Synthesis

Identifying the Molecular Basis of Host-Parasite Coevolution: Merging Models and Mechanisms

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Submitted November 26, 2013; Accepted February 26, 2014; Electronically published May 20, 2014

Online enhancement: supplementary PDF.

abstract: Mathematical models of the coevolutionary process have uncovered consequences of host-parasite interactions that go well beyond the traditional realm of the Red Queen, potentially explaining several important evolutionary transitions. However, these models also demonstrate that the specific consequences of coevolution are sensitive to the structure of the infection matrix, which is embedded in models to describe the likelihood of infection in encounters between specific host and parasite genotypes. Traditional cross-infection approaches to estimating infection matrices might be unreliable because evolutionary dynamics and experimental sampling lead to missing genotypes. Consequently, our goal is to identify the likely structure of infection matrices by synthesizing molecular mechanisms of host immune defense and parasite counterdefense with coevolutionary models. This synthesis reveals that the molecular mechanisms of immune reactions, although complex and diverse, conform to two basic models commonly used within coevolutionary theory: matching infection and targeted recognition. Our synthesis also overturns conventional wisdom, revealing that the general models are not taxonomically restricted but are applicable to plants, invertebrates, and vertebrates. Finally, our synthesis identifies several important areas for future research that should improve the explanatory power of coevolutionary models. The most important among these include empirical studies to identify the molecular hotspots of genotypic specificity and theoretical studies examining the consequences of matrices that more accurately represent multistep infection processes and quantitative defenses.

Keywords: infectious disease, gene-for-gene interaction, infection genetics, genotype-by-genotype interactions, immune defenses, innate immunity, matching alleles.

Introduction

The vast majority of species interact with at least one and more often a multitude of parasite species. In many cases, these interactions are characterized by high levels of genetic specificity, where only a subset of parasite genotypes can infect any particular host genotype (Carius et al. 2001; Lively et al. 2004; Schulenburg and Ewbank 2004; Little et al. 2006; Poullain et al. 2007). Under such conditions, parasite genotypes that can infect a greater number of host individuals should increase in frequency and host genotypes that are susceptible to a greater number of parasite genotypes should decrease in frequency. This coevolutionary process causes frequency distributions of host and parasite genotypes to shift reciprocally over time (Hamilton 1980; Seger 1988).

Efforts to understand the consequences of host-parasite coevolution have taken a wide variety of approaches, but much work has relied on analysis of population genetic models. Early theoretical studies focused on understanding the basic dynamics of coevolution (Mode 1958; Jayakar 1970; Seger 1988) and on evaluating the Red Queen hypothesis for the evolution of sex (Hamilton 1980; Bell and Maynard Smith 1987). These models revealed that coevolution can generate diverse gene-frequency dynamics ranging from selective sweeps to sustained cycles. More recent work has refined the conditions under which coevolution favors sexual reproduction or recombination (Otto and Nuismer 2004; Agrawal 2006; Salathé et al. 2008; Kouyos et al. 2009), while other recent theory has expanded coevolution's reach by showing that it might drive other important evolutionary transitions. For instance, coevolution can generate selection for changes in ploidy levels (Nuismer and Otto 2004; Oswald and Nuismer 2007), patterns of mate choice (Nuismer et al. 2008; Otto et al. 2008), rates of mutation (M'Gonigle et al. 2009), and even mating system (Agrawal and Lively 2001). A common thread emerging from these models is that the specific outcome of coevolution (e.g., increased or decreased ploidy, assortative vs. disassortative mating, etc.) often depends on the underlying genetic model of infection and resistance. Consequently, the full utility of these models cannot be realized until we have a better understanding

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Am. Nat. 2014. Vol. 184, pp. 1–13. 0003-0147/2014/18401-55118$15.00.
DOI: 10.1086/676591

