Update TRENDS in Parasitology Vol.xxx No.x

Full text provided by www.sciencedirect.com ScienceDirect

Research Focus

Virulence and resistance in malaria: who drives the outcome of the infection?

Thierry Lefèvre[1], Marta Sanchez[1], Fleur Ponton[1], David Hughes[2] and Frédéric Thomas[1]

[1] Génétique et Evolution des Maladies Infectieuses, UMR CNRS/IRD 2724, IRD, 911 Avenue Agropolis, BP 64501, 34394 Montpellier Cedex 5, France
[2] Centre for Social Evolution, Institute of Biology, Universitetsparken 15, DK-21000 Copenhagen, Denmark

Theoretical and experimental studies have established the dynamic nature of virulence and that, like all traits, it has evolved. Understanding parasite evolution offers a conceptual framework for diverse fields and can contribute greatly to decision-making in disease control. Recently, Grech *et al*. investigated the effects of host genotype-by-parasite genotype interactions on the expression of virulence in an artificial rodent-malaria system. They found that both parasite and host effects explained most of the variance in the virulence, resistance and transmission potential. These findings are a major contribution to the emerging debate on the pros and cons of a coevolutionary approach of virulence evolution; they also hold great potential for more effective control strategies.

Predicting the evolution of virulence

Predicting the conditions that cause parasites to harm their hosts is of central importance in biological sciences, not only because parasites vary in how they interfere with the ecology and evolution of free-living organisms, but also because of applied benefits in medicine (particularly public health strategies) and epidemiology. There is increasing interest in the effects that natural selection has on the traits of parasites, and on virulence in particular.

Despite considerable progress made by evolutionary biologists in understanding the factors that influence the outcome of infections, scientists are still divided on the way to assess the problem. As pointed out by Grech *et al*. [1], 'two not mutually exclusive literatures' coexist on this topic: parasite-centred and coevolutionary models. The parasite-centred approach typically assumes that virulence is determined mainly by the parasite genotype. In parasite-centred models, virulence is then modelled as an optimality problem (see Glossary), which assumes that a given pathogen strain has a virulence phenotype that is stable across a range of host genotypes. Conversely, coevolutionary models, such as the gene-for-gene and matching-allele models, emphasize that the parasite and the host genotypes together determine virulence. The fitness loss is then determined by interactions between parasite and host genotypes, with particular parasite strains being harmful for some host genotypes, and benign in others (Figure 1). Analogous arguments can be made for host resistance. For instance, if genetic variation for resistance depends mainly on a host effect, then the evolution of resistance can (as before) be modelled as a host-centred optimality problem.

Despite the existence of suitable systems with which to test these hypotheses (e.g. Refs [2,3]), theoretical speculation has proven more attractive than data collection (e.g. Refs [4–9]), and a real understanding of the interactions between host and parasite is still lacking.

The rodent-malaria system as a model for virulence evolution

An attempt to combine the two approaches has been described by Grech *et al*. [1], who used a rodent (laboratory mice)-malaria (*Plasmodium chabaudi*) model system to determine whether host-by-parasite interactions were involved in determining factors such as the virulence, resistance and transmission potential of the pathogen.

Glossary

Fully cross-factored experiment: experimental design in which all levels of one treatment are tested in combination with all levels of the other treatment.
Gene-for-gene model: for a host resistance gene, there is a corresponding avirulence gene in the parasite with which it interacts. The outcome of the interaction depends on the combination of alleles at the locus in the genomes of the two interacting species. In host–parasite interactions, it means that one parasite genotype has 'universal virulence' (i.e. it can infect all host genotypes).
Matching-allele model: each parasite genotype functions as either an avirulence allele or a virulence allele depending on the host genotype. Similarly, each host genotype functions as either a resistance or a susceptibility allele depending on the parasite genotype. Here, infection (or resistance) requires an exact match between resistance and virulence genotypes.
Optimality problem: optimality theory in evolutionary biology aims to test insights into the biological constraints that influence the outcome of evolution. Optimality models serve to improve our understanding of adaptations, rather than to demonstrate that natural selection produces optimal solutions (for more details see Ref. [20]).
Proximate mechanisms: the biochemical, developmental and physiological mechanisms that determine a trait of an organism. [As opposed to ultimate mechanisms: all evolutionary mechanisms (i.e. natural selection, genetic drift, migration and mutations) that determine a trait.]
State-dependent nature of virulence: the plastic part of virulence owing to environmental conditions (i.e. phenotypic plasticity). Parasites might perceive their immediate and external environment, and respond appropriately through adaptive phenotypic plasticity (i.e. in a state-dependent manner) to maximize their fitness.

