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EDITORIAL

Acute and chronic disease caused by enteroviruses

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This issue of *Virulence* includes an article demonstrating long-lasting changes induced by Coxsackievirus B4 infection of human pancreas ductal-like cells.[1] Coxsackievirus B4 is a member of the enterovirus genus within the *Picornaviridae* family. Despite decades of studies, details of the pathogenesis and genetics of enteroviruses remain enigmatic, and new disease associations continue to emerge.

These non-enveloped single-stranded RNA viruses are known to cause a diverse range of acute infections in humans, such as herpangina, myocarditis and pericarditis, hand-foot-and-mouth disease (HFMD), and neonatal sepsis.[2,3] In particular, they are the commonest cause of viral (or aseptic) meningitis,[4-6] and several members of the enterovirus family: polioviruses (types 1–3), enterovirus (EV) 71, and more recently, EV D68 are able to cause severe central nervous system (CNS) infections resulting in fatal encephalitis and long-term focal neurologic deficits, such as acute flaccid paralysis.[7,8S]

The Coxsackieviruses (named after the town Coxsackie, NY, USA, where it was first discovered) were initially grouped into Coxsackie A viruses and Coxsackie B viruses on the basis that they respectively induced flaccid or spastic paralysis in mouse models.[9] Another member of the enterovirus genus, **echo**viruses (for **e**nteric, **c**ytopathic, **h**uman, **o**rphan virus), was so named because of their unknown associations with human disease at the time of their discovery. Numerous other enterovirus species, discovered since 1970, have been simply given sequential numbers as part of their species classification.

Originally classified by serotyping, enterovirus types that cause human infection are now grouped into 4 species (EV-A to EV-D) on the basis of genetic similarity. The genus now also includes 3 species of rhinoviruses (RV-A to RV-C; causes of the common cold) and 5 species that infect animals.[10] More recently, a new genus, the parechoviruses, containing similar, but genetically distinct viruses formerly classified as enteroviruses, was also created within the *Picornaviridae*.[10] These viruses can cause a similar range of clinical disease to enteroviruses,[11-14] though any link to more chronic disease has yet to be investigated on the same scale.

Enterovirus genomes are single-stranded, positive-sense RNA, averaging 7.4 kilobases in length. They are comprised of a 5′-untranslated region (5′UTR), a coding region that is translated into a single polyprotein and a short 3′ untranslated region with a 3′ polyadenylated tail.[15] The 5′UTR is relatively well-conserved and commonly used as a target for PCR assays used to detect enteroviruses in clinical samples.

Both the 5′UTR and the 3′UTR are involved in regulation of genome replication and translation of the polyprotein. This is then cleaved during post-translational processing into 11 mature proteins including the structural proteins (VP1 to VP-4) that form the viral capsid, an RNA-dependent RNA polymerase, and the proteases that cleave the polyprotein.[15] There is a high degree of genetic diversity in the genes encoding the structural proteins which results in the large number of different enterovirus serotypes; the sequence of the VP1 region shows the highest correlation with the traditional serotyping methods and it is this region that is most often used for identification of enteroviruses.[16]

Enteroviruses are transmitted by the faecal-oral and respiratory routes. The incubation period is typically just a few days, with replication initially occurring in the upper respiratory tract (via inhalation or contact with oral or nasal mucous membranes), or the gastrointestinal

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tract (via ingestion). Enteroviruses (more so than rhinoviruses) are able to withstand the acidic conditions of the stomach, allowing them to replicate within the mucosal cells of the gastrointestinal tract.[17] From here enteroviruses can enter the bloodstream, via the lymphatic system, to infect other tissues. The nature of any subsequent extra-gastrointestinal enterovirus infection is then dependent on various host factors such as immunosuppression, but also on the presence and distribution of cellular receptors specific for particular viral capsid protein epitopes.

Primary receptors have been identified for several enteroviruses, including the poliovirus receptor for the 3 poliovirus types,[18] decay accelerating factor (DAF) for several Coxsackieviruses and echoviruses,[19] and the Coxsackie-adenovirus receptor (CAR) for Coxsackievirus B1-B6 that is expressed on the surface of several tissue types including heart, brain and endothelial cells.[20,21] This distribution permits the wide range of systemic infections demonstrated by these viruses - including pancreatitis. The presence of such receptors in the pancreas, together with the detection of several different enterovirus types, including CV-B4, in these tissues and in the blood of patients with type 1 diabetes (T1D - previously referred to as insulin-dependent diabetes mellitus – IDDM) has led investigators to examine the relationship between enteroviruses and T1D.[22]

Besides T1D, enteroviruses have also been investigated over the last several decades as possible causes of other chronic diseases, including juvenile dermatomyositis,[23] schizophrenia,[24,25] and primary Sjogren's syndrome.[26] In particular, researchers from Taiwan have been investigating multiple possible disease associations linked to enterovirus infection, most likely stimulated by a massive, severe outbreak of EV71 there in 1998, resulting in 78 deaths and over 100,000 cases of HFMD.[27-29] Disease associations that have been investigated include: attention-deficit-hyperactivity disorder,[30] allergic disorders (allergic rhinitis and atopic dermatitis),[31] the risk of developing leukemia (where they found a negative association),[32] tic disorders[33] and depression.[34]

Many of these chronic disease association studies have failed to progress further, usually after the publication of one or more follow-up significant negative studies.[35-37] However, the link between enterovirus infections and T1D has persisted, and even gained in strength. Although enteroviruses are commonly known for their cytolytic effects which could certainly damage the insulin-producing β-islet cells in the pancreas through direct infection,[38,39] another (and probably not mutually exclusive) route of destruction may be the stimulation of host autoimmune reactivity to these cells, triggered and maintained by persistent enterovirus infection of the pancreas.[40-43]

The authors of the study in this issue examining the persistence of Coxsackie B4 in human pancreas ductal-like cells are already well-published in this field.[40,42,44] They have been careful to state that although there is an increasing amount of evidence supporting the association between enterovirus infection and T1D, a definitive causal pathway is yet to be proven.[42] Their current study adds more support to the autoimmune hypothesis of persistent enterovirus infection (via various viral genotypic and phenotypic adaptations), inducing the destruction of β-islet cells, ultimately leading to T1D.

Type 1 diabetes has been and continues to be a huge healthcare burden, worldwide.[45] If enteroviruses are found to be a major contributor to its development, then renewed efforts at developing an effective polyvalent enterovirus vaccine,[46,47] and antiviral agents such as pleconaril[48-51] are certain to follow. This will enable the protection against and/or treatment of enterovirus infections during childhood, to prevent, or at least reduce, both the short-term and long-term complications of these viruses.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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