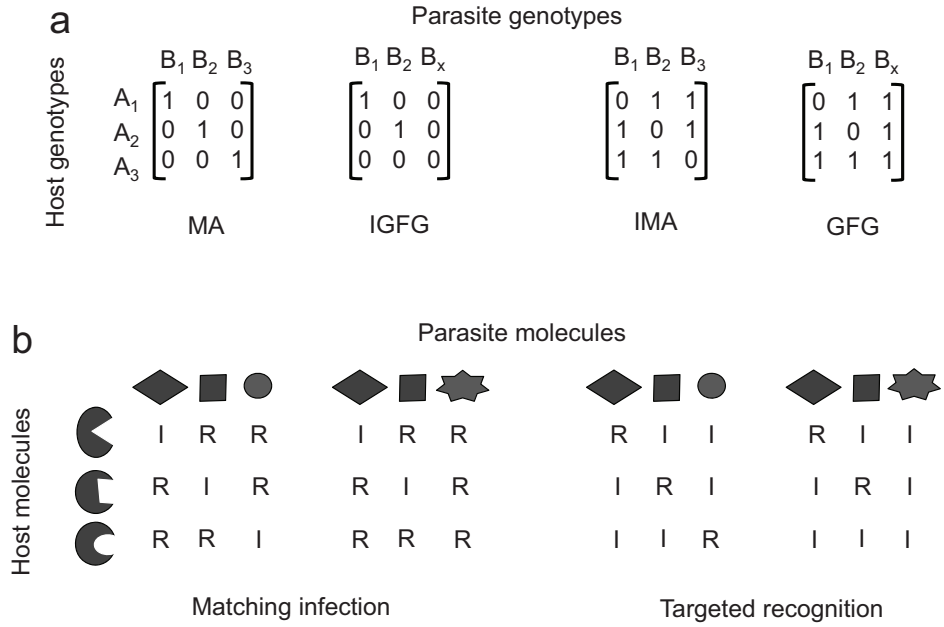

Figure 1: Structure of infection matrices. *a*, In coevolutionary models, the infection matrix specifies the probability that an encounter between a specific host and parasite genotype leads to infection. This matrix might take any form, although most models focus on one of four specific structures. These four structures are shown for the case where host and parasite are characterized by three haploid genotypes and the probability of infection is either 0 or 1. In matching-allele (MA) and inverse gene-for-gene (IGFG) matrices, infection occurs when genotypes match. In inverse matching-allele (IMA) and gene-for-gene (GFG) matrices, infection is thwarted when genotypes match. IGFG and GFG result when the parasite has a genotype (B_x) that does not correspond to a host genotype, leading to 0 or 1 probability of infection, respectively. *b*, Molecular models of infection and resistance, shown below the corresponding infection, assuming that different molecules are coded by unique genotypes. Under matching infection, molecular matches lead to infection, while a mismatch is observed as resistance. MA and IGFG matrices are consistent with this model of molecular interactions. Under targeted recognition, infection is thwarted when molecules match, while a mismatch leads to infection. IMA and GFG matrices are consistent with this model of molecular interactions. IGFG and GFG result when parasites have a molecule that does not correspond to a host molecule, leading to resistance or infection, respectively.

of which specific genetic models best describe the molecular basis of coevolution. To this end, we synthesize our current understanding of the molecular mechanisms of host-parasite interaction and the genetic models of host-parasite interaction that underpin coevolutionary theory. We begin by reviewing the basic structure of coevolutionary models and introduce the concept of an infection matrix that captures the genetic basis of infection and resistance. We then review recent studies of molecular immunology in plants and animals, synthesize the models and mechanisms to ascertain the accuracy and relevance of the infection matrices long used as the basis for most coevolutionary models, and suggest new modeling strategies that more realistically represent molecular interactions between host and parasite.

The Structure of Coevolutionary Models

Population genetic models of host-parasite coevolution describe host and parasite species by vectors of genotype frequencies **H** and **P**, respectively. The outcome of an interaction (infect vs. resist) between specific host and parasite genotypes is generally integrated into coevolutionary models using some form of infection matrix, $\boldsymbol{\alpha}$ (fig. 1*a*). It is this infection matrix that captures the genotype-by-genotype (G × G) interactions essential to coevolution. Historically, the most commonly used infection matrices were the inverse matching-allele (IMA), gene-for-gene (GFG), and matching-allele (MA) models, although the new inverse gene-for-gene (IGFG) matrix has gained some recent popularity.

When an encounter between individuals results in infection, most models assume host fitness is reduced by some fixed amount s_h, whereas pathogen fitness is increased by some fixed amount s_p. In some cases, constitutive costs of resistance or infectivity are included, reducing the fitness of specific genotypes (e.g., virulent or resistant alleles in the GFG model) by a fixed amount. It is important to realize, however, that such constitutive costs do not influence the infection matrix, $\boldsymbol{\alpha}$, but instead

reduce only the base fitness of each genotype by some amount, *c*. With these assumptions, the fitness of genotypes within host and parasite populations is defined by the following vectors:

$$\mathbf{W_h} = 1 - s_h \boldsymbol{\alpha} \mathbf{P} - \boldsymbol{c}_h, \quad (1a)$$

$$\mathbf{W_p} = 1 + s_p \boldsymbol{\alpha} \mathbf{H} - \boldsymbol{c}_p. \quad (1b)$$

With equation (1a), (1b) in hand, coevolutionary dynamics can be predicted using standard population genetic equations.

Although the specific coevolutionary dynamics that emerge depend on the fitness consequences of infection/resistance, *s*, and costs of resistance/infectivity, *c*, it is the infection matrix, $\boldsymbol{\alpha}$, that plays the dominant role in shaping coevolutionary dynamics and driving major evolutionary transitions. Because of its central importance to coevolution, much effort has been expended on attempts to infer the structure of the infection matrix, $\boldsymbol{\alpha}$, in natural populations. These efforts have generally relied on the pattern of compatibility between multiple host genotypes and multiple pathogen genotypes assessed using a cross-infection study (Burdon and Jarosz 1991; Burdon 1994; Carius et al. 2001; Thompson and Burdon 1992; Luijckx et al. 2012). Although such studies provide some insight into the genetic basis of infection and resistance, a fundamental disconnect exists between infection matrices inferred in this way and those that form the basis of coevolutionary models.

This disconnect arises because the infection matrix used in coevolutionary models includes all possible genotypic variants given the dimensions of the matrix (number of loci and alleles), whereas the infection matrix estimated from genotype-specific patterns of compatibility includes (at best) only the genetic variation currently segregating within a particular population. Consequently, for any true infection matrix, $\boldsymbol{\alpha}$, the infection matrix, $\boldsymbol{\alpha}'$, inferred from a cross-infection study will change over time and space as the specific subset of genotypes segregating within host and parasite populations changes in response to drift, selection, and mutation (fig. 2). Because of this evolutionary sampling problem and additional issues associated with experimental sampling first recognized by Frank (1994), estimating the true infection matrix, $\boldsymbol{\alpha}$, using cross-infection studies is potentially misleading when the goal is the prediction of coevolutionary dynamics over long time frames.

