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The evolution of sexual dimorphism and its potential impact on host–pathogen coevolution

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Sex and infection are intimately linked. Many diseases are spread by sexual contact, males are thought to evolve exaggerated sexual signals to demonstrate their immune robustness, and pathogens have been shown to direct the evolution of recombination. In all of these examples, infection is influencing the evolution of male and female fitness, but less is known about how sex differences influence pathogen fitness. A defining characteristic of sexual dimorphism is not only divergent phenotypes, but also a complex genetic architecture involving changes in genetic correlations among shared fitness traits, and differences in the accumulation of mutations—all of which may affect selection on an invading pathogen. Here, we outline the implications that the genetics of sexual dimorphism can have for host–pathogen coevolution and argue that male–female differences influence more than just the environment that a pathogen experiences.

KEY WORDS: **Coevolution, genotype-by-environment interactions, genetic correlations, host–pathogen interactions, mutation, sexual conflict, sexual selection.**

The Interplay between Sexual Dimorphism and Infection

Within any population there is often no bigger difference between individuals than the dimorphism that can occur between males and females. Driven by the fundamental differences in reproductive investment between the sexes, males and females commonly vary in body size and shape, reproductive investment, longevity, choosiness (investment in selecting a mate) and the degree of sexual ornamentation (Schärer et al. 2012). Sex-specific differences also extend to a host's investment in immune defense (Zuk and Stoehr 2002). Males, for example, are typically thought of as the "sicker sex" (Zuk 2009), investing fewer resources in maintaining an effective immune response in favor of their costly sexual displays (but see Box 1 for discussion). Each sex, therefore, differs in important properties that help to define pathogen fitness, such as encounter rates, degree of resistance, exploitative potential (body or organ size), and resource availability (e.g., Christe et al. 2007).

Despite the well-documented differences between males and females in behavior, physiology, and immunity, only recently has the interplay between sexual dimorphism and infection been considered in light of infectious disease evolution (Box 1). Duneau and Ebert (2012) were first to develop explicit hypotheses on how a pathogen should adapt to selection imposed by each sex, noting that this process might eventually lead to pathogens that are either optimally adapted to one sex, or are able to plastically respond to the challenges of sexual dimorphism. Building on this insight, Cousineau and Alizon (2014) modeled how the evolution of pathogen virulence depends on whether sexual dimorphism occurs in the probability of becoming infected (resistance) or in mitigating the damage caused by a pathogen once infected (tolerance). Together, these two studies highlight how sex differences can be an underappreciated driver of pathogen evolution; yet they only formalize one component of sex-specific pathogen evolution—the evolutionary optima of a pathogen when faced with sexual dimorphism in a host's internal environment.

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Box 1: Insight into the Impact of Male–Female Differences on Pathogen Adaptation

Evidence for the interplay between host sex and pathogen evolution is rare, but awareness that heterogeneity between sexes can influence disease evolution is growing. In birds and mammals, surveys of the literature have found that males are often more susceptible to infection and consequently experience higher infection rates and intensities than females (Poulin 1996; Schalk et al. 1997; Zuk 2009; Cousineau and Alizon 2014). This pattern, however, is not necessarily universal, and predictions for which sex should invest more in immunity will likely vary with the study species or environmental context, particularly in invertebrates (McCurdy et al. 1998; Sheridan et al. 2000; Stoehr and Kokko 2006). Indeed, what matters most is not whether males or females are generally the "sicker sex," but that sexual dimorphism in host resistance exists and can drive pathogen adaptation to the differences between male and female hosts (Christe et al. 2007; e.g., Duneau et al. 2012). With the widespread occurrence of sex-ratio biases, social hierarchies, and differences in male and female explorative behaviors (Duneau and Ebert 2012 and Table 2 therein), there is ample opportunity for pathogens to encounter males and females at different rates, and experience differences in the patterns of selection that a sexually dimorphic host can generate.