Corresponding author: Thomas, F. (frederic.thomas@mpl.ird.fr).
Available online xxxxxx.

  doi:10.1016/j.pt.2007.04.012

Please cite this article in press as: Lefèvre, T. et al., Virulence and resistance in malaria: who drives the outcome of the infection?, Trends Parasitol. (2007), doi:10.1016/j.pt.2007.04.012

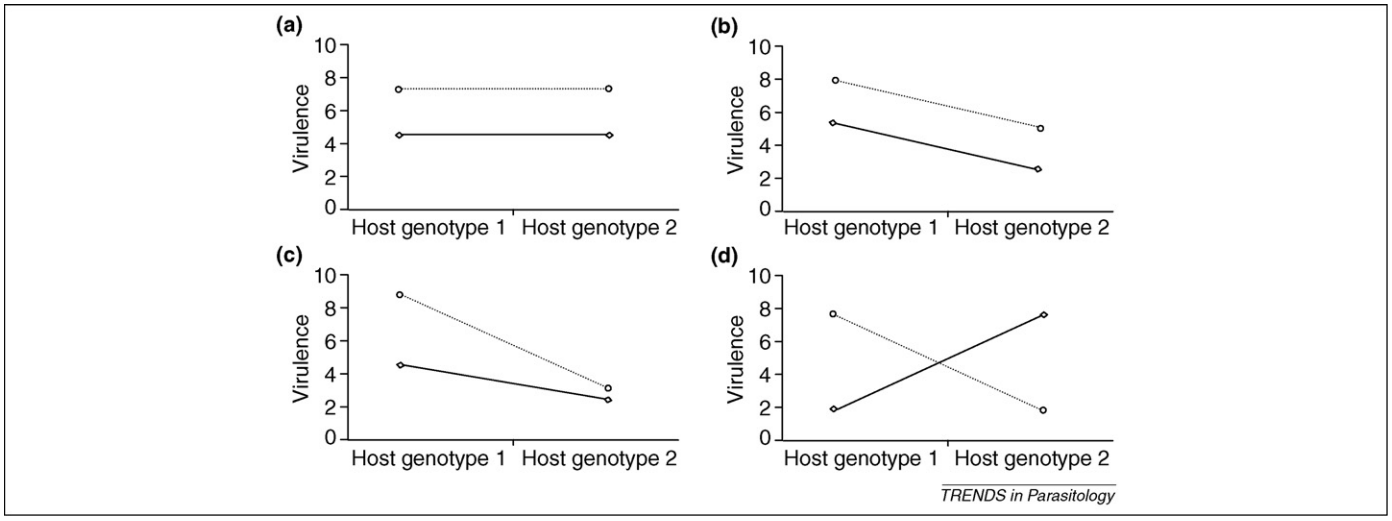

Figure 1. Host, parasite and host-by-parasite interaction effects, showing a parasite main effect only **(a)**; additive parasite and host main effects **(b)**; nonadditive host and parasite interactions without crossing reaction norms where pathogen differences are more apparent in one of the host genotypes **(c)**; and host-by-parasite interactions with crossing reaction norms of the sort assumed in most coevolutionary models **(d)**. In (d), parasite genotypes that are virulent in one host genotype are less virulent in the other and vice versa. Parasite 1 is indicated by a broken line and parasite 2 by an unbroken line. Modified, with permission, from Ref. [1].

There are several advantages to using *P. chabaudi* to assess such questions. The availability of a range of *P. chabaudi* clones and of distinct hosts enabled the authors to test distinct assumptions derived from the two kinds of model. Importantly, this study was performed through a fully cross-factored experiment, using four parasite genotypes of *P. chabaudi* and four inbred mouse strains. The results indicated that all possible scenarios are met (Figure 1), depending on the measure of virulence chosen. However, most of the variance in virulence, in resistance to parasites and in transmission potential, is explained mainly by parasite and host effects. Host-by-parasite interactions, although significant, had limited effects.