Moving from Pattern to Mechanism

An alternative to cross-infection studies for estimating the infection matrix is to predict its structure using a detailed understanding of the molecular mechanisms underpinning infection and resistance. Specifically, if general mechanistic rules of molecular interaction can be identified, infection matrices can be constructed that are not limited to those genotypes currently segregating within, or sampled from, host and parasite populations. Consequently, it becomes possible to predict the structure of infection matrices in a way that corresponds to their usage within coevolutionary models as the full scope of the evolutionarily possible.

Here we focus on evaluating support for two general mechanistic models of molecular interaction hypothesized to be the basis for commonly used infection matrices: targeted recognition and matching infection (fig. 1*b*). Both the IMA and GFG infection matrices are commonly justified under targeted recognition (Gabriel and Rolfe 1990; Frank 1993; Dodds et al. 2006; Ravensdale et al. 2011), where infection results when the host genotype does not recognize the parasite genotype. In contrast, both the MA and IGFG infection matrices have been justified using the logic of matching infection (Hamilton 1980; Agrawal and Lively 2002; Fenton et al. 2009; Schmid-Hempel 2011; Fenton et al. 2012), where parasites succeed in infecting the host when their genotype matches that of the host. To evaluate support for these two mechanistic models, we synthesize the wealth of new information generated by studies of molecular immunology and common forms of infection matrices. Our goals are to determine (1) whether the two molecular models commonly used to justify existing infection matrices—targeted recognition and matching infection—capture the essential features of immune defenses and parasite infectivity or whether there is need for new molecular models, (2) whether specific molecular models are general or limited and taxonomically restricted (e.g., found in plants but not animals), and (3) how new infection matrices might better represent the molecular mechanisms that underlie the infection process and coevolution. By exploring the molecular mechanisms of defense and counterdefense, we can critically evaluate support for the infection matrices commonly used in mathematical models of coevolution.

What Are the General Rules of Molecular Interactions Governing Infection and Resistance?

The past decade has seen an explosion of studies of the molecular interactions of plant and animal defenses and parasite counterdefenses, and despite the observed diversity and complexity, these molecular interactions conform to a handful of general strategies (Medzhitov and Janeway 2002; Medzhitov and Biron 2003; Ausubel 2005; Sikora et al. 2005; Jones and Dangl 2006; Schmid-Hempel 2009). To describe these general strategies of molecular interactions, we reviewed recent empirical studies of molecular mechanisms that are active in two stages of host defenses