In developing the arguments for the link between host sex heterogeneity and infectious disease, Duneau and Ebert (2012) established the evolutionary requirements for how host sex could drive pathogen evolution. Based on the expectation that a pathogen will adapt to the characteristics of its most common host (Lively 1989), they outlined how the degree of host sexual dimorphism, and the probability of encountering the opposite sex, will define how a pathogen evolves. A generalist pathogen is predicted to evolve if the frequency of encountering multiple sexes is high and fitness trade-offs between environments are small. Conversely, pathogens are expected to become specialized to one sex when the sexes strongly differ, but the pathogen is unlikely to encounter both sexes. Finally, a pathogen may evolve a plastic response to host sex if both the frequency of experiencing male and female hosts, together with the fitness differences between environments, is high.

Complementing this work, Cousineau and Alizon (2014) focused on the evolution of pathogen virulence in response to how males and females defend against infection. In surveying a diverse range of mammalian pathogens, from viruses like influenza to macroparasites such as *Schistosoma* (Cousineau and Alizon 2014 and Table 1 therein), they found that males are typically more susceptible to initial infection than females, but are better able to cope with higher pathogen loads once infected. With these differences in mind, Cousineau and Alizon (2014) modeled how sex differences in either resistance or tolerance shape pathogen evolution. Sexual dimorphism in resistance was found to yield an increase in pathogen virulence only when pathogen transmission occurs only between members of opposite sexes, as this is when the most resistant sex will always be encountered. Conversely, dimorphism in tolerance accelerated the evolution of virulence under any pattern of contact between the sexes. Their results demonstrate how pathogen virulence will depend on a complex interaction between the degree of sexual dimorphism, the form of defense (resistance or tolerance), and the pattern of contact between the sexes.

In this article, we outline the unrecognized implications that sexual dimorphism can have for the genetic basis of host–pathogen coevolution. The struggle between pathogens and hosts has long fascinated biologists, and has been fundamental to our understanding of the very basis of male and female differences—the origin of sexual recombination (see Box 2). Driven by differences in the type of gametes they produce, however, each sex is often pushed toward different evolutionary optima, a process that often requires some important genetic architecture to proceed. The decline in positive genetic correlations among shared fitness traits, the cyclical coevolution of sex-specific behaviors, and the differential accumulation of mutations are all aspects of genetic architecture that underlie the evolution of sexual dimorphism. Drawing on the type of insights common to studies of mate choice evolution, we discuss three key implications arising from the complex genetics of male–female differences: (i) the importance of genotype-by-environment interactions for shaping the evolutionary potential of a pathogen; (ii) the role of cross-sex genetic correlations in enhancing or constraining host–pathogen coevolutionary cycles; and (iii) the potential for sex-specific mutation patterns to influence the rate at which a host can respond to the threat of parasitism.

The Sex-Specific Evolutionary Potential of an Invading Pathogen

Host populations are rarely homogeneous, and pathogens will encounter individuals that differ in age, nutritional condition, body

size, immune status, and physiology (Schmid-Hempel 2013). By modeling the epidemiological characteristics of disease when there are two or more host classes, theory has established how this heterogeneity can affect the evolution of pathogen fitness (Regoes et al. 2000; Gandon 2004; Williams 2012). These approaches have recently been extended to include variability in the internal host environment as caused by male–female differences (Box 1). For simplicity, however, the emerging study of sex-specific pathogen evolution has yet to consider explicitly how the impact of host sex may depend on the genotype of the invading pathogen. Such genotype-specific responses are nonetheless a common feature of both a host and pathogen's response to environmental change (reviewed in Wolinska and King 2009). Here, we consider the adaptive implications of male–female differences in light of the extensive body of research on the evolutionary importance of such genotype-by-environment interactions (GxEs, see Hunt et al. 2004; Ingleby et al. 2010). We focus on two important aspects of GxEs—the maintenance of genetic variation, and the change in evolutionary potential.

In general, GxEs arise when the relative fitness of different genotypes, or sometimes strains in the case of pathogens, is dependent on the environment in which that they are expressed (Fig. 1). In the absence of a GxE (Fig. 1A), the relative differences among pathogen genotypes remain unaltered in each sex, and so it is only the overall degree of sexual dimorphism in resistance that influences pathogen evolution. This scenario is most analogous to the theoretical considerations of host sex heterogeneity so far, whereby one sex, typically females, is more able to suppress pathogen fitness. The evolution of disease thus progresses depending on how often the invading pathogens encounter the two environmental classes and how well invading pathogens are able to exploit host resources and transmit to new uninfected animals (e.g., Box 1). However, a more complicated scenario for host–pathogen coevolution, and one that is likely to be biologically widespread, occurs when the response of a pathogen to the sex of a host is genotype specific—either involving a change in genotype rank order, or a change in the scale of genetic variation.