Such conclusions are in accordance with those obtained in two other malaria studies, which examined both host and parasite genotypes simultaneously [10,11]. Thus, Grech *et al*. [1] suggest that parasite responses to selection on virulence depend mainly on host heterogeneity, at least in the context of malaria infections. In other words, they give more support to parasite-centred approaches than to the prevailing paradigm of a coevolutionary approach in which host-by-parasite interactions predominate.

Relevance for the human-malaria system?

The study performed by Grech and colleagues is important for several reasons. Understanding the processes that determine parasite evolution is of interest for scientists attempting to establish links between fundamental ecology and applied disciplines (e.g. epidemiology and medicine). This study [1] is one of the few times that host-by-parasite interactions have been tested for in a vertebrate system. Even if the model studied is an artificial rodent-malaria system, links with the human-malaria system exist. For example, large variation in virulence and resistance is observed [12]. People infected with each of the four human *Plasmodium* species (*Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium ovale* and *Plasmodium malariae*) can be asymptomatic or might present different degrees of disease symptoms. Large variation in symptoms is observed from relatively minor symptoms (e.g. temporary fever, chills, headache, sweats, nausea and vomiting) to severe fever, cerebral malaria, coma and death. In Thailand, for example, Chotivanich *et al*. [13] reported that 'a patient may arrive at the hospital with a parasitemia >40% and be able to walk, whereas others may die with <1% parasitemia'. In addition, parasite variation in immunogenic antigens, variation in host immune memory [14] and variation owing to environmental features, such as seasonality, make understanding why the outcome of infection in humans is so variable difficult.

A potential limitation of this work (which is acknowledged by the authors) is that the choice of host strains and/or of parasite clones might not be representative of the genetic diversity of *Plasmodium*–host interactions in the field. No one system is going to give all the answers and, even if it does, there is no guarantee that those answers are generally applicable to the real world. Further examples are needed before generalizations can be made.

Another limitation of the Grech *et al*. study is linked to the choice of model. First, they describe their host–parasite system as a medically relevant model; however, *P. chabaudi* does not infect humans. Second, using laboratory mice can be problematic because mice are not a natural host of *P. chabaudi* and, therefore, evolution is unlikely to have acted on this system. Thus, care must be taken in extrapolating results from these models to human malaria [15]. In our opinion, this work is an example of the kind of research that should be conducted and extended upon to explain virulence variation rather than a demonstration of which party drives the outcome of host–parasite interactions.

Beyond genetic factors

When a character is variable for both genetic and environmental reasons, two individuals might differ because they have: (i) different genotypes; (ii) different environmental experiences; or (iii) both. Virulence is a

Please cite this article in press as: Lefèvre, T. et al., Virulence and resistance in malaria: who drives the outcome of the infection?, Trends Parasitol. (2007), doi:10.1016/j.pt.2007.04.012

character whose phenotypic expression depends on both genetic (two genomes; the parasite and the host) and environmental factors. By adopting the same experimental design, it would be interesting to investigate, for a given host genotype, the effect of: (i) age of the host; (ii) body condition; and (iii) immunocompetence. For example, all things being equal, *P. falciparum* is more virulent in children than in adults. In children, the fitness cost of host mortality for the parasite might balance the fitness benefits of higher transmission rates and slower clearance rates [16].

Unfortunately, the extent to which the interactions between host environmental experiences and parasite genotypes influence the expression of virulence is poorly documented and would benefit from being studied with the approach proposed by Grech *et al.* Such a study, using laboratory systems, would enable examination of the state-dependent nature of variations in virulence and resistance, and its causes (i.e. state-dependent adaptive response of the parasite and/or of the hosts, or consequences of other phenomena). Additionally, the experimental design proposed by Grech *et al.* is a promising approach to explore questions related to mixed infections.

Future challenges

Because of its central role in the study of host–parasite interactions, virulence is extensively studied by biologists across disparate disciplines. There have been several efforts to bring together the different approaches to virulence theory [17]. However, the continued separation between subdisciplines, such as evolutionary ecology and medicine, is a limitation that needs to be overcome if we are to understand complex processes such as virulence.

