VIEWPOINT

The Ecology of Genetically Diverse Infections

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Microparasite infections often consist of genetically distinct clonal lineages. Ecological interactions between these lineages within hosts can influence disease severity, epidemiology, and evolution. Many medical and veterinary interventions have an impact on genetic diversity within infections, but there is little understanding of the long-term consequences of such interventions for public and animal health. Indeed, much of the theory in this area is based on assumptions contradicted by the available data.

Advances in methods of genotyping are revealing that, in many infectious diseases, hosts are infected with more than one genotype of the same pathogen (*1–4*). Multiclone infections arise from infection with a genetically diverse innoculum or from reinfection before an existing infection is cleared. When clones share resources or host immune responses, the population dynamics of individual clones will be affected by the presence of others (*5*). Clonal performance can be enhanced if, for instance, numerically dominant clones are immunosupressive. But competitive interactions, in which coinfecting genotypes reduce the in-host growth rates, densities, or persistence of particular genotypes, have attracted the most attention from theoreticians and empiricists. Competition can affect host health or infectiousness and affect the transmission success (fitness) of individual clones, thus shaping the evolution of traits such as virulence and drug resistance. Competitive interactions will also play an important role in determining the fate of mutants and antigenic variants that arise de novo during the course of an infection.

Evidence of In-Host Competition

The ecology of genetic diversity within naturally acquired infections has perhaps been most studied in populations of *Plasmodium falciparum*, the main causal agent of human malaria. For these parasites, which are haploid in human blood, routine polymerase chain reaction (PCR) technology can be used to amplify a number of highly polymorphic markers. Consequently, a large body of data is being generated, and several authors have argued that the patterns that are emerging point to in-host competition. First, in older children and adults, parasite titers do not increase with the number of clones present (*6*), indicating that clonal densities within hosts are not regulated independently. Second, some studies show that infections provoking clinical attacks contain fewer clones than asymptomatic infections. This has been interpreted as overgrowth of asymptomatic infections by novel uncontrolled clones, or as evidence that diverse infections better protect against superinfection (*6*, *7*). Either explanation involves competitive suppression. Third, in an area of high transmission in Senegal, there was rapid turnover of genotypes within infections. Nearby, where transmission was less intense, turnover was less marked, suggesting that superinfection leads to competitive exclusion (*8*). Finally, across populations, the average number of clones per host rises less than linearly with the presumed force of infection (*3*), which is consistent with some sort of density-dependent regulation of clonal diversity.

Although they are suggestive of competition, these patterns also have other interpretations (*9*, *10*). To date, most studies involve nonquantitative measures of parasite diversity from cross-sectional surveys or incomplete time series on relatively few patients. Improvements in PCR and statistical methodology will undoubtedly help refine the picture. But as ecologists know only too well from the controversies of the 1980s, it is very hard to conclusively demonstrate competition using observational data alone.

Animal models of malaria demonstrate that substantial competition can occur between coinfecting clones (Fig. 1, A and B) (*11–14*). More generally, for a wide range of microparasites, experiments comparing the performance of clones alone and in mixed infections have demonstrated negative effects of the presence of other clones (Fig. 1, C and D) (*15–21*). Indeed, we know of no in vivo experiments that have failed to demonstrate competition during at least some parts of an infection. In some cases, suppression by competitors is more effective than that achieved by candidate vaccines; for example, competitive exclusion forms a basis for measures to control *Salmonella* and *Campylobacter* infection in chickens (*18*, *19*).

Mechanisms

All three types of competition among free-living organisms that are recognized by ecologists—exploitation, interference, and apparent (*22*)—could characterize interactions between clones in infections. Exploitation competition, a passive process in which an individual clone is affected by the amount of resource remaining after others have exploited it, must occur: Resource limitation is a known cause of intraclone competition in vivo, and conspecific clones will usually have overlapping resource requirements (*4*). The potential for interference competition (direct attack or exclusion by mechanical or chemical means) certainly exists. Several pathogens are known to actively synthesize molecules that reduce or even eliminate the success of their competitors in vitro, including bacteriocins (*23*) and molecules that block cell entry by subsequent viruses (*24*).