In situations where the rank order of fitness among genotypes changes (Fig. 1B), GxEs have the potential to influence the maintenance of genetic polymorphisms in natural populations. As long as there is gene flow between environments, no one genotype will be consistently favored, allowing fluctuating selection to maintain genetic variation in fitness (Gillespie and Turelli 1989). This process helps to explain why male sexual traits typically show significant heritability (Pomiankowski and Møller 1995), despite the prediction that female choice should rapidly erode genetic variation in sexual signals (Kirkpatrick and Ryan 1991). Similar arguments help explain why we observe considerable variation in infectious disease characteristics, despite the expectation that selection should favor completely resistant hosts or infective

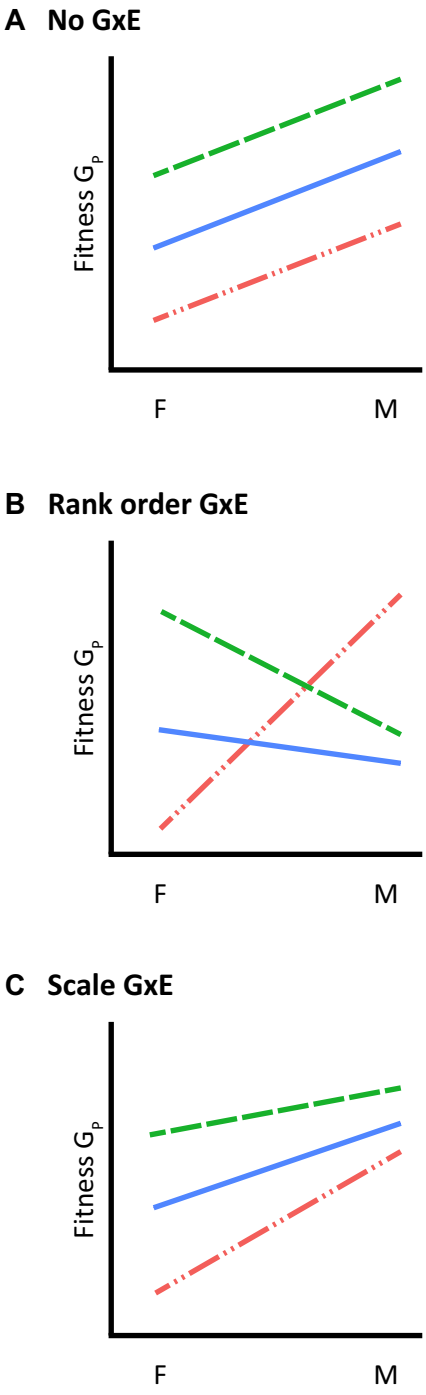

Figure 1. Conceptual reaction norms for the relative fitness of three pathogen genotypes (G_P) and two host sexes (male or female). (A) In the absence of a $G_P \times E$, pathogen genotypes (represented by different colors) may differ in their fitness, and each sex may be more or less resistant, but the effects are the same for each genotype. In the presence of a $G_P \times E$, (B) the rank order of the pathogen genotypes may change between the sexes, or (C) the scale of genetic variation changes between the sexes, but the rank order of pathogen genotypes remains the same. Each scenario has different consequences for the intensity of a selection response and the maintenance of genetic variation.

pathogens (e.g., Blanford et al. 2003; Vale et al. 2008; Hall and Ebert 2012). Indeed, environment-specific responses of pathogens may be almost universal, with GxEs occurring for a wide range of environmental conditions such as temperature, food quality, and the maternal environment (Wolinska and King 2009). Given the widespread potential for heterogeneity to arise due to male and female differences, we therefore suggest that sex driven GxEs may be another factor helping to maintain genetic variation in pathogen populations.