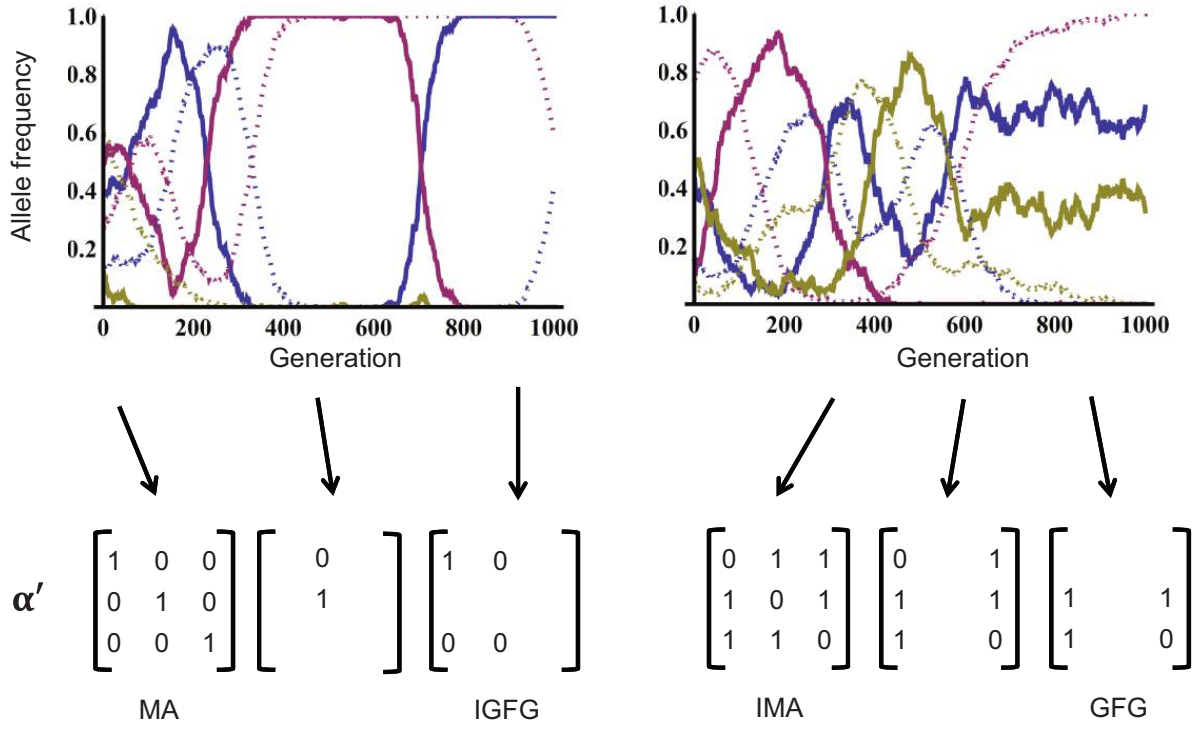

Figure 2: Coevolutionary dynamics (*upper panels*) and realized infection matrices, α' (*lower panels*), for a case where the true infection matrix, α, is of a matching-allele (MA) form (*left*) and an inverse matching-allele (IMA) form (*right*). Coevolutionary dynamics were simulated for a scenario where each species had three possible alleles, each of which was initially present within the population at appreciable frequency. *Upper panels*, the frequency of each allele over time, with solid lines representing host alleles and dashed lines representing parasite alleles. Each generation began with coevolutionary selection using fitnesses calculated from equation (1). The fitness consequences of infection, s, for host and pathogen were set to 0.05 and 0.04, respectively, in all cases. Following selection, mutation occurred among alleles at a rate of 1×10^{-5}. Finally, the next generation was created by randomly sampling 1,000 host individuals and 6,000 parasite individuals. Simulations were run for 1,000 generations. The realized infection matrix, α', was sampled at three time points (arrows) based on the genotypes segregating within the host and parasite populations. *Left panels*, matching alleles show the realized infection matrix, α', at generations 5, 455, 905; *right panels*, inverse matching alleles at generations 350, 600, 950. Consequently, the realized infection matrix, α', evolves over time, generating the "evolutionary sampling" described in the main text. GFG = gene for gene; IGFG = inverse gene for gene.

in plants and animals: barrier defenses and innate immune defenses.

In the first stage, barrier defenses guard against entry of parasites into cells and tissues prior to contact with innate defenses (Parker et al. 2011). Some barrier defenses can be overcome via molecular mimicry by the pathogen, consistent with the logic of matching infection. Parasite attachment to host cells or molecules is often an important first step in crossing cell and tissue barriers. Attachment and entry is often promoted when pathogens mimic the target of host receptors for nutrients, symbionts, or commensal bacteria (table 1). The structural architecture and active binding sites of pathogen molecules appear to have undergone convergent evolution with host molecules (Sikora et al. 2005). The extent of genetically based molecular polymorphism is not well known but is essential for evaluating the extent to which barrier defenses contribute to the structure of infection matrices. One tantalizing hint that barrier defenses may play a key role comes from recent studies in *Daphnia*, suggesting that gut barrier defenses are the cause of well-known G × G interaction in that system (Duneau et al. 2011).

The second stage of an infection process occurs after contact with the systemic innate immune system of plants, invertebrates, jawless vertebrates, and jawed vertebrates and is characterized by a bewildering array of molecular interactions. Again, despite the outward appearance of complexity, a synthesis of this array of interactions is possible because major components of innate defense systems are either conserved, convergent, or operate on the same logic (Ausubel 2005). These innate mechanisms can be categorized into three general strategies: (1) recognition

of pattern, specifically of signals on cells that are associated with pathogens, (2) recognition of modified self, resulting from either pathogen alteration or damage, and (3) recognition of missing self, or the absence of a self-recognition signal on a cell (Medzhitov and Janeway 2002; Medzhitov and Biron 2003).

The recognition of pattern strategy is ubiquitous in plants and all animal groups. This strategy is defined by host pattern recognition receptors (PRRs) that can recognize pathogen-associated molecular patterns (PAMPs; Hoffmann et al. 1999; Jones and Dangl 2006). Different groups of pathogens, including eukaryotic and metazoan parasites (Matzinger 2002; Schmid-Hempel 2011), are recognized and identified by distinct evolutionarily conserved PAMPs, leading to targeted recognition interactions (table 1).

The recognition of modified self strategy is best illustrated by the guard hypothesis in plants (Jones and Dangl 2006) or the danger model in vertebrates (Matzinger 2002; Köhl 2006). Rather than targeted recognition of PAMPs, this strategy employs recognition of parasite activity or damage, such as parasite-modified proteins or cells. Evidence for this strategy comes from several systems, including *Arabidopsis thaliana* and the bacteria *Pseudomonas syringae* and the complement system of the vertebrate innate immune system (table 1). For example, plant innate host defense molecules bind directly to host molecules that have been damaged by pathogen effector molecules (see supplementary materials, available online; fig. S2; figs. S1–S3 are included in the supplementary materials). According to this hypothesis, many of the *R* loci in plants that were once thought to be involved in direct pattern recognition of pathogen avirulence (Avr) effector proteins might be directly recognizing altered host molecules (Ausubel 2005; Jones and Dangl 2006). One advantage to this strategy is the ability of the host to detect modification of a single host molecule rather than the proteins of multiple pathogens that have targeted that host molecule.

The type of interaction matrix that captures the recognition of modified self strategy depends on the detailed actions of parasite effector molecules (supplementary materials; fig. S2). A targeted recognition matrix would be appropriate if different parasite genotypes produced distinct modifications to host molecules, leading to genotype-specific interactions based on molecular variation. Alternatively, if, as expected, all pathogen effector proteins lead to the same host damage among which host genotypes cannot discriminate, then the modified self hypothesis would not contribute to G × G specificity nor to the coevolutionary process (Dodds and Rathjen 2010).

