Of mice, macaques and men: scaling of virus dynamics and immune responses

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In this Opinion piece, I argue that the dynamics of viruses and the cellular immune response depend on the body size of the host. I use allometric scaling theory to interpret observed quantitative differences in the infection dynamics of lymphocytic choriomeningitis virus (LCMV) in mice (*Mus musculus*), simian immunodeficiency virus (SIV) in rhesus macaques (*Macaca mulatta*) and human immunodeficiency virus (HIV) in humans.

It is well-known that the average metabolic rate of cells is typically lower in larger species (Kleiber, 1932). Allometric theory predicts that the total metabolic rate of an organism scales approximately as $M^{3/4}$, with M being the body mass (West et al., 1997). Assuming invariant size and volume of cells between species, the metabolic rate of a single infected cell then scales as $M^{-1/4}$. Other properties such as the lifespan of an animal or the number of certain cell types have also been found to depend on body size (Peters, 1983; Schmidt-Nielsen, 1984; Calder, 1996; Savage et al., 2007). The metabolic rate will also affect the rate at which cells synthesize DNA and proteins and could therefore influence the replication rate of viruses.

HIV research is often based on experimental studies in macaques. Despite being a non-natural host, macaques can be infected with SIV, the simian counterpart of HIV. The viral replication dynamics within a host has been found to be slightly more rapid in macaques than in humans (Little et al., 1999; Brandin et al., 2006; Althaus et al., 2009; Ribeiro et al., 2010). In this light, it is interesting to compare the dynamics at which immune escape variants evade recognition from $CD8^+$ cytotoxic T lymphocyte (CTL) responses in the two host species. The observation that escape rates in macaques appear to be faster compared to humans suggests more efficient CTL-mediated killing of infected cells in macaques (Asquith and McLean, 2007). However, the rate of immune escape strongly depends on the overall viral turnover (Althaus and De Boer, 2012). In other words, more rapid immune escape in SIV-infected macaques does not necessarily imply more efficient killing but could be a result of the faster replication rate of SIV in the macaque species. With a 10-fold difference in body mass between humans ($\sim$70 kg) and macaques ($\sim$7 kg), allometric scaling predicts a roughly 2-fold difference in the metabolic rate of a single cell between the two species. This factor can account for the reported differences in the mean of the escape rates (Asquith et al., 2006; Asquith and McLean, 2007), but the differences in the viral turnover rates between humans and macaques seem to be less pronounced.

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Another quantity that could be affected by the metabolic rate or the viral turnover is the time to disease progression, i.e., the time to acquired immunodeficiency syndrome (AIDS). Cable et al. (2007) found an allometric relationship for the time to disease progression for a small set of pathogens in different host species. The wide variation in disease progression of HIV-infected humans, ranging from years to decades (Fraser et al., 2007), makes it difficult to compare it to the more rapid disease progression of 1 to 2 years in SIV-infected macaques (Kestler et al., 1990). In addition, host genetic factors have been found to be strongly associated with disease progression (Fellay et al., 2007). However, it is tempting to speculate whether allometric scaling could at least partly account for the observed differences in disease progression between humans and macaques.

One can also argue that quantitative processes of the cellular immune response are affected by allometric scaling. In the case of T cell responses, Wiegel and Perelson (2004) derived some general principles on how the number of naive T cells scales with body size. Lymphocyte trafficking, i.e., the circulation of T cells through blood, tissues and the lymphatic system in order to recognize antigen and eliminate virus-infected cells, has also been suggested to underlie general scaling laws (Perelson and Wiegel, 2009). Scaling principles could also be reflected in the varying life spans of naive and memory T cells between mice and men (De Boer and Perelson, 2013). In addition, the proliferation rate of $CD8^+$ T cell responses during the acute phase of an infection could be linked to the metabolic rate of the host. Unfortunately, only little data is available on the kinetics of $CD8^+$ T cell responses upon viral infections in different host species. However, the rapid expansion of $CD8^+$ T cells in mice after infection with LCMV at a rate of around 2.0 per day (De Boer et al., 2001, 2003; Althaus et al., 2007), compared to the slower expansion rate of $CD8^+$ T cell responses upon SIV-infection in macaques of about 1.0 per day (Davenport et al., 2004), shows a 2 to 3-fold difference in proliferation rates. Here, allometric theory predicts a roughly 4-fold difference between the metabolic rates of a single cell in mice ($\sim$20 g) and macaques ($\sim$7 kg).

In summary, there are indications that $CD8^+$ T cell responses develop slower upon viral infections in larger animals. Whether this influences the ability of the cellular immune responses to eradicate viruses during the acute phase of an infection remains unclear, especially if virus replication also underlies allometric scaling principles. Others have argued that the response rate of immune systems does not change systematically with body size. Instead, the sub-modular architecture of the immune system, where the number and size of lymph nodes increase sublinearly with body size, could balance the tradeoff between the local detection of pathogens and the global host response (Banerjee and Moses, 2010).

Discrepancies between experimental findings of the mice and human immune system have been described and illustrate that using mice as preclinical models for the study of human diseases can be challenging (Mestas and Hughes, 2004). Besides those differences that could be a result of separate evolution, I have highlighted some apparent quantitative differences between the dynamics of viruses and immune responses in mice, macaques and men. This suggests that allometric scaling principles should be considered for the interpretation of observed differences in the infection dynamics between host species. However, additional data on the kinetics of virus replication and the dynamics of T cell responses in different host species will be required to shed more light on the

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question whether the nature of viral infections is affected by the body size of their hosts.

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