A more subtle version of a GxE can also occur when the relative fitness of a pathogen genotype changes across environments, but rank order of the genotypes remains the same (Fig. 1C). Such changes in the scale of variation do not directly help to maintain genetic variation, as one genotype is always superior. Instead genotypes differ in their sensitivity to the alternative environments, altering the intensity of any response to selection as the expression of genetic variance has now changed in each environment (Hoffmann and Merilä 1999). Work on infectious disease has already shown that pathogen genetic variability can increase or decrease with environmental change, such as with the age of a host (Mideo et al. 2011; Clerc et al. 2015). More broadly across a landscape of environmental variability, it has also been suggested that changes in genetic variation can substantially influence the intensity of host–pathogen coevolution, creating evolutionary "cold spots" or "hot spots," depending on the degree of difference among genotypes in each environment (Thompson 1994; Gomulkiewicz et al. 2000). Extrapolating the results would suggest that host sex is another possible environmental variable that could enhance or constrain pathogen evolution, contributing to local hot spots or cold spots in the environmental landscape that a pathogen experiences.

Genotype-by-environment interactions clearly have potential to shape the evolutionary dynamics experienced by an invading pathogen; but their precise outcome will depend on the type of trait experiencing such interactions. Broadly speaking, the fitness of a pathogen depends on a variety of traits related to the force of infection (the number of infections acquired over time), namely, infection rates, transmission potential, and the length of the infection period (Anderson and May 1991). Evolutionary theory, however, makes distinctions between the outcomes that arise from each of these different parameter types (e.g., Anderson and May 1982; van Baalen 1998; Gandon et al. 2002; Råberg et al. 2009). As discussed in Box 1, for example, variation in investment between males and females in resistance (limiting pathogen burden) or tolerance (limiting severity of pathogen burden), will lead to different evolutionary outcomes for a pathogen. Similar arguments could also be made for changes in pathogen genetic variation that arise for traits related to either partial (quantitative) or complete (qualitative) resistance against a pathogen (Gandon and Michalakis 2000). Thus, while the general form of a GxE (rank order or scale changes) defines the broad evolutionary relevance of an interaction between males, females, and pathogens—the precise outcome will depend on the trait and host–pathogen system of study.

Sex-Specific Selection and the Constraint of Host-Pathogen Dynamics

Central to the understanding of Red Queen dynamics are the repeated coevolutionary cycles between hosts and pathogens (Box 2). At the heart of this process are the genetic associations that build up and break down between the antagonistic combatants, whereby selection on one party results in a correlated response in the other (Fig. 2A). But what if there is an additional party in this process that is also undergoing coevolution with one of the combatants? While the Red Queen concept has been applied to a wide range of evolutionary problems, such scenarios have traditionally been limited to simple two party systems in isolation—either host and pathogen, or predator and prey (Brockhurst et al. 2014). A rare example of a study examining coevolutionary patterns within a three-party system is that of Dercole et al. (2010) which modeled predator–prey coevolution in a three species food chain (Fig. 2B). The inclusion of a coevolving super-predator forced the normally stable evolutionary cycles between predator and prey to become chaotic, with both the direction and strength of selection becoming intrinsically unpredictable beyond a short evolutionary time. In stark contrast to the predictable cycles of typical Red Queen dynamics, therefore, the addition of another external source of genetic variation vastly complicates the process of coevolution.

Here, we consider what happens to Red Queen dynamics when the genetic architecture of sexual dimorphism is introduced into the Red Queen process (Fig. 2C). A defining characteristic of sexual populations is that males and females can undergo their own coevolutionary struggle, as each sex experiences contrasting patterns of natural and sexual selection (Parker 2006; Cox and Calsbeek 2009). At the heart of this tension are the cross-sex genetic correlations among homologous traits (r_{MF}) that arise as a consequence of a shared gene pool (Lande 1980, 1987; Bonduriansky and Chenoweth 2009). Tight genetic correlations between shared traits act to prevent phenotypic divergence between males and females. With different evolutionary optima for each sex, this inevitably constrains adaptation, as selection on one sex will now produce a correlated response in the other. To overcome these limitations, r_{MF} values should diminish or even become negative. When selection is concordant but varies in strength, a decline in r_{MF} allows shared traits to evolve independently and more readily reach their separate optima (Lande 1980). However, if selection is sexually antagonistic and differs in its di-

