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EDITORIAL

Prior immune exposure can protect or can enhance pathology in the enteroviruses: what predicts the outcome?

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In this issue of *Virulence*, Elmastour et al. link the increased pathology of secondary coxsackievirus infections to enhancement of infection by antibody to the coxsackievirus. This editorial demonstrates that this is a phenomenon has been found in other murine models of human disease in which enterovirus persists beyond the acute stage.

How is it possible for a second enterovirus infection to lead to more severe disease even when the infection is of the same serotype? The poliovirus vaccines have demonstrated the ability of enteroviruses to generate an immune response capable of preventing a pathogenic level of secondary infection.[1] However, Elmastour et al[2] as well as several previous studies[2-8] using the mouse model of infection with coxsackievirus B (CVB) serotypes have demonstrated that enteroviruses can result in an enhanced level of disease in both the heart and the pancreas after a second infection. This has been attributed to effects of antigenic mimicry in which the immune response, including the antibody response, reacts to non-viral antigens in the tissue,[9] to a primed T cell response via common epitopes resulting in increased inflammation,[3] to bystander activation of autoimmunity which is enhanced by repetitive infections[10] or to antibody dependent enhancement (ADE) of disease via increased uptake of viruses and infection of monocytes or macrophage resulting in spread of the virus to tissues and protection from the adaptive immune response.[6,11,12] The latter phenomenon has been explored in studies of dengue virus disease (reviewed[13]).

As observed in the murine model, the second infection with an enterovirus can only enhance disease because the primary infection does not provide sufficient immune response to permit sufficient virus clearance. Clearly when homotypic secondary infections occur, there is a low level of effective antibody response in animals in which if the second infection occurs to any extent. In the current study by Dr. Hober and colleagues,[2] the secondary infection is successful and enhances the degree of disease over that seen with just a primary infection at the time of the secondary infection. In homotypic secondary enterovirus infections in which higher levels of neutralizing antibody are induced by the primary infection, there is protection against the secondary infection and only in cases in which there is a reduced immune response to the primary infection, does a secondary infection increase the level of disease observed over that from a primary infection alone.[6] When heterotypic infections are used, the immune response from the first infection is likely to be less able to provide protective immunity against the second infection due to dissimilarity in the viral antigens. In several studies using heterotypic enterovirus infections in the murine model, the prior infection increases the extent of disease induced by the infection of the second enterovirus serotype.[3,8] An exception to this was an observation of weanling CD-1 mice inoculated with CVB3 in which some degree of reduction of myocarditis was observed when the mice had survived an earlier infection with CVB4[5].

When the secondary enterovirus infection enhances pathology, there is an association with increased viral load of the secondary infection. In Elmastour et al,[2] A/J mice with a prior infection at 21 d of age with CVB4 and another at day 55 have levels of viral RNA and cytopathic virus at days 72 and 89 which are increased beyond an additive amount from mice inoculated only once. There was significant increase in viral RNA in the heart and pancreas in A/J mice with a prior CVB2 infection upon challenge with CVB3 in another study of

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homotypic versus heterotypic secondary challenge at the early stage of infection.[8] However, in this study by McManus and colleagues, disease in the mice infected twice with CVB3 was reduced compared with single CVB3 infection. A study of enhancement of hyperglycemia in SJL mice using reinfection with CVB4 after primary infection with the same virus,[4] did not find increased virus replication with assays of plaque forming units. This study did not assay viral replication by RT-PCR or in situ hybridization as in the other studies.[2,8] All in all, there is more virus and more disease when a low level of neutralizing antibody has been generated (as in heterotypic infection). When that level is high in homotypic infections, there is the expected protection against the secondary infection.

A mechanism for enhancement of replication may be the mechanism by which IgG generated from enterovirus infection enhances macrophage or monocyte infection of the enterovirus, an enhancement suggested to be dependent upon Fc receptor (reviewed[14]). Both Kishimoto et al[6] and Elmastour et al[2] found IgG generated from the infection could enhance infection of monocytic or splenic cells. Infectivity is enhanced at antibody levels which are less than completely neutralizing. Kishimoto et al.[6] demonstrated that whole antibody but not the Fab fragment could produce this effect and that monoclonal ab to Fc gamma receptor I and II could block this enhancement. Experiments using CVBs[2,12,15] provide an example of this, in which an enhancing infection of monocytes or lymphocytes is triggered by the presence of antibody from mice or humans with prior infection with these viruses. Presumably infection of these cells leads to the rapid spread of the virus from the gastrointestinal tract to sites of known enterovirus pathology, the CNS, the pancreas and the heart, a pathway to increased disease through the extrinsic or infective pathway of ADE[14] We know that the acute infection by these viruses causes inflammation and pathology at these sites and transport of the enterovirus within monocytes to these sites without additional exposure to the antibody and cell mediated immune defenses may enhance infection and pathology.

The intrinsic pathways of ADE, in which intracellular activation of the innate immune response leads to cytopathology and inflammation due to expression of interferon stimulated genes (ISGs) may also be stimulated in these secondary infections.[14] In addition, TRIM21 activation by internalization of antibody bound to virus capsid could potentially play a role in the intrinsic pathways but should decrease virus replication.[16] It is likely that these well adapted viruses which evolved in human populations exposed to multiple serotypes,[17] evolved responses to this mechanism of enhanced neutralization. One ability of these cytoplasmic RNA viruses, is the rapid translation of viral proteins due to the translation of the genomic RNA via cap-independent translation.[18] As these viral proteins include two proteases known to cleave host proteins involved in the signaling cascades of the innate immune responses,[19,20] enteroviruses could abort the induced ISG expression prior to curtailing virus replication.

The mice used in these studies are highly susceptible to CVB-associated pathology and the secondary virus strain used in the work is also highly virulent. The A/J and C3H/He mice (reviewed[21]) and Swiss albino[22,23] mice are strains in which the CVBs have been shown to persist. It is possible that the mouse models used have a higher probability of enhanced infection due to the inability to clear enterovirus infection. This would suggest that this phenomenon is rare in the very outbred human population. However, the presence of enteroviruses has been noted in hearts of patients with myocarditis and cardiomyopathy[24-26] at stages beyond acute infection. If this persistence uses similar mechanisms of evasion of a protective immune response, some individuals may have an risk of enhanced pathology even when their immune system has been exposed to other similar enteroviruses. The mechanism of this enhancement merits study.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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