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Discussion

Immunity and the emergence of virulent pathogens

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ABSTRACT

The emergence/re-emergence of infectious diseases has been one of the major concerns for human and wildlife health. In spite of the medical and veterinary progresses as to prevent and cure infectious diseases, during the last decades we have witnessed the emergence/re-emergence of virulent pathogens that pose a threat to humans and wildlife. Many factors that might drive the emergence of these novel pathogens have been identified and several reviews have been published on this topic in the last years. Among the most cited and recognized drivers of pathogen emergence are climate change, habitat destruction, increased contact with reservoirs, etc. These factors mostly refer to environmental determinants of emergence. However, the immune system of the host is probably the most important environmental trait parasites have to cope with. Here, we wish to discuss how immune-mediated selection might affect the emergence/re-emergence of infectious diseases and drive the evolution of disease severity. Vaccination, natural (age-associated) and acquired immunodeficiencies, organ transplantation, environmental contamination with chemicals that disrupt immune functions form populations of hosts that might exert specific immune-mediated selection on a range of pathogens, shaping their virulence and evolution, and favoring their spread to other populations of hosts.

1. Introduction

Despite the euphoria that the development of antibiotics, antiparasitic drugs and vaccines has prompted in the 20th century, it is now clear that the hope of a definitive clearance of the risk of infectious diseases is a utopia. The evolution of drug-resistant strains and the emergence/re-emergence of pathogens that has occurred during the last decades indicate that pathogens and parasites remain a pervasive threat for human and wildlife health (Daszak et al., 2000; Morens et al., 2008). Jones et al. (2008) reviewed 335 emerging infectious disease "events" during the period 1940–2004 and found that their incidence has increased to reach a peak in the 1980s, and that microparasites (viruses and bacteria) constitute the vast majority of emerging infectious diseases (74.4%).

Identifying the determinants promoting the emergence/re-emergence of infectious diseases has been one of the main areas of research in the last years (Jones et al., 2008; Morens et al., 2004; Thompson et al., 2010; Weiss and McMichael, 2004). A number of ecological, demographic, and socio-economic factors likely increase the risk of emergence of novel pathogens. Climate change, deforestation, economic development and land use, increased risk of contact with reservoir species, international travel and commerce, reduced genetic variability of domestic animals are some of the factors that can explain why some pathogens have jumped from one species to another (for instance, humans) and found a suitable ground to establish a novel infection (Binder et al., 1999; Jones et al., 2008; Plowright et al., 2008; Schrag and Wiener, 1995).

Although these environmental factors are those that determine the likelihood of contact between the parasite and the novel host, the severity of the infection will mostly depend on some specific, intrinsic, factors such as for instance the capacity of the host immune response to clear the infection, or the capacity of the pathogen to persist in spite of the host immune response. Upon entering the host, the immune system certainly represents the most important environmental factor pathogens have to cope with (Frank, 2002). Given the extremely high evolutionary potential of pathogens (large populations, high genetic variation, short generation time), selection pressures exerted by the immune system should rapidly produce a micro-evolutionary change in the pathogen.

The threat posed by emerging infectious diseases depends both on the likelihood of the pathogen to encounter and shift from one host to another and on its capacity to adapt to the novel host. This means that in addition to the ecological view of pathogen emergence we also need to approach the problem in terms of the evolu-

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tionary forces that will shape parasite virulence and therefore disease severity (Alizon et al., 2009).

In this discussion article, we wish to make the point that the host immune system is one of the factors that can drive the emergence of novel diseases (Morris and Potter, 1997) and most importantly shape their evolution. Human interventions aiming at improving defenses (vaccination), or at reducing them (following, for instance, organ transplant), as well as natural (age-dependent) and acquired (infection-induced) immunodeficiencies generate populations of hosts where pathogens can experience different selection regimes and evolve towards increased levels of pathogenicity. Human activity can also interfere with the proper functioning of the immune response in free ranging animal populations since many environmental contaminants have immune suppressive properties (Galloway and Handy, 2003; Martin et al., 2010). We will first shortly remind the theoretical framework currently used to explain the evolution of parasite virulence; then, we will see how populations of hosts with specific immune profiles can contribute to the emergence of virulent strains of parasites.

