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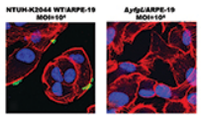

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EDITORIAL

Enterovirus infections: Pivoting role of the adaptive immune response

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Genus *Enterovirus* of the family *Picornaviridae* includes 12 species of which 7 species are human pathogens. Enteroviruses (EV) are transmitted via the fecal-oral route and respiratory transmission may also occur. Infections by EVs are common though majority of them remain asymptomatic. The symptomatic infections are often characterized by a minor illness with fever, diarrhea, vomiting and sometimes a rash.[1,2] Symptoms of the minor febrile illness are difficult to differentiate from the clinical features of other viral upper and lower respiratory infections. Enterovirus infections are also associated with serious conditions such as paralytic poliomyelitis, flaccid paralysis, aseptic meningitis, herpangia, hand-foot and mouth disease, acute hemorrhagic conjunctivitis, exanthemas, myocarditis, and fulminant diseases of the neonates.[1,2] Chronic diseases such as type 1 diabetes, chronic myocarditis and dilated cardiomyopathy have been related to EV infections.[1,3,4]

The incubation period between infection and onset of symptoms varies from 2–10 days. These viruses first infect the intestinal mucosa or upper respiratory tract, accompanied with a mild viremia and low viral loads. [1,5] The secondary spread is a result of the major viremia and spread of virus to secondary organs including the central nervous system and other tissues, causing severe complications including myocarditis, pancreatitis, meningitis, encephalitis.[1,5] Virus is shed in the feces for 2–4 weeks but maximal virus shedding occurs before the onset of symptoms. Incubation period is about 2-10 days.

Enteroviral infections and their consequences are influenced by the host immune system, expression of the receptors, tissue tropism, genetics (host and viral) and virulence of the virus.[1,6-10] Like all viral infections first the innate immunity is induced[1,11] followed by acquired or adaptive immunity[1,4,11,12] which is responsible for the clearance of EVs. IgM antibodies are present for 7-10 days and followed by the IgG. The neutralizing antibody response appears approximately from the second week of infection and reaches maximum at 5 weeks after infection and may exist lifelong. The antibodies are mainly directed toward the viral protein (VP1) antigen. Protection against a reinfection by the same serotype is often observed but is limited, and the nature of the reinfection maybe mild and subclinical.[1,13,14] Infections with different serotypes and heterotypic antibody responses to EVs (e.g. infections by different serotypes of coxsackieviruses) are common.[13,14]

Persistent infections have been associated with chronic diseases however with controversial observations and views.[4,15,16] Prolonged infections might develop in case of a defect in one of the antiviral mechanisms such as in patients suffering from X-linked agammaglobulinemia, and result in a fatal outcome.[1,11,12] Chronic infections may occur when the immune system partially loses its balance. Prolonged presence of viral RNAs upon intraperitoneal and oral routes of infection have been observed in experimental mouse models.[3,17-23]

Innate immune system is triggered and further induces the antiviral response and also the adaptive immunity. Initiation of the later (adaptive immunity) is related to viral clearance. B cells control the virus specific antibody production which either inactivates the virus directly via neutralization and opsonisation processes or commence the destruction the infected cells.[24] Neutralizing antibodies block viral proteins which bind to host receptors for virus entry into the cells. The virus-antibody complex is recognized by the complement proteins and the macrophages and neutrophils.[24]

The pattern recognition receptors on the cells allow the components of the innate immune response to recognize and respond to a broad range of viruses.[25] Anti-enterovirus neutralizing antibodies protect cells from infection,

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however, studies show that the non-neutralizing antibodies form a complex with the virus and may bind to the cell via the Fc-region-receptor of the antibody resulting in virus internalization.[26] Furthermore, virus attached to an antibody directed toward another serotype may activate the complement pathways. The C1q complement binds to this complex which in turn is recognized via the C1q receptor again allowing virus entry into the cell. IgG antibodies, opposite to the protection they confer may promote the dissemination of the virus in the body, creating an enhancement of the infection and intensifying the disease.[27] Antibody-dependent enhancement (ADE) has been reviewed very well by Sauter and Hober.[28] Some experimental mouse model studies suggest this phenomenon. Few authors[29,30] have shown that a heterologous challenge of adult mice with CVB3 after an initial infection with CVB2, was crucial for enhanced pathology. These results suggested cross-reactivity and enhanced immunopathology, a phenomenon known as original antigenic sin (OAS)[31] or related to ADE as observed in mice by different authors.[29,32,33,34] Homologous challenge with CVB4-E2 may cause enhanced pathology such as hyperglycaemia,[35] or as observed in pups of dams infected during gravidity both hyperglycemia and pancreatitis.[36]

In the article of this issue of *Virulence* authors Elmastour et al. 2016[37] show that antibodies in serum from Swiss albino outbred mice inoculated intraperitoneally with CVB4-E2 strain enhance the production of antiviral mediators *in vitro* in spleen cells by incubating the sera with the homologous virus. They tested this activity from the supernatants of the treated spleen cultures on L929 cells with encephalomyocarditis virus (EMCV) belonging to the genus *Cardiovirus* of the family *Picornaviridae*, as the challenging virus. This enhancing effect was dependent on the antibody dose only in the sera of mice infected with CVB4-E2 and absent in controls. On the contrary the serum of the CVB4-E2 infected mice (or the IgG component) enhanced the CVB4-E2 infection of the spleen cells *in vitro*. These finding are valuable as they may partially account for the enhanced pathology observed in the experimental mouse model studies. The ADE should be taken into account in developing vaccinations and vaccination programmes.

Disclosure of potential conflicts of interest

No potential conflicts of interest declared

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