The final strategy, recognition of missing self, is typically associated with the matching infection model of interaction, and the innate system of jawed vertebrates likely represents the only example of this strategy. Jawed vertebrates constitutively express markers of self (e.g., major histocompatibility complex [MHC] class I molecules) and host effector cells of the innate immune system attack and destroy pathogen cells because they lack a signal of self (Medzhitov and Janeway 2002; Lanier 2008*b*). For example, natural killer (NK) cells of the innate immune system bear inhibitory receptors that suppress a response when they recognize self-identity molecules. Pathogens that match the markers of self-identity and express them on the cell surface are not attacked by NK cells and evade innate immunity (table 1). Targets also include infected host cells in which intracellular pathogens have suppressed the expression of MHC class I molecules (for a specific example, see supplementary materials; fig. S3).

Despite the outward appearance of complexity in host defenses, an essential feature of the molecular details of both barrier and innate immunity is that the outcome of an interaction depends rather simply on molecular matching versus mismatching. A matching infection model is appropriate if infection succeeds when molecular matches occur. This model appears to be typical for barrier defenses and for innate immune defenses that employ the recognition of missing self strategy. On the other hand, a targeted recognition model is appropriate if infection is thwarted when molecular matches occur. This scenario appears to be typical for the recognition of pattern strategy of innate immune defenses and might also be appropriate for the recognition of modified self strategy.

Do Existing Matrices Capture Essential Features of Host-Parasite Molecular Interactions?

The essential feature of molecular mechanisms, which are the alternative consequences (infection or resistance) of molecular matches and mismatches, is captured in existing matrices. However, a pair of infection matrices is associated with each of these two very general and sufficient molecular models: MA and IGFG with matching infection and IMA and GFG with targeted recognition (fig. 1). This raises the question of which of the pair is most appropriate to use in coevolutionary modeling.

One consideration should be the timescale over which we wish to model the coevolutionary process. To address this consideration, it is useful to note that one major feature that distinguishes IGFG from MA and GFG from IMA is the absence of corresponding parasite and host genotypes (fig. 1; Fenton et al. 2009, reviewed in Schmid-Hempel 2011). Our synthesis suggests that the absence of genotypes from a matrix is not a necessary consequence of any mechanism of molecular interactions per se. It is clear, however, that the absence of genotypes or molecules is a possible outcome of experimental (Frank 1994) or evolutionary (fig. 2) sampling. Because IGFG and GFG

Table 1: Summary of immune defenses and the general strategies and models of molecular interaction

Immune defense category	Strategy	Molecular model	Host/parasite	Molecular interaction	Example references
Barrier	Pathogens mimic the target of a host receptor to gain attachment and entry	Matching infection			Sikora et al. 2005
			Plants/bacteria	Adhesion proteins are responsible for attachment to host tissue and are associated with host specificity	Mhedbi-Hajri et al. 2011
			Nematodes/bacteria	Protein mimics attach to the heparin-binding domain of the host cuticle	Sayre and Starr 1985; Mohan et al. 2001; Schmidt et al. 2008
			Daphnia/bacteria *Pasteuria ramosa*	Attachment to digestive tract wall precedes penetration; molecular details uncertain	Duneau et al. 2011
			Bacteria/phage	Phage tail fibers bind to host cell-surface proteins	Labrie et al. 2010
			Bacteria *Yersinia tuberculosis*/ vertebrate	Invasin protein binds to a receptor on the host cell surface by mimicking the host's fibronectin molecule, leading to infection	Leong et al. 1990
Innate	Recognition of pattern: host PRRs recognize PAMPs and signal downstream effectors	Targeted recognition			Hoffmann et al. 1999; Jones and Dangl 2006
			Plant/bacteria	Host FLS2 recognition molecule responds to flg22 and flagellin proteins in bacteria (PTI)	Chinchilla et al. 2006
			Plant/fungi	Host *R*-encoded NB-LRR proteins bind directly to the Avr effector proteins (ETI)	Dodds and Rathjen 2010; Ravensdale et al. 2011
			Bacteria/phage	CRISPRs specifically target previously infectious viral strains	Horvath and Barrangou 2010; Vale and Little 2010
			Snail/trematode	Host FREPs receptors recognize mucin molecules on the surface of their trematode parasite	Roger et al. 2008; Loker 2010
			Bumblebee/ trypanasome	Genotype-specific responses by host to intestinal parasites, molecular details unknown	Riddell et al. 2009, 2011

		Many invertebrates, some vertebrates/ bacteria or fungi	PGRP receptors recognize conserved pathogen molecular patterns and modulate innate immune defense pathways	Royet et al. 2011; Bier and Guichard 2012
		Vertebrate/virus and microbes	Complement proteins recognize and bind with conserved patterns on pathogens and mark them for destruction by immune effectors	Zipfel and Skerka 2009
Recognition of modified self: host receptors recognize modified host molecules that indicate pathogen attack and signal downstream effectors	Targeted recognition or no coevolution			Matzinger 2002; Jones and Dangl 2006
		Plant/bacteria: *Arabidopsis thaliana*/*Pseudomonas syringae*	Host molecule RIN4 damaged by pathogen effectors is recognized by host NB-LRR receptors RPM1, RPS2	Wilton et al. 2010
		Vertebrate/microbes	Complement proteins recognize modified or damaged self and translate danger into immune response	Köhl 2006
Recognition of missing self: pathogen mimics host self-recognition molecules to avoid attack	Matching infection			Medzhitov and Janeway 2002
		Jawed vertebrate/ virus	Pathogens that match the markers of self-identity and express them on the cell surface are not attacked by NK cells	Orange et al. 2002; Lanier 2008*a*

