Concerning the discovery of mechanism for enterovirus B infection published in *Cell*

To Professor Xie:

We just noticed that your team, collaborated with other two teams published a paper entitled “Human neonatal Fc receptor is the cellular uncoating receptor for enterovirus B” in *Cell*. This research is very important for understanding the mechanisms of pathogenesis of enterovirus and new drug development. Since most of the readers of our journal are pediatric clinicians, we have some questions related to the potential clinical application.

1. Enterovirus species B belongs to the non-encapsulated virus. Except for the viruses from the *Picornavirales* family, what other non-encapsulated viruses are there? What are the serious pediatric diseases caused by these viruses?

2. For enteroviruses, there are currently no effective antiviral drugs available; also no vaccine is available except for enterovirus 71. According to your research, is it possible to develop Fc receptor inhibitors to block the entry of virus, so as to treat or prevent viral infection? What are the possible approaches and how difficult is this kind of research and development?

3. What other aspects of your research do you think should pediatric clinicians pay attention to?

To the editor:

I would like to thanks the PI editor for his thoughtful insight into our work. Enterovirus species B (EV-B) belongs to the *Enterovirus* genus of the *Picornaviridae* family, and includes echovirus, Coxsackie B, Coxsackie A9, and a number of newly discovered EV-B serotypes. EV-B is an important viral pathogen in neonatal and infantile infections, potentially leading to neonatal sepsis, childhood viral encephalitis, meningitis, meningoencephalitis, and other diseases, which may result in serious sequelae and can be fatal in severe cases. In May 2019, serious hospital-acquired (nosocomial) infections caused by echovirus 11 occurred in the neonatal ward of a hospital in a southern city in China, leading to deaths of 5 children with underlying diseases, such as neonatal pneumonia. EV-B (e.g. echovirus) is the leading viral pathogen in children with encephalitis or meningitis, and has important clinical significance.

In our study, we identified neonatal Fc receptor (FcRn) as a universal uncoating receptor for a large group of EV-B viruses by CRISPR-Cas9 library screening. FcRn, expressed by the *FCGRT* gene, is a heterodimer composed of an α-chain and β2-microglobulin (β2m). As a key immune factor, FcRn transports protective maternal IgG antibodies to the fetus through the placenta and helps neonates absorb antibodies from breast milk via the gut. FcRn also mediates antibody “recovery” in adults, thus maintaining stable IgG concentrations. The study showed that this immune factor, which plays an important role in the fetus and infants, can be “hijacked” by EV-B to become a key receptor for the invasion of EV-B into host cells. Unlike the previously reported echovirus surface adsorption receptor CD55, FcRn is an uncoating receptor. After directly binding to the receptor, and with the action of both receptor and lipid membrane, virus particles complete decapsidation under physiological conditions, which is required for cell invasion, and release their genetic material into host cells.

We also used high-resolution cryo-electron microscopy to analyze the structures of EV-B bound to its adsorbent receptor (CD55) and uncoating receptor (FcRn) at atomic/ near-atomic resolutions and under varying pH conditions. This revealed the different mechanisms of these two receptors in the dual-receptor system at the molecular level, and systematically elucidated the mechanism via which enteroviruses invade host cells. We found that both echovirus 6 and echovirus 6-CD55 complex were stable under neutral and acidic conditions. FcRn binds to a canyon-like structural site formed by the VP1 protein on the surface of the icosahedral virus. FcRn induces allostery of viral surface proteins in acidic conditions, leading to the release of lipid molecules (also known as “pocket factors”) that maintain virion stability inside the canyon thereby initiating decapsulation and release of

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genetic material. A clear understanding of the mechanism by which enteroviruses invade host cells is particularly helpful for research on the pathogenesis of EV-B and new drug development, especially for research on the invasion mechanism of non-encapsulated viruses.