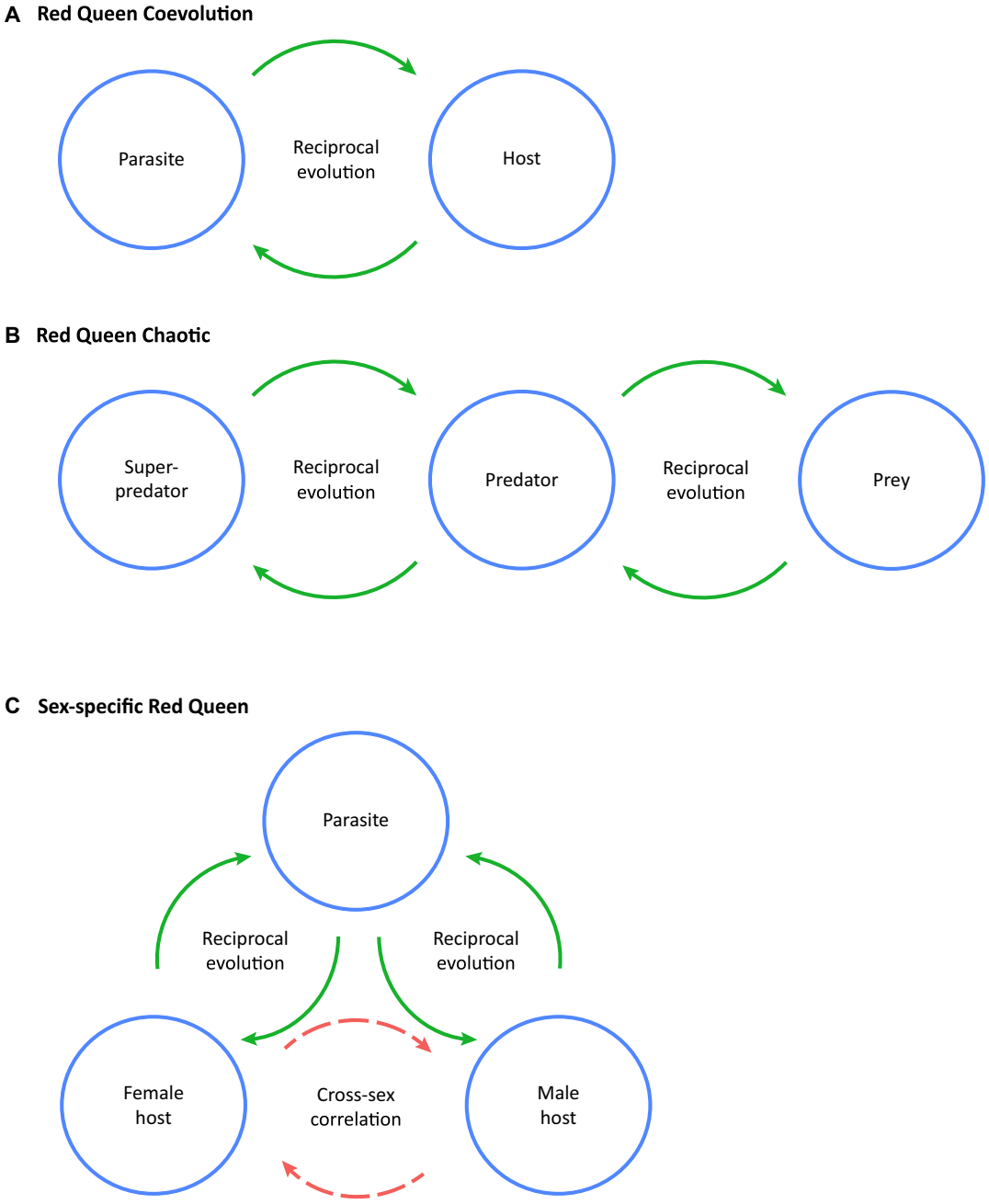

Figure 2. **Illustrative examples of different Red Queen interactions. (A) The basic Red Queen process describes hosts and pathogens as existing in an indefinite and predictable cycle of adaptation followed by a proportional counter adaptation (Brockhurst et al. 2014). (B) Red Queen "Chaotic" hypotheses (Dercole et al. 2010) describe the unpredictability of both strength and direction of selection of classic Red Queen models with the addition of a third coevolving species. (C) Similar to Red Queen Chaotic, patterns of host–pathogen coevolution with the added complexity of males and females may be difficult to predict using classic Red Queen models. In this scenario, pathogens will adapt to the different selective pressures presented by each sex, while the sexes will independently develop reciprocal adaptations as modulated by cross-sex correlations (r_{MF}).**