Apparent competition may be the most important type of competition. Increasing densities of one clone can have a negative effect on another (our definition of competition) by stimulating a host response that acts against both clones (*25*). Conjectures that concomitant immunity or premunition—host responses elicited by established parasites that prevent further infection by other parasites—is stimulated by microparasites such as *P. falciparum* have a long history (*26*), and are now the object of a resurgence of interest, if not conclusive data (*6*). There is experimental evidence consistent with concomitant immunity in other microparasites, although the mechanisms remain obscure (Fig. 1D). The success of several live attenuated vaccines demonstrates the potential potency of immune-mediated competition (*27*).

The impact of competition on clonal populations will almost certainly vary during an infection, with different life stages, for example, or as host responses render resource limitation irrelevant or shift from clone-transcending to clone-specific. Experimental studies have also shown that initial conditions, such as relative frequency at inoculation or, for superinfection, the temporal spacing and order of inoculation, can be important (*11*, *13*, *15*, *21*, *24*). So too can the presence of drugs. Moreover, growth rates in single infections do not always predict which clones will dominate in mixtures (*4*). Other

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factors, such as antigenic variation generated by individual clones, will also complicate the picture. Antigenic variation may also explain why competitive exclusion does not always occur, even in chronic infections in the absence of reinfection (*28*). These complexities make mathematical models more important for understanding the dynamics, but also less tractable.

Infectiousness

If competitive suppression does not occur, overall transmission will be higher from hosts with more clones. Infectiousness might also increase if, in response to competitive stress, pathogens reallocate resources from within-host replication to transmission-stage production, as they can do, for example, in response to drug stress (*29*). However, the relationship between in-host diversity and infectiousness has been little examined. One of the few transmission studies found that mixed-genotype infections of *P. chabaudi* were substantially more infectious to mosquitoes than were single-clone infections (*30*).

The epidemiological and evolutionary consequences of in-host competition depend crucially on how the competitive outcome within hosts affects transmission to new hosts. This will vary depending, in part, on whether in-host replicating stages are also the infectious stage or whether there are distinct nonreplicating transmission stages. The transmission rates of individual strains certainly can be reduced by in-host competition, particularly if they are introduced into an already infected host (*31*). But this is not always the case. In our *P. chabaudi* experiments, clones in multiply infected mice transmitted to mosquitoes as well as or even substantially better than they did from single-clone infections, despite marked competition within mice (Fig. 2). One explanation might be that clone-specific host responses dominate during the transmission phase, after competition has occurred, and that the presence of other clones can slow the development of these responses. Regardless of the mechanism, these data demonstrate that there need be no straightforward relationship between competitive outcome and transmissibility. Yet this relationship is key to predicting the evolution of medically relevant traits thought to correlate with competitive ability, such as drug resistance and virulence (*32*).

Disease Severity

By affecting pathogen densities, in-host competition could alter disease severity by altering either total pathogen densities or the densities of more or less virulent strains. More diverse infections could also provide greater protection against disease by protecting against superinfection (*6*, *7*). Finally, aggressive interference competition could result in collateral damage to the host.

It is too early to say whether competitive interactions affect host health in field situations. In falciparum malaria, for example, genetic diversity is often [but not always (*33*, *34*)] associated with disease severity, but both positively (*35*, *36*) and negatively (*6*, *37*). This contrary situation is apparently associated with age- and population-related differences in previous exposure and force of infection (*6*, *14*). A complicating factor is the effect of genetic diversity per se. The total pathogen burden will be higher if diverse infections occupy a broader niche space or are less easily controlled by the host. Mounting a response against genetically diverse infections may also be more costly to the host in terms of resources or immunopathology (*38*).

There is abundant experimental evidence that disease severity can be reduced by competitive interactions within hosts, with avirulent lines able to overgrow or exclude virulent variants (Fig. 1) (*15*, *20*, *39*). This protective effect often, but not always, requires the avirulent line to be administered first or at high frequency in the inoculum.

