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

Nora M. Chapman

Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE, USA

ARTICLE HISTORY Received 1 December 2016; Accepted 1 December 2016

KEYWORDS antibody-dependent enhancement; coxsackievirus; enterovirus

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. However, Elmastour et al as well as several previous studies 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, to a primed T cell response via common epitopes resulting in increased inflammation, to bystander activation of autoimmunity which is enhanced by repetitive infections 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. The latter phenomenon has been explored in studies of dengue virus disease (reviewed).

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, 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. 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. 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.

When the secondary enterovirus infection enhances pathology, there is an association with increased viral load of the secondary infection. In Elmastour et al., 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
homotypic versus heterotypic secondary challenge at the early stage of infection. 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, 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. 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). Both Kishimoto et al and Elmastour et al found IgG generated from the infection could enhance infection of monocyctic or splenic cells. Infectivity is enhanced at antibody levels which are less than completely neutralizing. Kishimoto et al demonstrated that whole antibody but not the Fab fragment could produce this effect and that monoclonal antibody to Fc gamma receptor I and II could block this enhancement. Experiments using CVBs 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. 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 cytokine production and inflammation due to expression of interferon stimulated genes (ISGs) may also be stimulated in these secondary infections. 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. It is likely that these well adapted viruses which evolved in human populations exposed to multiple serotypes, 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. As these viral proteins include two proteases known to cleave host proteins involved in the signaling cascades of the innate immune responses, 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) and Swiss albino 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 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.

Acknowledgments

The author thanks Dr. Kristen Drescher for useful comments on the manuscript.

ORCID

Nora M. Chapman http://orcid.org/0000-0002-3119-8772

References

[1] Pallansch MA, Oberste MS, Whitton JL. Enteroviruses: polioviruses, coxsackieviruses, echoviruses, and newer enteroviruses. 6 ed. In: Fields Virology, Knipe DM, Howley, PM, I CJ, Griffin, DE, Lamb RA, Martin MA, et al., Editor. 2013, Philadelphia: Wolters Kluwer/Lippincott Williams and Wilkins.
[2] Elmastour F, Jaidane H, Benkahla M, Agueuh-Oueslati L, Sane F, Halouani A, Engelman I, Bertin A, Mokni M, Gharbi J, et al. Anti-coxsackievirus B4 (CV-B4) enhancing activity of serum associated with increased viral load and pathology in mice reinfeected with CV-B4. Virulence 2017; 8(6):908-923; PMID:27792461; https://doi.org/10.1080/21505594.2016.1252018
[3] Beck MA, Chapman NM, McManus BM, Mullican JC, Tracy S. Secondary enterovirus infection in the murine model of myocarditis. Pathologic and immunologic aspects. Am J Pathol 1990; 136(3):669-81; PMID:2156432

[4] Horwitz MS, Illic A, Fine C, Rodriguez E, Sarvetnick N. Cocxackievirus-mediated hyperglycemia is enhanced by reinfecion and this occurs independent of T cells. Virology 2003; 314(2):510-20; PMID:14554080; https://doi.org/10.1016/S0042-6822(03)00462-8

[5] Khatib R, Reyes MP, Khatib G, Giraldo A. The effects of pre-existing cocxackievirus B4 myocardial disease on the expression of cocxackievirus B3 myocarditis. Can J Cardiol 1993; 9(5):444-7; PMID:8394194

[6] Kishimoto C, Kurokawa M, Ochiai H. Antibody-mediated immune enhancement in cocxackievirus B3 myocarditis. J Mol Cell Cardiol 2002; 34(9):1227-38; PMID:12392896; https://doi.org/10.1006/jmcc.2002.2087

[7] Okada I, Matsumori A, Tomioka N, Kawai C. Successive infection of cocxackievirus B3 and encephalomyocardi- virus: an animal model of chronic myocarditis. J Pathol 1992; 167(3):341-7; PMID:13255552; https://doi.org/10.1002/path.1711670313

[8] Yu JZ, Wilson JE, Wood SM, Kandolf R, Klingel K, Yang D, McManus BM. Secondary heterotypic versus homotypic infection by Coxackie B group viruses: impact on early and late histopathological lesions and virus genome prominence. Cardiovasc Pathol 1999; 8(2):93-102; PMID:10724506; https://doi.org/10.1016/S1054-8807(98)00025-8

[9] Huber SA, Cunningham MW. Streptococcal M protein peptide with similarity to myosin induces CD4+ T cell-dependent myocarditis in MRL/++ mice and induces partial tolerance against cocxackievirus myocarditis. J Immunol 1996; 156(9):3528-34; PMID:8617982

[10] von Herrath MG, Fujinami RS, Whitton JL. Microorganisms and autoimmunity: making the barren field fertile? Nat Rev Microbiol 2003; 1(2):151-7; PMID:15035044; https://doi.org/10.1038/nrmicro754

