Letter to the Editor

Response to Letter

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We were happy to provide Barton *et al.* with a chance to comment on our follow-up study of their report that herpesvirus latency confers symbiotic protection from bacterial infection (1). We had confirmed their findings that mice latently infected with the γ -herpesvirus (γ HV68) are protected from subsequent infection by *Listeria monocytogenes*. In our study, we addressed the longevity of the effect and showed that the protection waned between 5 and 6.5 mo after infection. In addition, we showed that serum levels of the cytokines IFN- γ and TNF- α , which Barton *et al.* had linked to the protective effect, were only transiently elevated and returned to baseline levels as early as 2 mo after γ HV68 infection. Because our data showed only a transient protective effect, we argued against the conclusions that herpesvirus latency conferred lifelong symbiotic protection from bacterial infection, and that herpesvirus vaccines might have unintended negative consequences for host immunity (9). Below is our response to several issues raised by Barton *et al.* concerning our study.

Is the Observed Cross-Protection Symbiosis?

Our data show that enhanced resistance of latently-infected mice against bacterial infection is not maintained for the full duration of viral latency. We interpreted this transient effect as failing to meet the definition of symbiosis, and argued against the conclusion that γ -herpesvirus latency provides a lifelong benefit to the host. Barton *et al.* countered that “there is no requirement that the benefits of mutualistic symbiosis be permanent; only that they improve the net fitness of the species.” We agree that a protective effect during childhood may translate into a reproductive advantage and in this sense provides a lifelong benefit.

Is the Dissociation Between Latent Infection (Which Is Lifelong) and Protection Against Heterologous Infection (Which Lasts Only Months) an Indication that Latency is not the Cause of the Cross-Protection?

Barton *et al.* convincingly demonstrated that a capacity to establish latency was essential for the protective effect. We never questioned this conclusion and we agree that latency undergoes changes throughout infection, as suggested in their letter. Further study of these changes will presumably lead to a mechanistic explanation for the waning of the protective effect.

is the Observed Cross-Protection of Sufficient Duration to be Physiologically Significant?

Barton *et al.* point out that the timing of the putative protection in humans is predicted to coincide with life-threatening childhood infections. Therefore, even transient protection (if it is confirmed in humans) would be beneficial. We agree with this general concept. However, two additional points are relevant to the possible physiological significance of cross-protection. First, the relative timing of the two infections may dictate whether the outcome is heterologous protection or exacerbation of disease. Obviously this is not something that can be controlled in nature. Second, the age at which the individual is infected with the herpesvirus may impact the protective outcome. The experiments reported thus far have only examined adult mice. The results might be different in young mice with an immature immune system, as γ HV68 dissemination and latency have been shown to differ between pups and adults (7). These issues can be examined in the mouse model, but also must be examined in humans.

Do These Studies Have Implications for Human Vaccination?

These studies are highly significant because of their potential relevance for human herpesvirus infections. However, currently we lack any evidence that humans benefit from latent herpesvirus infections. As Barton *et al.* point out, our studies, and theirs, provide a strong rationale for epidemiological studies of that nature.

Because there is currently no evidence that the protective effects described in mice has relevance for humans, and to the contrary, we know that herpesvirus infections are associated with significant debilitating and life-threatening disease in humans, we argue the importance of continuing efforts to develop herpesvirus vaccines. We do not agree with the suggestion of Barton *et al.* that such vaccines should strive to maintain benefits of herpesvirus infection, since such benefits have yet to be demonstrated in humans. We further argue that there are specific high-risk groups for herpesvirus-associated sequelae for whom the need for a prophylactic vaccine is a high priority, regardless of concerns over the loss of any putative protective effects of the infection. These include the holoendemic malarial populations in equatorial

Africa, where there is a high incidence of Burkitt's lymphoma; geographical areas including Southeast Asia, where there is an enhanced incidence of EBV-associated nasopharyngeal carcinoma; and EBV-negative adolescents in whom late-onset infection causes debilitating infectious mononucleosis and increased susceptibility to Hodgkin's disease (2–4,8). We also point out that well-documented effects of persistent pathogens on the T-cell repertoire, such as that dramatically illustrated by CMV, provide another example of the negative impact of a herpesvirus infection that presently outweighs any putative beneficial effect. Whereas CMV infection is overtly benign in immunocompetent adults, it induces large clonal expansions in the CD8 T-cell repertoire as these individuals age, resulting in immunosenescence (5,6).

Protective effects of human herpesvirus infections may have played a more significant role in eras prior to the introduction of bacterial vaccines, antibiotics, and improved sanitation, which have greatly reduced the burden of bacterial disease in the developed world. However, we believe that today the well-established pathological impact of herpesvirus infections far outweighs any documented benefits. The development of herpesvirus vaccines thus remains an important goal that should not be constrained by requirements to maintain any putative transient protective effects of latent infection.

Our study confirmed the striking observation of Barton *et al.*, that latent herpesvirus infection can protect against bacterial infection. However, we also observed a significant limitation in that this heterologous protection is short-lived. The possibility that latent herpesvirus infections confer humans with significant benefits certainly warrants further investigation. Additional mechanistic studies can be carried out in mice, but we believe the key focus needs to shift to clinical and epidemiological studies in humans.

Respectfully submitted,
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References

1. Barton ES, White DW, Cathelyn JS, et al.: Herpesvirus latency confers symbiotic protection from bacterial infection. *Nature* 2007;447:326–329.
2. Henle W, and Henle G: Epidemiologic aspects of Epstein-Barr virus (EBV)-associated diseases. *Ann NY Acad Sci* 1980;354:326–331.
3. Hjalgrim H, Smedby KE, Rostgaard K, et al.: Infectious mononucleosis, childhood social environment, and risk of Hodgkin lymphoma. *Cancer Res* 2007;67:2382–2388.
4. Morrow RH, Kisuule A, Pike MC, and Smith PG: Burkitt's lymphoma in the Mengo Districts of Uganda: epidemiologic features and their relationship to malaria. *J Natl Cancer Inst* 1976;56:479–483.
5. Nikolich-Zugich J: Ageing and life-long maintenance of T-cell subsets in the face of latent persistent infections. *Nat Rev Immunol* 2008;8:512–522.
6. Pawelec G, Akbar A, Caruso C, Solana R, Grubeck-Loebenstein B, and Wikby A: Human immunosenescence: is it infectious? *Immunol Rev* 2005;205:257–268.
7. Ptaschinski C, and Rochford R: Infection of neonates with murine gammaherpesvirus 68 results in enhanced viral persistence in lungs and absence of infectious mononucleosis syndrome. *J Gen Virol* 2008;89:1114–1121.
8. Rickinson AB, and Kieff E: Epstein-Barr virus. In: *Fields Virology*. (Knipe DM, and Howley PM, eds.). Lippincott Williams & Wilkins, Baltimore, 2001, pp. 2575–2628.
9. Yager EJ, Szaba FM, Kummer LW, Lanzer KG, Burkum CE, Smiley ST, and Blackman MA: γ -Herpesvirus-induced protection against bacterial infection is transient. *Viral Immunol* 2009 (in press).