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Variation in host resistance could limit the spread of more broadly virulent pathogens

Victoria C Barclay

Center for Infectious Disease Dynamics; Department of Biology; Penn State University; University Park, PA USA

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One major question in studies on the ecology and evolution of infectious diseases is whether enhanced host resistance will drive the evolution of more virulent parasites. To date, theory,[1-4] laboratory studies,[5-9] and field studies[10,11] have all shown an association between increased host resistance and higher frequencies of virulent strains, suggesting that enhanced host immunity could have the undesirable side effect of favoring virulent pathogen genotypes during co-infection.[9,12,13] There is also evidence, however, that selection through susceptible hosts could lead to pathogen genotypes that are more capable of infecting and causing disease in highly resistant host genotypes.[14,15] What could account for the difference in results? In all of the vertebrate host–pathogen experiments to date, evolved pathogen virulence has been evaluated in the same host genotype as the evolution took place,[8,9] and so one explanation is that the evolution of more broadly virulent pathogens in a vertebrate host–pathogen system could be limited by pathogen fitness trade-offs during infection of hosts with different levels of genotypic resistance. In this issue of *Virulence*,[16] Kubinak and Potts present an elegant set of experiments which test and support this hypothesis.

The gold standard for empirically studying pathogen adaptation is serial passage, which involves repeated transmission of a pathogen through a succession of hosts.[17,18] Recently, Kubinak et al.[19] serially passaged Friend virus (FV) through a single strain of inbred congenic mice to test how differences at MHC (major histocompatibility complex) loci could influence patterns of viral adaptation and virulence evolution. Consistent with others,[8,9,18] the authors found that serial passage led to rapid increases in viral fitness and, consequently, more virulent disease. Importantly however, passage through one host genotype resulted in reduced fitness in another host genotype. This implies that pathogen adaption is host-genotype specific, and supports models of antagonistic host–pathogen coevolution (also known as the Red Queen).[20,21] In this issue of *Virulence*,[16] Kubinak and Potts expand on those previous studies by serially passaging FV through strains of mice genotypically distinct in resistance to the virus. They then infected each host genotype with each of the post-passage virus stocks, and tested overall pathogen virulence of the evolved lines compared to unpassaged stock. They found that viruses passaged through the most resistant host genotype were more virulent to their respective host than viruses passaged through less resistant hosts, but that such pathogen specialization resulted in lower mean virulence across hosts of different genotypes. This suggests that evolving to evade a strong immune response in one host comes at the substantial cost of being less able to evade the immune response of other hosts.

The results of Kubinak and Potts show a trade-off between the host traits of resistance and tolerance. Whereas resistance is defined by the ability of a host to limit parasite burden, tolerance is defined by the degree to which host health is affected by a given parasite burden: i.e., for a given pathogen load, more tolerant hosts suffer less than less tolerant ones.[22] Intriguingly, the most resistant host genotype was, overall, the least tolerant. Since the most resistant host selected for the most specialized viruses, and resistance in this system is associated with more severe disease, the authors imply that, in the short-term, selection may favor less resistant and more tolerant host genotypes that suffer less from the fitness cost associated with mounting a stronger immune response. Next, the authors plan to characterize the nature of the immune response mounted by hosts that vary in levels of resistance and tolerance to look for differences in immunopathological markers. Such experiments would be very valuable in providing further evidence of antagonistic pleiotropic relationships between host resistance and tolerance mechanisms.[22-24]

How do the Kubinak and Potts results relate to previous studies on host resistance and the ecology and evolution of infectious disease? Consistent with others,[5,8,9] they demonstrate that serial passage of FV through more resistant hosts selects for pathogen genotypes of greater virulence than those passaged through less resistant hosts, supporting claims that some types of vaccines or drugs may select for the evolution of more virulent pathogen genotypes.[4,9,25,26] However, their result that such pathogen specialization could reduce overall mean virulence is an important finding when we consider the spread and severity of disease associated with infectious agents in natural populations. For example, the undesirable side effects of increased pathogen virulence due to selection by drugs or vaccines could be limited if there is enough variation in host resistance in the population to limit the fitness of those pathogens. This finding is also

*Correspondence to: Victoria C Barclay; Email: vcb11@psu.edu
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highly relevant for agricultural contexts, where populations of low host genetic diversity and selective breeding for disease resistance are common. Important next questions would address how variation in resistance due to inherent differences in resistance genes, acquired immunity, or selection by drugs and vaccines, and their interactions with each other, affect overall pathogen virulence using more host and pathogen genotypes.

What makes this current study by Kubinak and Potts unique is that it focuses on experimentally defining the relationship between host resistance, pathogen adaptation, and virulence evolution in a vertebrate host–pathogen system. Indeed, recent studies have demonstrated that antagonistic coevolution can play a major role in determining rates of molecular evolution in other systems,[27-29] and that variability in host resistance could result in fitness trade-offs for the pathogen.[14] All of the previous work in vertebrates, however, has been performed in a mouse malaria system,[8,9] where evolved pathogen virulence has been evaluated in cohorts of host mice of the same genotype. Even in a world where antagonistic coevolution appears to be favoring specialization,[30] it is unlikely that a pathogen will only encounter a single host genotype, or vice versa. Kubinak and Potts demonstrate the importance of considering this diversity.

In multi-host disease systems (i.e., Lyme disease, malaria, sleeping sickness, etc.), the likelihood of a susceptible host contacting an infected host can be lowered by reducing the number of infected hosts, or by increasing host diversity, also known as the dilution effect.[31,32] Additionally, single-host diseases of wild animal populations (e.g., Tasmanian devil facial tumor disease),[33-35] inbred livestock,[36] and inbred crops,[37] along with emerging wildlife diseases,[38] are posited to be a consequence of low host diversity. Collectively, these studies by Kubinak and Potts nicely support arguments for the dilution effect as a mechanism for reducing disease spread over evolutionary time and that increased within-host species genetic diversity should limit disease spread by providing a selective advantage to hosts carrying rare resistance alleles.[19,38]

In agreement with the authors, the crucial next questions to ask are whether the observed effects are found using more host genotypes and different pathogens, and whether the effects occur in nature. For example, if we were to identify the key resistance genes that lead to specialization, could we breed for host resistance in a farm setting in a more intelligent way? By breeding for multiple lines of highly resistant hosts, and housing these hosts together, can we prevent the evolution of hypervirulent pathogens? Clearly, such data will lead to a better understanding of the overall implications of host resistance on the ecology and evolution of infectious diseases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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