Virulence Evolution

Curiously, this body of experimental work directly contradicts the assumptions of a

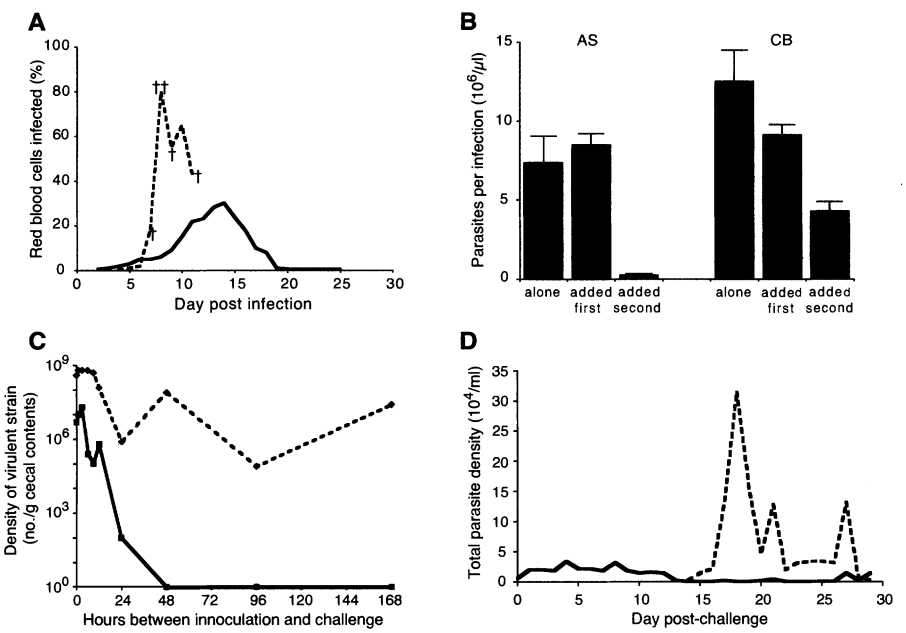

Fig. 1. Examples of within-host competition. (**A**) *P. berghei* in mice. When a virulent strain was inoculated into naïve mice (dotted line), parasitemias reached high levels and mice died (†). When the virulent strain was inoculated into mice infected 3 days earlier with a mild strain, total parasite densities were much lower and no mice died (solid line) (*11*). [Reprinted with permission from B. J. Hargreaves *et al.*, *Annals of Tropical Medicine and Parasitology* **69**, 289 (1975), fig. 2, and Taylor & Francis Ltd. (www.tandf.co.uk/journals)] (**B**) *P. chabaudi* in mice. The number of parasites of clone AS or CB in mice infected with each clone alone or in mixed infections with the clones added 3 days apart is shown (*4*, *14*). (**C**) *S. typhimurium* in chickens. Infection resulting from challenge with a virulent strain in chicks previously inoculated, when a day old, with a mild strain (solid line) or previously uninfected (dotted line) is shown. The presence of a mild strain reduces the density of the virulent strain, and this effect increases as the time between inoculation and challenge increases. Densities were measured 3 days after challenge (*15*). (**D**) *T. congolense* in cattle. Naïve cattle challenged by tsetse flies infected with line IL-285 became patent after 2 weeks and had high parasitemias (dotted line); no such infection was generated in cattle with chronic infections of line IL-311 that were given the same challenge (solid line). Chemotherapy confirmed that chronic infection, rather than antigen-specific immunity, was responsible for the protection (*16*). [Reprinted with permission from W. I. Morrison, P. W. Wells, S. K. Moloo, J. Paris, and M. Murray and *The Journal of Parasitology*]

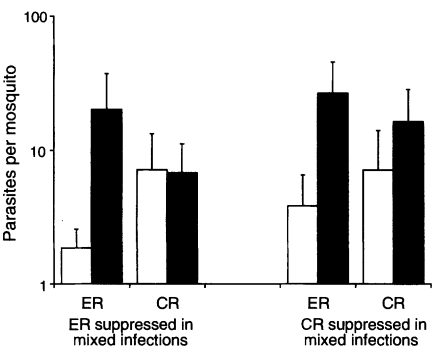

Fig. 2. Transmission of individual clones of *P. chabaudi* from mice to mosquitoes. Despite competitive suppression within mice (*49*), clones ER and CR transmitted as well or better from mixed clone infections (black bars) than from single-clone infections (white bars). Severe competitive suppression (<10% of the numbers found in control mice) of clone ER (left panel) or clone CR (right panel) was induced by appropriate initial conditions. Data are geometric means of a total of 64 mice, made up of four replicates of each set of initial conditions (*13*, *30*).

large body of theory dealing with the consequences of in-host genetic diversity for the evolution of virulence. The basic idea is that the host is a resource and that virulence (harm to the host) is an unavoidable side effect of host exploitation. Natural selection is then assumed to optimize the pathogen's rate of exploitation of the host by balancing the fitness costs (the risk of host death and hence pathogen death) against the fitness advantages (resources available for transmission or for evading host defenses). Many authors have pointed out that the optimal rate of host exploitation, and hence virulence, is higher in genetically diverse infections because in-host relatedness is reduced (*40*–*43*). Parasites that slowly exploit hosts will be outcompeted by those exploiting hosts more rapidly. Even if host life expectancy is reduced so that all parasites do worse, prudent parasites do disproportionately worse and are thus eliminated by natural selection.