Note: Illustrative examples from a range of plants and animals are provided with references. PRR = pattern recognition receptor, PAMP = pathogen-associated molecular patterns, FLS2 = flagellin-sensing 2, PTI = PAMP-triggered immunity, NB-LRR = nucleotide-binding site leucine-rich repeat, Avr = avirulence, ETI = effector-triggered immunity, CRISPR = clustered regularly interspaced short palindromic repeat, FREP = fibrinogen-related proteins, PGRP = peptidoglycan-recognition proteins, NK = natural killer.

matrices do not include all possible corresponding genotypic variants in host and parasite, these matrices are most appropriate in models where the goal is the prediction of coevolutionary dynamics over the short term. On the other hand, MA and IMA would be more appropriate anytime all possible corresponding molecular forms and genotypes are expected to occur periodically, such as over long timescales when the goal is predicting major evolutionary transitions.

Infection matrices do not incorporate costs of resistance and infectivity, although such costs are often integrated into IGFG and GFG models in a post hoc effort to maintain genetic polymorphism (Jayakar 1970; Sasaki 2000; Fenton et al. 2009). However, our synthesis of underlying molecular mechanisms provides no reason to believe costs should be unique to IGFG and GFG models. Instead, our synthesis of molecular mechanisms in barrier and innate immunity suggests that costs are ubiquitous and not specific distinguishing features of any particular model of molecular interaction or infection matrix. For example, both barrier and innate defenses require receptor molecules that incur constitutive costs associated with producing and maintaining these proteins. Both barrier and innate defenses also incur fitness costs of polymorphism. These costs are anticipated in barrier defenses because parasites target important functional pathways to gain entry, so genetic variation in host receptors might incur a cost due to compromised or lost function (Sikora et al. 2005). Similarly, when innate defenses employ the recognition of pattern strategy, receptors target highly conserved functional proteins, constraining their evolutionary flexibility (Dodds and Rathjen 2010). All innate immunity also incurs inducible costs from downstream molecular and cellular processes used to kill parasites (reviewed in Rigby et al. 2002; Schmid-Hempel 2011). Thus, our synthesis of molecular mechanisms suggests that costs are ubiquitous and in no way diagnostic of the underlying mechanisms of infection and resistance.

Are Specific Molecular Models or Infection Matrices Taxonomically Restricted?

Traditionally, specific infection matrices have been thought to apply to different organisms (GFG for plants, MA for invertebrates, and IMA for vertebrates). In contrast to this tradition, we find little compelling evidence for a consistent taxonomic bias in the distribution of matching infection versus targeted recognition models of interaction (table 1). Matching infection operates in molecular barrier defenses of both plants and animals and under the strategy of recognition of missing self in the innate immune system of jawed vertebrates. However, there is little support for matching infection mechanisms in the innate immune defenses of invertebrates. There is no evidence for the presence of self-identity molecules and receptors of self-signals outside colonial or chordate invertebrates, despite considerable effort to find them (Loker et al. 2004; Vallet-Gely et al. 2008). This absence of data casts doubt on the idea that innate immune defenses of invertebrate animals generally operate under mechanisms envisioned by recognition of missing self. The self/nonself or allorecognition system of some colonial invertebrates (e.g., sponges, cnidarians, early chordates) is often used to motivate the use of the MA matrix for invertebrate animals. In fact, some possess an allorecognition system that is analogous to vertebrate self-recognition (Grosberg and Hart 2000). However, the molecular underpinnings are different and not shared with innate recognition molecules in other invertebrates (Nicotra et al. 2009). Thus, MA matrices might be most appropriate if genotype-specific interactions occur in barrier defenses of plants or animals or in innate system molecules of jawed vertebrates but not invertebrates.

Targeted recognition, which is often used to justify a GFG matrix, occurs under the recognition of pattern strategy of the innate immune system of plants and invertebrate and vertebrate animals. Targeted recognition might also be appropriate for the recognition of modified self strategy, which is known for plants and vertebrate animals, if different pathogen effectors that alter host molecules or cells have unique recognition signatures.

Overall, it appears that both matching infection and targeted recognition mechanisms are broadly applicable across major plant and animal taxonomic groups, justifying the widespread use of MA, IMA, and related infection matrices in coevolutionary models. However, there is considerable uncertainty about which molecular mechanism or infection matrix explains genotypic specificity in coevolutionary interactions.

Which Specific Infection Models Best Explain Genotype-Specific Interactions?

Although the taxonomic breadth and generality of matching infection and targeted recognition models are encouraging for theoreticians constructing general coevolutionary models, our ability to choose among infection matrices is limited because little is known about the molecular basis of genotype specificity for any natural system. Genotype-specific molecular polymorphism is expected to evolve because hosts and parasites use evasion in the form of molecular polymorphism as countermeasures (Schmid-Hempel 2008, 2009). However, for both barrier and innate defenses, the extent of genetically based molecular polymorphism within host and pathogen populations remains relatively unknown, even in systems like *Drosophila* (Lazzaro et al. 2006). One reason to doubt the existence of