[11] Hofer D, Sane F, Jaidane H, Riedweg K, Goffard A, Desaiiloud R. Immunology in the clinic review series; focus on type 1 diabetes and viruses: role of antibodies enhancing the infection with Coxsackievirus-B in the pathogenesis of type 1 diabetes. Clin Exp Immunol 2012; 168(1):47-51; PMID:22385236; https://doi.org/10.1111/j.1365-2249.2011.04559.x

[12] Girn J, Kavoshi M, Chantler J. Enhancement of cocxackievirus B3 infection by antibody to a different cocxackievirus strain. J Gen Virol 2002; 83(Pt 2):351-8; PMID:11807228; https://doi.org/10.1099/0022-1317-83-2-351

[13] Rothman AL. Immunity to dengue virus: a tale of original antigenic sin and tropical cytokine storms. Nat Rev Immunol 2011; 11(8):532-43; PMID:21760609; https://doi.org/10.1038/nri3014

[14] Taylor A, Foo SS, Bruzzzone R, Dinh LV, King NJ, Mahalingam S. Fc receptors in antibody-dependent enhance- ment of viral infections. Immunol Rev 2015; 268(1):340-64; PMID:26497532; https://doi.org/10.1111/imr.12367

[15] Elmastour F, Jaidane H, Aguech-Oueslati L, Benkahla MA, Aouni M, Gharbi J, Sane F, Hofer D. Immunoglobulin G-dependent enhancement of the infection with Coxsackievirus B4 in a murine system. Virulence 2016; 7(5):527-35; PMID:27030584; https://doi.org/10.1080/20150559.2016.1152442

[16] Fletcher AJ, James LC. Coordinated neutralization and immune activation by the cytosolic antibody receptor TRIM21. J Virol 2016; 90(10):4856-9; PMID:26937031; https://doi.org/10.1128/JVI.00050-16

[17] Chapman NM, Coppieters K, von Herrath M, Tracy S. The microbiology of human hygiene and its impact on type 1 diabetes. Islets 2012; 4(4):253-61; PMID:22996796; https://doi.org/10.4161/isl.21570

[18] Racaniello VR. Picornaviridae: The Viruses and their Replication, in Fields Virology, Knipe DM, Howley PM, I CJ, Griffin DE, Lamb RA, Martin MA, et al., Editor. 2013, Philadelphia: Wolters Kluwer/Lippincott Williams and Wilkins.

[19] Feng Q, Langeréis MA, Lork M, Nguyen M, Hato SV, Lanke K, Emdad L, Bhoopathi P, Fisher PB, Lloyd RE, et al. Enterovirus 2Apro targets MDAX and MAVS in infected cells. J Virol 2014; 88(6):3369-78; PMID:24390337; https://doi.org/10.1128/JVI.02712-13

[20] Lind K, Svedin E, Domseng E, Kapell S, Laitinen O, Moll M, Flodström-Tullberg M. Coxsackie virus counters the host innate immune response by blocking type III interferon expression. J Gen Virol 2016; 97(6):1-12; PMID:26935471; https://doi.org/10.1099/jgv.0.000443

[21] Chapman NM, Kim KS. Persistent cocxackievirus infection: enterovirus persistence in chronic myocarditis and dilated cardiomypathy. Curr Top Microbiol Immunol 2008; 323:275-92; PMID:18357775

[22] El Hiar R, Hofer D, Jaidane H, Sané F, M’hadheb-Gharbi MB, Caloone D, Gharbi J, Aouni M. Prolonged viral RNA detection in the central nervous system of one-week-old Swiss albino mice following cocxackievirus B4 and echovirus 9 infection. Intervirology 2012; 55(6):435-41; PMID:22398876; https://doi.org/10.1159/000335549

[23] Jaidane H, Gharbi J, Lobert PE, Lucas B, Hiar R, M’hadheb MB, Brilot F, Genyen V, Aouni M, Hober D. Prolonged viral RNA detection in blood and lymphoid tissues from cocxackievirus B4 orally-inoculated Swiss mice. Microbiol Immunol 2006; 50(12):971-4; PMID:17179665; https://doi.org/10.1111/j.1348-0421.2006.tb03874.x

[24] Bouin A, Nguyen Y, Wehbe M, Renois F, Fornes P, Banisadr F, Metz D, Andreoletti L. Major persistent 5’ terminally deleted cocxackievirus B3 populations in human endomyocardial tissues. Emerg Infect Dis 2016; 22(8):1488-90; PMID:27434549; https://doi.org/10.3201/eid2208.160186

[25] Chapman NM, Kim KS, Drescher KM, Oka K, Tracy S. 5’ terminal deletions in the genome of a cocxackievirus B2 strain occurred naturally in human heart. Virology 2008; 375(2):480-491; PMID:18378272; https://doi.org/10.1016/j.virol.2008.02.030

[26] Rey L, Lambert V, Wattré P, Andréoletti L. Detection of enteroviruses ribonucleic acid sequences in endomyocardial tissue from adult patients with chronic dilated cardiomypathy by a rapid RT-PCR and hybridization assay. J Med Virol 2001; 64(2):133-40; PMID:11360245; https://doi.org/10.1002/jmv.1028