Yet when virulent and avirulent lines have been deliberately competed in controlled experiments, it has been the avirulent strain that has won (Fig. 1) (*15*, *20*, *39*). The extent to which this is a consequence of experimentalists testing situations that are most likely to reduce virulence is unclear. Several lines of indirect evidence do accord with the assumptions of the theoretical models. Live attenuated vaccines can revert to virulent forms, which dominate attenuated forms (*40*), and serial passage experiments usually select for increasing replication rate and virulence in the host in which they have been passaged (*44*). The key to resolving the issue is experimental elucidation of the relationship between virulence and competitive ability. Quite possibly there is no simple generality.

Even the theoretical prediction that genetically diverse infections generate selection for increased virulence depends on assumptions about the nature of the competition. Chao *et al.* (*45*) have pointed out that faster rates of host exploitation need not be the only adaptation favored by competition. Traits that involve exploitation or inhibition of competing genotypes, such as the production of allelopathic substances, can also be selected. These can lead to less effective exploitation of the host and hence to reduced virulence. Defective interfering viruses may represent a different sort of example. These are mutant viruses that parasitize wild-type viruses and, in so doing, reduce virus titers, infectiousness, and virulence—at least in vitro. Thus, to predict even the direction of virulence evolution in response to competition, we need to know more about the precise way in which pathogen genotypes interact within hosts and how this affects the fitness of those genotypes and of the host.

Drug Resistance

Drug-resistant mutants must compete with wild-type parasites in the hosts in which they arise and then, as they spread, with unrelated parasites in other hosts. Simple models show that the rate at which resistance spreads, and hence the clinically useful life-span of a drug, depends on the details of this competition. If drug-sensitive strains are competitively superior in hosts not receiving chemotherapy, the evolution of resistance will be slowed. If resistant strains are able to increase their transmission from hosts from which competitors have been eliminated by chemotherapy, the spread of resistance will be hastened. This is a major issue in the malaria literature (*46*). Key, again, is the relationship between in-host competitive ability and transmission rates. Models of drug resistance typically assume a positive relationship; the possibility of a negative relationship, as suggested by the only relevant data we have (Fig. 2), has yet to be incorporated into drug resistance models.

Implications of Intervention

Many disease control measures will alter the number of genotypes interacting within infections, either by reducing the force of infection (for example, by means of vector control) or by directly altering the population dynamics of subsets of the circulating genotypes (for example, by the use of strain-specific vaccines). The possible consequences of this for public health are only beginning to be investigated (*47*). The unintentioned competitive release of drug-resistant or virulent strains is one possibility. Another is that disease incidence could also rise or fall, depending in part on whether competition decreases (*31*) or enhances (Fig. 2) transmission.

Even highly effective, strain-transcending vaccines will alter population-wide levels of in-host competition. Epidemiology is a special case of metapopulation ecology, with hosts seen as patches and vaccination as patch destruction. Simple ecological models of competition in metapopulations show that habitat (patch) destruction can lead to increases in the total number of patches occupied by an inferior competitor and even to an increase in the total number of patches occupied (*48*). By direct analogy, there are circumstances in which some levels of vaccine coverage will, by reducing the prevalence of competitively superior strains, lead to an increase in the prevalence of competitively inferior strains and even of the disease as a whole. How this affects population-wide health depends crucially on the relationships between competitive ability and traits such as virulence.

Many ecological and evolutionary consequences of altering levels of pathogen competition will become obvious only on time scales longer than those of clinical trials. Advances in molecular technology are making it increasing easy to study the ecology of the clonal communities that constitute many infections. Such data will be an important part of the information required to anticipate the consequences of future intervention programs—and to understand the public health experiments we have already set in train.