Non-encapsulated viruses include Picornavirales, Adenoviridae, Caliciviridae, Reoviridae, Astroviridae, Lactoviridae, Parvoviridae, and double-stranded RNA viruses. During infection with a non-encapsulated virus, the viral capsid protein acts as an adsorbent protein that binds to the receptor molecule of the host cell, thereby assisting entry of the virion into the cell. The non-enveloped virus can cause serious intestinal and respiratory infections in children. For instance, the human adenoviruses of the Adenoviridae can cause severe and even fatal pneumonia, enteritis, and conjunctivitis in children. Similarly, characteristics of norovirus of the Caliciviridae include rapid genetic variation, strong environmental resistance, low infective dose, short incubation period after infection, long shedding duration, short duration of immune protection, and diverse transmission routes. Furthermore, all age groups are susceptible to norovirus infections. As result, norovirus is highly contagious and spreads rapidly, often resulting in outbreaks. In recent years, norovirus outbreaks have frequently occurred in many areas of China, causing acute gastroenteritis in children, and symptoms including diarrhea and vomiting. The rotavirus of the Reoviridae family mainly invades intestinal epithelial cells, leading to cell damage and diarrhea. Rotavirus is more prevalent during summer, autumn, and winter, with the fecal-oral route being the main route of transmission. Rotavirus infections manifest as acute gastroenteritis, which is characterized by osmotic diarrhea. In severe cases it can lead to dehydration, which may even result in death. In China, about 10 million infants and young children aged 0–2 years suffer from rotavirus-related gastroenteritis every year, accounting for one fourth of all children in this age group. Thus, rotavirus is the leading cause of severe diarrhea in infants and young children. Human astrovirus of the Astroviridae family is also an important viral cause of infantile diarrhea. Human papillomavirus types 6 and 11 of the Papillomaviridae are the major causative factors of recurrent respiratory papillomatosis (RRP) in children. RRP is highly recurrent and invasive, often affecting the glottis, and can result in difficult breathing (or even suffocation) and malignancy. Treatment often requires multiple operations and tracheotomy, causing heavy economic and mental problems to children and their families.

For enteroviruses, there are currently no effective antiviral drugs available; except for enterovirus 71, no vaccine exists for the prevention of EV-B. FcRn is an unusual Fc receptor widely expressed in vascular endothelial cells, professional antigen presenting cells, intestinal epithelial cells, and central nervous system endothelial cells and choroid plexus. Its main roles are to transport maternal IgG antibodies to the fetus and to maintain receptor levels in adults, so as to prolong serum IgG half-life and maintain stable serum IgG concentrations. Since many autoimmune diseases are associated with IgG, antibodies against FcRn are currently available to reduce the degradation of IgG by blocking FcRn, thereby alleviating the clinical symptoms of these diseases. In theory, blocking FcRn with anti-FcRn antibodies can prevent echoviruses from entering host cells thereby preventing infection. However, due to the widespread distribution of FcRn and its important physiological functions, further rigorous experiments are needed to assess the safety and potential side effects of blocking FcRn using anti-FcRn antibodies to control echovirus infections.

Enterovirus is an important viral pathogen in children, especially in newborns and young children. It can cause serious and fatal infections, and can also cause serious nosocomial infections in neonatal wards. Clinicians should pay particular attention to suspected enterovirus infections and related diseases. Specimens should be collected and sent for laboratory testing in a timely manner to aid early diagnosis and treatment. For cases of nosocomial infections, rapid infection control measures should be taken to prevent the spread of infection.

Xiangpeng Chen, Zhengde Xie
Beijing Key Laboratory of Pediatric Respiratory Infection Diseases, Key Laboratory of Major Diseases in Children, Ministry of Education, National Clinical Research Center for Respiratory Diseases, National Key Discipline of Pediatrics (Capital Medical University), Beijing Pediatric Research Institute, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing, China.

Correspondence
Zhengde Xie, Beijing Pediatric Research Institute, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing, China.

Email: xiezengde@bch.com.cn

CONFLICT OF INTEREST
None.

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