2. Host immunity and the evolution of parasite virulence

Parasite virulence is defined as the damage suffered from the host upon infection (Frank, 1996). In an evolutionary perspective, infection is costly if it reduces host fitness; therefore, parasite virulence is usually measured as the reduction in host survival/fecundity following the infection. Given that host mortality ends the infectious period as well, virulence has been considered as a maladaptive trait for the parasite. However, in the last decades both theoretical and experimental works have shown that the evolution of virulence depends on the trade-off between the benefits of parasite multiplication/reproduction in terms of transmission and the cost in terms of reduced infectious period (Alizon et al., 2009; de Roode et al., 2008; Mackinnon and Read, 2004b). The trade-off model of parasite virulence rests on the assumption that the infection-induced host damage (the virulence) is an increasing function of parasite multiplication/reproduction. Multiplication/reproduction is obviously an essential component of parasite transmission; strains producing large numbers of propagules having more opportunities to be successfully transmitted to a novel host. Excessive parasite multiplication/reproduction might, however, drain too much energy away from the host and/or induce too much damage, possibly resulting in the death of the host. Host death also stops the transmission of the parasite. Virulence, therefore, evolves under the action of two selective forces pushing in opposite directions: positive selection on traits that increase transmission and negative selection on traits that shorten the infectious period. Any factor that alters the strength of these two opposing forces should induce a shift in the optimal virulence value. A few studies have provided evidence in support to the assumptions and predictions of the trade-off model of parasite virulence, in a range of host-parasite associations (Atkins et al., 2011; de Roode et al., 2008; Jensen et al., 2006; Mackinnon and Read, 1999). It is however worth noting that the trade-off model might not apply to all pathogens for several reasons. For instance, the cost paid by the host upon infection might be more due to an over-reacting immune response, and if immune potency is not an increasing function of parasite density, there might be a decoupling between parasite multiplication and virulence (Graham et al., 2005).

As mentioned above, the immune system is surely the main environmental factor parasites have to cope with once they have managed to enter the host. The consequences of immune mediated selection on the diversity of parasite strains have been extensively studied using mathematical models, population genetics and experimental approaches (Antia and Lipsitch, 1997; Buckee et al., 2008; Coombs et al., 2007; Fenton et al., 2006; Mackinnon and Read, 2004a; Nash, 1997; Raberg et al., 2006; Ross and Rodrigo, 2002; van Baalen, 1998; Wodarz, 2006). For instance, it has been suggested that the intensity of the immune response drives the rate at which viral populations can adapt to their hosts (Grenfell et al., 2004). When there is no immune response, there is no selection pressure to escape immunity and the dominant viral strain with the highest replicative potential dominates the viral population. If viral replication determines the virulence of the pathogens, this can favor highly virulent strains. At the other extreme, when the immune response is so strong that infection is rapidly cleared, there might be no time for the viral population to mutate into immune escape strains. Viral adaptation is therefore maximal at intermediate level of immune selection were immune escaping viral strains can enjoy an appreciable selective advantage (Grenfell et al., 2004). This example refers to the average individual immunity; however, the emergence of epidemic waves also largely depends on the average population immunity (herd immunity). The duration of immune protection following a primary infection varies tremendously between pathogens; measles induce a life-long protection whereas influenza viruses arise as seasonal epidemics following the emergence of viral variants that elicit a very limited cross-immunity. Relaxed immune-mediated selection at the two biological levels (individual vs. population) might produce somehow unexpected results. *Bordetella pertussis* is the agent of whooping cough, a bacterial disease of childhood. Infection with *B. pertussis* induces a protective immunity that wanes with time. Re-exposure boosts the response of the primed immune system, clearing the infection with no disease symptoms or transmission. Following the vaccination campaigns, the incidence of whooping cough has declined in North America and Europe. However, in spite of large vaccine coverage, the incidence of whooping cough has increased in the last 20 years, especially in teenagers and adults (even those who had been vaccinated in their childhood). Lavine et al. (2011) have recently put forward a possible solution to this apparent paradox. Before the vaccination epoch, whooping cough was prevalent among children; adults who had been exposed to the bacterium during their infancy were regularly re-exposed to the pathogen with a subsequent boosting of their primed immune response. This resulted in rapid clearance and asymptomatic disease in adults. The massive vaccination campaigns have substantially contributed to reduce the circulation of the bacterium, preventing the boosting of the immune response before immunity completely decays. Natural boosting of the prime immune response in the pre-vaccine era therefore maintained a high level of herd immunity, in spite of a decaying individual immunity.

The immune response can also affect the evolution of parasite virulence by determining the likelihood of infection by multiple parasite strains, because the immune system might be less prone to clear mixed infections (de Roode et al., 2005). When different parasite strains compete within the host for common resources, genotypes with the fastest replication rate are expected to outcompete the other strains, which should favor the most virulent genotypes (Bell et al., 2006; Ben-Ami et al., 2008). Contrary to this view, a recent theoretical model has suggested that when the immune response is impaired, competition among parasite strains can promote the evolution of a reduced level of virulence (Choisy and de Roode, 2010). These selected examples illustrate the complex relationship between host immunity, the emergence of novel parasite strains and the evolution of virulence. Depending on the specific traits of the interaction, including the environmental conditions where the interaction takes place, host immunity can favor or impede the emergence of novel strains, as well as select for increasingly virulent or benign parasites.

Host immunity is a highly variable trait that depends both on genetic and environmental factors (Lazzaro and Little, 2009). As al-