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VIEWPOINT

Evolution of Cell Recognition by Viruses

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Evolution of receptor specificity by viruses has several implications for viral pathogenesis, host range, virus-mediated gene targeting, and viral adaptation after organ transplantation and xenotransplantation, as well as for the emergence of viral diseases. Recent evidence suggests that minimal changes in viral genomes may trigger a shift in receptor usage for virus entry, even into the same cell type. A capacity to exploit alternative entry pathways may reflect the ancient evolutionary origins of viruses and a possible role as agents of horizontal gene transfers among cells.

Although viral entry into cells is not the only determinant of cell tropism, ever since the first evidence that animal viruses (*1*) and bacterial viruses (*2*) enter cells through specific receptors, considerable effort has been put into the identification of those structures that mediate cell recognition by viruses and the transfer of their genetic material into cells. The picture of how viruses exploit surface cellular macromolecules to initiate their infectious cycles has become increasingly complex (*3*, *4*). Receptors used by viruses belong to widely different families of proteins, carbohydrates, or lipids, often in complex cell surface matrix structures (*4*, *5*) (Table 1). Some of them are involved in immune modulation, signaling pathways, or cell adhesion or have no known function.

A Receptor for Several Viruses, a Virus for Several Receptors

A survey of different virus groups illustrates that receptor usage does not generally show any obvious correlation with virus phylogeny (Table 1). It is often not possible to anticipate its use of one type of receptor molecule or another (*3*–*5*). For example, at least two receptors have been proposed to mediate entry of human hepatitis C virus (HCV) into hepatocytes: CD81, a member of the tetraspanin superfamily of proteins (*6*), and the low-density lipoprotein receptor (LDLR) (*7*). Comparison of these proposed receptors for HCV with the receptor for hepatitis A virus (a mucine-like class I integral membrane glycoprotein) and for duck hepatitis B virus (the C-domain of carboxypeptidase D, pg180) (*8*) indicates that despite their specificity for the same target organ, hepatitis viruses use disparate molecules for entry into hepatocytes. The picornaviruses, which encompass several important human and animal pathogens and share structural features in their capsids, may use several macromolecules as receptors (*9*). Likewise, some receptors are shared by coronaviruses associated with different pathologies (*5*) (Table 1).

Perhaps the most emblematic example of cross-phyla sharing of a receptor is coxsackievirus adenovirus receptor (CAR) (*10*). CAR is used by adenoviruses 2 and 5, which are agents of respiratory disease in children, as well as by coxsackieviruses B1 to B6, which are associated with febrile illness, meningitis, and some cardiopathies. Of the many examples, the interaction of the human influenza A virus hemagglutinin with *N*-acetylneuraminic acid, and the ensuing conformational alterations involved in pH-dependent membrane fusion, are one of the best characterized at the structural and functional levels (*11*) (Table 1).

Thus, the susceptibility of different cell types to a virus, in the absence of a characterized receptor indicates the existence of alternative receptors. Herpes simplex viruses interact with one of at least three virus entry-mediator proteins (Hve A is a member of the tumor necrosis factor receptor protein family and Hev B and Hev C are two members of the immunoglobulin superfamily), yet cells lacking these receptors may still allow efficient penetration of the virus. The related tumor-causing Epstein-Barr virus (EBV) shows a marked B lymphotropism owing to expression of a specific receptor, CD21 (or CR2). Again, EBV can replicate in differentiated epithelial cells that do not express CD21, implying the participation of some other unidentified receptor (*5*). Furthermore, receptor expression alone may not be sufficient for a productive viral infection. Mice made transgenic for the functional form of the poliovirus receptor (PVR) become susceptible to poliovirus and develop limb paralysis. Yet, the distribution of PVR mRNA in human and mice tissues does not match the replication sites of the virus (*12*, *13*).

Modulation, Expansion, and Shifts in Receptor Usage

The reasons why structures implicated in immune responses, cell signaling, cell-cell recognition, recruitment, and inflammation abound among viral receptors (*5*, *9*) are not obvious. Possibly, these structures are subsets of the most abundant type of molecules found on cell surfaces capable of triggering the uptake of virus particles and the irreversible conformational changes that must precede uncoating and genome replication. Given the population structure of RNA viruses (*14*), key issues for understanding changes in host cell specificity are the genetic distances that a viral genome must bridge and the selective forces involved.

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