rection, a negative genetic correlation between traits can build up as alleles are favored that benefit one sex, but are detrimental to the other (intralocus sexual conflict, reviewed in Bonduriansky and Chenoweth 2009). Evolution in sexual populations, therefore, is characterized by a spectrum of r_{MF} values, from the strong and positive values for many shared traits, through to those which diminish from unity as traits become more closely related to fitness (Poissant et al. 2010; Griffin et al. 2013).

An initial glimpse into the consequences of sexual dimorphism for disease is offered by models that have previously

explored the impact of separate sexes on the rate of adaptation for a species in general (Lande 1980; Connallon and Clark 2014). Strong and positive correlations between traits are predicted to enhance the rate of adaptation only when selection on males and females is tightly aligned (Lande 1980). This is essentially the null model for host–pathogen dynamics, reflecting that male and female defense components are assumed to share the exact same genetic architecture, and undergo stable coevolutionary cycles as part of a normal two-party system (sensu Dercole et al. 2010). As the fitness correlation between the sexes diminishes ($r_{MF} < 1$), however, so to can the rate of adaptation if selection remains sexually concordant (e.g., Connallon and Clark 2014). With the uncoupling of male and female resistance ($r_{MF} \approx 0$), adaptive changes in one sex would no longer be reflected in the other due to a lack of any correlated response. Chaotic cycling is now a possibility, as by uncoupling male and female traits, Red Queen dynamics will most closely reflect the three-party dynamic of Dercole et al (2010). Finally, as cross-sex genetic correlations change sign ($r_{MF} < 0$), the change in resistance of both sexes can become suboptimal, with selection on one sex directly impeding the adaptive evolution of the other (Connallon and Clark 2014). Thus, under the constant threat of parasitism, the genetic architecture of sexual dimorphism could potentially reduce the rate of host adaptation, thereby modifying the process of host–pathogen coevolution.

Despite the well-developed predictions for the evolution of infectious disease (Box 2) and sexual dimorphism (Lande 1980; Bonduriansky and Chenoweth 2009; Connallon and Clark 2014), evolutionary theory has yet to explore the implications of sex-specific adaptation for host–pathogen coevolution. Yet the evolutionary decoupling of male and female resistance is likely, at least in part, given the presence of considerable sexual dimorphism in traits related to host resistance (Vincent and Sharp 2014). What remains unclear, however, is the ecological and evolutionary conditions that permit cross-sex genetic correlations to constrain or enhance the rate at which hosts can adapt to pathogens. While the work by Dercole et al. (2010) has shown that genetic variation introduced by another evolving party can fundamentally change the direction and strength of selection during Red Queen dynamics, it is important to note that genetic constraints can eventually be overcome if selection is strong enough. Studies of sexual dimorphism, in general, have shown that stressful conditions can cause r_{MF} for fitness to change sign and become more positive as increased sexually concordant selection favors overall genetic quality (Long et al. 2012; Berger et al. 2014). Identifying how strong and frequent Red Queen cycles need to be before sexual dimorphism ceases to matter will be essential for unravelling the potential importance of cross-sex genetic correlations for host–pathogen coevolution.

The Implications of Male-Biased Mutation for Genetic Variability in Resistance

A key requirement for host–pathogen coevolution via selective sweeps is that novel pathogen infectivity and host resistance alleles must constantly arise for coevolution to occur (Box 2). In this case, mutations are commonly the source of novel genetic variation and provide the raw fuel for evolutionary change. However, while the consequences of mutation on the rate of evolution are well understood (Maynard Smith 1976), an important consideration is how differences in mutation rates among hosts may impact on pathogen evolution. It is well known that genes involved in defense against a pathogen, such as those within the major histocompatibility complex or plant Resistance (R) pathways, evolve at high rates (Bergelson et al. 2001; Borghans et al. 2004). Additionally, theoretical studies have shown populations with higher mutation rates are better able to track the constantly moving optima driven by their antagonistic species (Gandon and Michalakis 2002; Salathé et al. 2005; Tellier et al. 2014). Less attention, however, has been directed toward the implications for infectious disease if some individuals within a population are more likely to accumulate mutations. We discuss how biases in mutation rate between males and females, together with the observation that the fitness consequences of mutations are often more severe in males, may fundamentally alter the outcome of host–pathogen coevolution.

