is a derived character	Resistance is a derived character	Resistance is an ancestral character
Genetic variation for resistance	Polymorphism for resistance within- and between-host populations	Not expected, unless costs prevent fixation of resistance genes	Not expected, but may be incidentally present
Number of genes contributing to genetic variation in resistance	One to few genes	One to several genes	More genes with increasing phylogenetic distance from the source host
Identification of candidate genes	QTL associations and signals of molecular evolution in resistance and infectivity genes present	QTL associations and signals of molecular evolution for resistance weak; absent for pathogen infectivity	QTL associations and signals of molecular evolution absent in the host

pathogen infectivity). In nonhosts, infection failure may be either due to general resistance mechanisms, as in the case of one-sided evolution, or may be due to genetic changes in the pathogen that have little to do with adaptive genetic changes in the host. Studying the genetics of nonhost resistance, and especially nonevolved resistance, is therefore likely to be misleading with regards to mechanisms underlying current coevolving systems. Strong evidence for this comes from molecular mechanisms of host and nonhost resistance in plant populations. In *Arabidopsis*, the pathway for resistance to its normal and putatively coevolved pathogens is very different from pathways for resistance to the nonhost pathogen *Blumeria graminis* that normally infects barley (Schultze-Lefert and Panstruga 2011). It is unclear if these and other nonhost resistance pathways are incidental nonevolved pathways or if they represent mechanisms that are the result of one-sided evolution. Based on molecular evidence, Schultze-Lefert and Panstruga (2011) also conclude that the relative contribution of coevolved pathways to resistance will decline with increasing phylogenetic distance between the host and nonhost species.

Animal models of human infectious disease are often chosen because the symptoms and other features of infection are similar to those in humans. For example, ferrets are used for the study of resistance/infectivity to influenza (Barnard 2009), rabbits for studying syphilis (Tantalo et al. 2005), and armadillos for leprosy (Vijayaraghavan 2009). The genetic architecture for host resistance and pathogen infectivity in these systems is likely to be very different from those in the source host, humans. Studies of resistance in these model systems may end up studying gene action related to pathogen failure, rather than evolved resistance as it would appear in a human host. At best, it may be studying generalized resistance that is the product of one-sided evolution, and this is likely to be very important in many human diseases. Serial passaging is often used in the course of developing animal models of human infectious diseases. Here, it is the pathogen that "is evolved" to be infectious and to overcome defenses of the animal used as a model; any host resistance is not an evolved response, and may have little to do with what occurs in human infectious disease. It is therefore not surprising that the

applicability of mouse models to humans (Mestas and Hughes 2004) and the *Drosophila* model to other insects (Gerardo et al. 2010) has been increasingly questioned.

Conclusion

We have presented a framework for the evolution of resistance to pathogens, focusing on the broad patterns of specificity and host range. We have argued that the term "nonhost resistance" encompasses both evolved and nonevolved resistances. We use the term "nonevolved" in the sense that this type of resistance is the result of pathogen evolution by specialization on its source host rather than direct selection for resistance in the host itself. Nonevolved resistance therefore is attributable to evolution of the pathogen rather than of the host. Hosts can also diverge genetically due to drift and other factors unrelated to the presence of the pathogen, and this may also lead to failure of novel host–pathogen interactions. We further distinguish resistance that is the product of coevolution from resistance that is the product of one-sided evolution of the host against pathogens that infect but cannot maintain self-sustaining populations. Thus, resistance of hosts to pathogens can have very different evolutionary origins. We have deliberately avoided detailed discussion of intraspecific genetic variation in host–pathogen specificities, largely for reasons of space, but also because these specificities are likely to be very different from those found across species and more distantly related taxa. Distinguishing the contrasting evolutionary origins of resistance mechanisms will be a difficult undertaking, but we believe it is possible by combining evidence from population genetics, phylogenetics, biogeography, and the molecular and functional aspects of the genes and pathways involved. Perhaps more important than simply documenting such contrasting origins of resistance, is recognizing the possibility of alternative evolutionary pathways when trying to understand the phenomenon of specificity in host–pathogen interactions. The distinction between evolved resistance and nonevolved resistance is also important in applied contexts, such as in developing animal models of diseases of humans or livestock, in establishing biological control programs, and in studies of plant–pathogen interactions with a view to crop improvement. We present a broad range of testable predictions based on our conceptual model and we hope these predictions will lead to experimental work and further studies on their applicability.

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