One possible solution is the use of emerging technologies to address the proximate mechanisms involved during the interactions between host and pathogen. Techniques taken from the field of post-genomics provide a comprehensive view of the expression of entire genomes, and might help to decipher the molecular and physiological basis of virulence and resistance variation. Here exists an opportunity for evolutionary ecologists and molecular biologists to address jointly exciting questions, such as what a host effect, a parasite effect and an interaction between the effects means at the proximate level. Having such answers, which are then framed within a solid theoretical framework and complemented by accurate understanding of other important ecosystem properties, we are more able to guide effective control of malaria, in what Grech *et al.* term 'a real-world approach' [18,19].

References

1 Grech, K. *et al.* (2006) Host–parasite interactions for virulence and resistance in a malaria model system. *J. Evol. Biol.* 19, 1620–1630
2 Webster, J.P. *et al.* (2004) Do hosts and parasites coevolve? Empirical support from the *Schistosoma* system. *Am. Nat.* 164, S33–S51
3 Thompson, J.N. and Burdon, J.J. (1992) Gene-for-gene coevolution between plants and parasites. *Nature* 360, 121–125
4 Frank, S.A. (1996) Models of parasite virulence. *Q. Rev. Biol.* 71, 37–78
5 Sasaki, A. (2000) Host–parasite coevolution in a multilocus gene-for-gene system. *Proc. R. Soc. B* 267, 2183–2188
6 Gandon, S. *et al.* (2002) The evolution of parasite virulence, superinfection, and host resistance. *Am. Nat.* 159, 658–669
7 Restif, O. and Koella, J.C. (2003) Shared control of epidemiological traits in a coevolutionary model of host-parasite interactions. *Am. Nat.* 161, 827–836
8 Andre, J.B. *et al.* (2003) Within-host parasite dynamics, emerging trade-off, and evolution of virulence with immune system. *Evolution* 57, 1489–1497
9 Day, T. and Proulx, S.R. (2004) A general theory for the evolutionary dynamics of virulence. *Am. Nat.* 163, 40–63
10 Mackinnon, M. *et al.* (2002) Virulence in rodent malaria; host genotype by parasite genotype interactions. *Infect. Genet. Evol.* 1, 287–296
11 de Roode, J.C. *et al.* (2004) Host heterogeneity is a determinant of competitive exclusion or coexistence in genetically diverse malaria infections. *Proc. R. Soc. B* 271, 1073–1080
12 Miller, L.H. *et al.* (2002) The pathogenic basis of malaria. *Nature* 415, 673–679
13 Chotivanich, K. *et al.* (2000) Parasite multiplication potential and the severity of falciparum malaria. *J. Infect. Dis.* 181, 1206–1209
14 Richie, T.L. and Saul, A. (2002) Progress and challenges for malaria vaccines. *Nature* 415, 694–701
15 Taylor-Robinson, A.W. (1995) Regulation of immunity to malaria: valuable lessons learned from murine models. *Parasitol. Today* 11, 334–341
16 Makinnon, M.J. and Read, A.F. (2003) Virulence in malaria: an evolutionary viewpoint. *Phil. Trans. R. Soc. B* 359, 965–986
17 Read, A.F. *et al.* (2004) The evolution of pathogen virulence in response to animal and public health interventions. In *Infectious Disease and Host–Pathogen Evolution* (Dronamraj, K., ed.), pp. 265–292, Cambridge University Press
18 Lefèvre, T. *et al.* (2006) New prospects for research on manipulation of insect vectors by pathogens. *PLoS Pathog.* 2, 633–635
19 Hughes, D.P. and Boomsma, J.J. (2006) Muscling out malaria. *Trends Ecol. Evol.* 21, 533–534
20 Parker, G.A. and Maynard Smith, J. (1990) Optimality theory in evolutionary biology. *Nature* 348, 27–33

Please cite this article in press as: Lefèvre, T. et al., Virulence and resistance in malaria: who drives the outcome of the infection?, Trends Parasitol. (2007), doi:10.1016/j.pt.2007.04.012