Although the occurrence of novel mutations has traditionally been considered to be random, it has long been proposed that the rate at which mutations arise may be higher in males than females (Haldane 1935). The mutation bias stems from a fundamental difference in the production of male and female gametes, with spermatogenesis requiring more cell divisions than oogenesis, and thus more opportunity for replication errors (Hurst and Ellegren 1998). Consequentially, if adaptation depends on the supply of beneficial new mutations, then sex biases in mutation will substantially alter the rates of evolutionary change. Indeed, in the context of sex linkage, theory has shown how male-biased mutation can accelerate the accumulation of beneficial changes on specific chromosomes, with male sexual displays predicted to evolve most rapidly when Z-linked (Kirkpatrick and Hall 2004). However, reducing the waiting-time for an adaptive mutation to arise is even more important in the context of Red Queen dynamics and selective sweeps, where pathogens typically have effective population sizes that far outstrip that of their hosts (i.e., Lanfear et al. 2014). While the potential for male-biased mutation to accelerate host–pathogen coevolution has not yet been considered, a study of baculovirus resistance in the codling moth linked the rapid emergence of host resistance to the rise of

Z-linked resistance alleles (Asser-Kaiser et al. 2007), suggesting a role, at least in principle, for male-biased mutation.

In general, however, most mutations are predicted to be deleterious (Eyre-Walker and Keightley 2007). Theory has previously explored the link between pathogens, mutations, and sex, in terms of the maintenance of sexual recombination. By magnifying the negative effects of mutation accumulation, pathogens strengthen the opportunity for sex to overcome the advantages of remaining asexual (Park et al. 2010). Yet an interesting finding from studies of spontaneous mutation is that the severity of the fitness loss is felt much stronger by males, even though mutations are generally sexually concordant (Sharp and Agrawal 2013). Driving this pattern is the elevated intensity of selection acting on male mating success, whereas females are typically able to find a mate even if under mutational duress (Agrawal 2001; Whitlock and Agrawal 2009). But what about the consequences of mutation load for the ability of a male to fight or tolerate infection? To date, only Sharp and Vincent (2015) have considered how pathogens and mutation interact with male–female differences. Their results show how pathogen exposure further exacerbates the fitness loss experienced by males, again contributing to the effective purging of deleterious alleles. Nonetheless, the evolutionary implications of this process for pathogen transmission or virulence remain unexplored. On one hand males are more susceptible to infection and less likely impose strong selection on pathogen infectivity; but on the other, total selection on males is likely to be stronger and males are predicted to evolve more rapidly. Understanding the tension between these two contrasting patterns will shed light on whether males or females are the optimal sex for a pathogen to exploit.

Box 2: Pathogens, Red Queen Dynamics, and Sex

Infections are a powerful evolutionary force, driving "arms races" between hosts and pathogens, as host are forced to repeatedly evolve counter-adaptations to the constant threat of parasitism (May and Anderson 1983). This process of cyclical adaptation and counter-adaptation is commonly known as a "Red Queen" dynamic (Van Valen 1973; Bell 1982). Originally attributed to the probability of taxon extinction, the Red Queen process has come to define an important concept in biology—the role of biotic interactions for rapidly shaping evolutionary outcomes (reviewed in Brockhurst et al. 2014). Of particular interest for infectious disease are the ways in which antagonistic interactions can lead to perpetual evolutionary change (Woolhouse et al. 2002; Lively 2010). Models of coevolution by negative frequency-dependent selection, for example, describe a process whereby pathogens adapt to the most common host, providing a selective advantage to rare host genotypes (Hamilton 1980). Selection thus occurs in a time-lagged and negative frequency-dependent manner and genetic diversity within a population is maintained (e.g., Dybdahl and Lively 1998). Antagonistic coevolution can also occur via recurrent selective sweeps. Here, coevolution proceeds via the repeated occurrence, spread, and fixation of beneficial mutations, which inevitably reduces genetic diversity within populations (Levin 1981; Buckling and Rainey 2002).