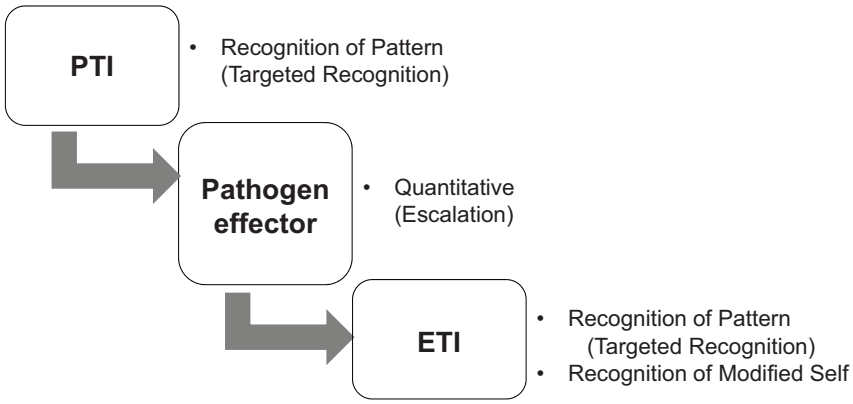

Figure 3: Phases of plant innate defenses and the likely model of interaction for each phase. The first phase occurs when receptors recognize pathogen-associated molecular patterns (PAMPs) and initiate signaling and effector steps in the defense cascade. This first phase is PAMP-triggered immunity (PTI). As a counterdefense, a wide diversity of plant parasites, from prokaryotes to insects, produce effector proteins that are delivered into plant cells. Pathogen effector proteins interfere with or suppress PTI responses. Quantitative overexpression of pathogen effectors has been shown to permit further colonization of the host. A second phase of host defense occurs within the cell that is triggered by pathogen effectors and is called effector-triggered immunity (ETI). Under the recognition of pattern scenario for ETI, selection by host recognition would act directly on the sequence that codes for recognized parasite molecules and molecular interactions would be best described by targeted recognition. Under the recognition of modified self scenario for ETI, targeted recognition is probably inappropriate if parasite effectors do not produce genotype-specific modifications to host molecules.

polymorphism for barrier defenses is that parasites target receptors with essential function, such that evolutionary change in host receptors could be costly (Brockhurst et al. 2005). Similarly, for innate defenses that employ recognition of pattern, genetically based molecular variation in pathogen molecules is expected to be constrained because host receptors typically target molecules that are functionally essential (e.g., structural pathogen molecules such as flagellin in microbes and chitin in fungi) and are thus highly conserved (Dodds and Rathjen 2010). As a consequence, alternate molecular forms might involve costly trade-offs with other functions, limiting levels of genetically based molecular polymorphism. This constraint could reduce the potential for coevolution. On the other hand, there is evidence of variation in both host receptors and targeted pathogen molecules in *Arabidopsis* and their pathogens (Jones and Dangl 2006) and in *Drosophila* PRRs (Lazzaro et al. 2004). Developing a better understanding of the extent to which barrier and innate defense molecules and parasite molecules are variable and evolutionary labile within natural host and parasite populations is central to evaluating their contribution to infection matrices and host-parasite coevolution.

In very general terms, determining the most appropriate model or matrix might depend on the stage of the infection process (barrier or innate) in which genotype-specific interactions occur (table 1). Using plant-pathogen interactions as an example, the most appropriate matrices might be either matching infection or targeted recognition or both, depending on whether barrier or innate defenses or both, respectively, are the likely source of genotypic specificity (fig. 3). Thus, an important goal for future empirical research is to first identify the phase of immune defense that determines G × G interactions in natural systems. In principle, this can be determined by identifying the time point after experimental infection at which genotype-specific infectivity becomes detectable. Such an experiment is easiest for clonal organisms and when genotype specificity is already established (e.g., Duneau et al. 2011).

Another logical course of action is to identify molecular hotspots of coevolution. For example, transcriptome studies of strains or clones involved in reciprocal cross-infection trials can be used to find candidate molecules and genes involved in genotype-specific resistance and infectivity mechanisms. So far, only the host transcriptome has been studied this way in natural systems (Barribeau et al. 2014). Once candidates are found, molecular hotspots of coevolution will be only those genetic regions that produce variable molecular forms or can produce them through mutation. The potential to discover molecular hotspots involved in resistance and infectivity within and among populations exists (Ravensdale et al. 2011), and we know of one thorough population-level scan for polymorphism in a natural plant/pathogen system (Thrall et al. 2012). However, for the most part, these molecular hotspots of coevolution have begun to be identified mainly in experimental coevolutionary systems (bacteria-phage) and generally focus on only pathogen genes controlling infectivity

(Paterson et al. 2010; Scanlan et al. 2011; Meyer et al. 2012). One very promising study of molecular hotspots of parasite infectivity shows how mutations in poliovirus can be translated into molecular variation and mapped onto fitness (Acevedo et al. 2014). Even in these experimental systems, much remains to be studied, including the reciprocal changes in both host and parasite molecules involved in the interactions and the coevolutionary dynamics of both host and pathogen genes.

Are Existing Matrices Sufficient to Capture Essential Features of Host-Parasite Molecular Interactions?

Although existing infection matrices incorporate essential features of the molecular interactions involved in defense, most existing models do not reflect the abundant evidence for multiphase infection processes. Rather than the single-step infection matrix employed by most coevolutionary models (eq. [1a], [1b]), our synthesis of molecular mechanisms suggests that two-step processes are likely common and perhaps ubiquitous (see also Auld et al. 2010). Recent models have begun to explore such two-step processes when both steps are mediated by traditional qualitative infection matrices. For instance, Agrawal and Lively (2003) studied a model coupling MA and GFG matrices, and Fenton et al. (2012) studied a model coupling IGFG and GFG matrices. However, our review suggests that these approaches might not be sufficiently general for long-term coevolutionary prediction.

Our review suggests several possible biologically realistic two-step sequences. Infection that requires an encounter with barrier and innate defenses might best be modeled with a matching infection matrix (MA) followed by a targeted recognition infection matrix (IMA). Within the innate defenses operating under the recognition of pattern strategy, assignment of a single IMA might be potentially inadequate because host pattern recognition works in concert with other phases of immune response that ultimately determine the outcome of the interaction. In plants, two phases of pattern recognition occur in a sequence (PAMP-triggered immunity [PTI] and effector-triggered immunity [ETI]; fig. 3), where each phase involves targeted recognition by plant receptor molecules (e.g., Chinchilla et al. 2006, reviewed in Jones and Dangl 2006). The second phase of pattern recognition occurs within the cell and, under the classic interpretation, results from molecular recognition by host *R*-encoded proteins of pathogen Avr effector proteins (Bergelson et al. 2001; Thrall and Burdon 2003; Dodds et al. 2006; Ravensdale et al. 2011; Thrall et al. 2012). Such two-step qualitative defenses suggest the need for models incorporating two traditional IMA infection matrices in sequence.

Assignment of a single targeted recognition infection matrix to recognition of pattern defense is also potentially inadequate because innate defenses are comprised of qualitative recognition and quantitative downstream phases. For example, pattern recognition receptors in both plants and animals are necessarily coupled to downstream effector molecules or cells that ultimately lead to pathogen destruction (e.g., Zipfel et al. 2004; Jones and Dangl 2006; Royet et al. 2011). In the downstream phase of defense, resistance is often related to the production of greater levels of effectors. (For a specific example in snails, see supplementary materials; fig. S1; Bayne 2009; Hanington et al. 2010; Loker 2010; Mone et al. 2010). Furthermore, parasite counterdefenses can also be escalatory. One such counterdefense is the production of decoys (for an example, see fig. S1) sometimes called the smokescreen hypothesis, where successful infection results from increasing the secretion of decoy molecules (Roger et al. 2008; Loker 2010). Another escalatory parasite counterdefense measure is modulation and interference (Schmid-Hempel 2009). Here pathogen molecules bind to and incapacitate host receptors (Urban et al. 2006), host signaling molecules that would otherwise activate downstream defenses (Dodds and Rathjen 2010), or host effector molecules or cells that would otherwise kill the pathogen (Vallet-Gely et al. 2008).

These scenarios involving recognition and downstream defenses call for coevolution models where the first step is based on a qualitative molecular interaction (i.e., matching infection or targeted recognition) and the second step by a quantitative molecular arms race where the outcome depends on the difference between parasite and host quantitative traits (e.g., Gavrilets 1997; Nuismer et al. 2007). For instance, successful defense might require that host recognition molecules match parasite molecular patterns and that the host produces a sufficient quantity of receptors or effectors to overwhelm the parasite's production of counterdefense molecules. In general, such a model is relevant when genotype-specific interaction depends on the combined effects of innate recognition and downstream defenses and counterdefenses.

Conclusions

Predicting coevolutionary dynamics and their importance for major evolutionary transitions depends on a detailed understanding of the infection matrix. Rather than attempting to infer the structure of infection matrices from cross-infection studies of extant genotypes, we have reviewed recent advances in molecular immunology with the goal of deriving a new synthesis of molecular mechanisms and coevolutionary models, based on first principles of molecular interaction. Our synthesis suggests that diverse and complex immune mechanisms can be accurately distilled into just two models: matching infection and targeted

recognition. Based on this distillation, both models appear to be taxonomically widespread and capable of capturing many essential features of molecular interactions. At the same time, however, we do not know which of the two models explains the genotype-by-genotype interaction essential for coevolution. Quantifying the contribution of each model to the G × G interactions within natural populations is an important empirical challenge. To address these unanswered questions, we believe that a promising direction for future work is to identify candidate categories of defense that contribute to genotypic specificity and identify molecular hotspots of coevolution.

Finally, our review suggests that infection is frequently at least a two-step process. For example, two phases of recognition in sequence appear to be ubiquitous (e.g., barrier followed by innate defenses in plants and animals or PTI followed by ETI in plants). Analyses of models with two discrete infection matrices indicate that the nuances of coevolutionary dynamics differ from traditional single-matrix models. An important goal for future theoretical studies should be to evaluate the extent to which these multistep processes have meaningful consequences for coevolutionary dynamics. Additionally, our synthesis suggests that a common form of a two-step infection process may be one that combines qualitative and quantitative steps involving recognition and subsequent escalation of downstream defenses and parasite counterdefenses, for which the coevolutionary consequences are unknown. Thus, a second important focus for future research is to evaluate whether two-step models that couple discrete and quantitative traits change our understanding of the coevolutionary process and its consequences for major evolutionary transitions.

Acknowledgments

We would like to thank the National Science Foundation for support to C.E.J. through the Integrative Graduate Education and Research Traineeship (IGERT) Program in Evolutionary Modeling and to S.L.N. through grants DMS-0540392 and DEB-1118947.

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Associate Editor: Edmund D. Brodie III
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