Not only has the pervasive nature of the host–pathogen antagonism been fundamental to our understanding of infectious disease evolution, it has also provided an explanation for the very basis of male and female differences—the origin and maintenance of sexual recombination (Jaenike 1978; Hamilton et al. 1990; Lively 2010). In this context, sex is most strongly associated with negative frequency-dependent oscillations between host and pathogen genotypes. By breaking up statistical associations among loci, and increasing the frequency of rare alleles under the threat of parasitism (Peters and Lively 1999), recombination allows sexual organisms to overcome the "twofold" reproductive advantage of asexual competitors (Maynard Smith 1978). Although widely accepted as a fundamental component of infectious disease evolution, it is difficult to demonstrate Red Queen patterns in the field (but see Dybdahl and Lively 1998; Decaestecker et al. 2007; Koskella and Lively 2007; Thrall et al. 2012), and correlative evidence from genomic studies is not without its controversy (Hall and Ebert 2013). Nonetheless, the antagonistic coevolution between hosts and pathogens is integral to the evolution of sex, and the genesis of reproductive and behavioral differences between males and females.

Future Directions

While recent attention has been given to the role that sex differences play in pathogen evolution, we believe that this review highlights unrecognized ways in which sexual dimorphism can impact on the genetic basis of host–pathogen coevolution. A logical next step will be to formalize theory that explores the interplay between sex-specific adaptation and the rapid coevolutionary cycles that result from host-pathogen coevolution. Key to this process will be understanding the impact of male–female genetic correlations on rates of adaptation when patterns of selection change rapidly in both direction and magnitude. In general, theory predicts that when selection is sexually concordant, positive genetic correlations will accelerate adaptation to natural selection, whereas negative correlations will constrain how quickly a population can adapt to change (or vice versa with sexually antagonistic selection, Lande 1980, 1987; Bonduriansky and Chenoweth 2009).

However, the constraints that arise from cross-sex genetic correlations have yet to be studied in the context of a rapidly changing environment, such as the once provided by a coevolving pathogen (but for some related contexts, see Chevin 2013; Kopp and Matuszewski 2014). We may expect that if resistance is strongly positively correlated between the sexes, then host adaptation to a pathogen will proceed as expected by current theory. For other genetic correlation values, however, the rate of coevolution may decline or become unpredictable, particularly in the sex that less sensitive to the threat of infection (sensu Connallon and Clark 2014).

Complementing theory will be empirical work that explicitly examines the impact of host sexual dimorphism on pathogen adaptation. While it is both empirically and theoretically well-established that males and females can differ in their susceptibility to infectious disease (Sheridan et al. 2000; Cousineau and Alizon 2014), progress now depends on estimating and interpreting parameters directly relevant to the impact of host sex on pathogen populations (e.g., infection rates, transmission potential, and infection period (Anderson and May 1991)). Study systems well suited to this work will utilize hosts that are sexually dimorphic in immunity, plus have experimentally manipulable sex ratios or sex-role reversal—thus presenting the pathogen with two selectively distinct environments, as well as variability in the frequency of encountering each environment (e.g., Rolff 2002; Duneau et al. 2012; Masri et al. 2013). Additionally, comparisons between populations that have differed for many generations in the rate at which a pathogen encounters each sex offer a powerful way to find evidence for sex-driven pathogen evolution, whether via the classic cross-infection experiments (discussed in Schmid-Hempel 2013), or more modern developments in unravelling molecular signals of local adaptation (Balenger and Zuk 2014).

Concluding Remarks

We believe that an emerging challenge for disease research is to consider how the evolution of male–female differences permeates through the process of host–pathogen coevolution. The view that the sexes differ in a range of characteristics is well established and has recently been implicated in host resistance and pathogen adaptation (Duneau and Ebert 2012; Cousineau and Alizon 2014). Recognizing the importance of the genetic architecture of sexual dimorphism in these contexts, however, will offer new opportunities to understand the drivers and constraints placed on host–pathogen coevolution. Encouraged by the universal nature of sexual dimorphism and the recent results discussed in this review, we anticipate a greater exploration of male–female differences will offer new insight into how infectious disease evolves and the opportunities available to predict or control the spread of pathogens.

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