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Review

Recent progress in understanding coxsackievirus replication, dissemination, and pathogenesis

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ABSTRACT

Coxsackieviruses (CVs) are relatively common viruses associated with a number of serious human diseases, including myocarditis and meningo-encephalitis. These viruses are considered cytolytic yet can persist for extended periods of time within certain host tissues requiring evasion from the host immune response and a greatly reduced rate of replication. A member of Picornaviridae family, CVs have been historically considered non-enveloped viruses – although recent evidence suggest that CV and other picornaviruses hijack host membranes and acquire an envelope. Acquisition of an envelope might provide distinct benefits to CV virions, such as resistance to neutralizing antibodies and efficient nonlytic viral spread. CV exhibits a unique tropism for progenitor cells in the host which may help to explain the susceptibility of the young host to infection and the establishment of chronic disease in adults. CVs have also been shown to exploit autophagy to maximize viral replication and assist in unconventional release from target cells. In this article, we review recent progress in clarifying virus replication and dissemination within the host cell, identifying determinants of tropism, and defining strategies utilized by the virus to evade the host immune response. Also, we will highlight unanswered questions and provide future perspectives regarding the potential mechanisms of CV pathogenesis.

Contents

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Introduction

Enteroviruses (EVs) are widely distributed in nature and frequently cause heart and central nervous system (CNS) diseases (Whitton et al., 2005; Muir and van Loon, 1997). EVs are members of the Picornaviridae family which include notable members such as foot-and-mouth disease virus, poliovirus (PV), rhinovirus and hepatitis A. Some EVs, particularly enterovirus-71 (EV71) in Asia, are considered to be serious emerging CNS pathogens (Shih et al., 2011). The EV genus includes an important member, coxsackievirus (CV), which cause severe morbidity and mortality in the newborn and young host (Tebruegge and Curtis, 2009; Romero, 2008). These viruses have a small, positive-sense single stranded RNA genome, and infection occurs primarily through the fecal–oral route (Whitton et al., 2005; Feng et al., 2014b). Approximately 15 million diagnosed cases of EV infections occurred in the US in 1996, revealing that EV remains a substantial problematic viral infection (Sawyer, 2002). The original classification of EVs included the four groups: Coxsackie A viruses, Coxsackie B (CVB) viruses, ECHO (***E***nteric ***C***ytopathic ***H***uman ***O***rphan) viruses and PVs. A new classification system was devised utilizing consecutive numbers for each new isolate (such as EV71, EV72, etc.) due to significant overlap between the historically-named EVs (Oberste et al., 2002).

In utero and childhood infection is under-recognized but carries long-term consequences whereby intellectual and cognitive abilities of the patient might be compromised (Chiriboga-Klein et al., 1989; Euscher et al., 2001; Chang et al., 2007; Chamberlain et al., 1983). A relatively common pediatric virus, CV typically causes mild infections ranging from subclinical to flu-like symptoms and mild gastroenteritis (Weller et al., 1989). CV has been shown to infect the heart, pancreas, and CNS (Arnesjo et al., 1976; Rhoades et al., 2011). In rare cases CVs cause severe systemic inflammatory diseases such meningo-encephalitis, pancreatitis, and myocarditis, all of which can be fatal or result in lasting organ dysfunction, including dilated cardiomyopathy and encephalomyelitis (David et al., 1993; Hyypia et al., 1993). The remarkable distribution of CV infections can be appreciated by the high seroprevalence in many countries around the world. In one study, IgG antibodies against CV were detected in 6.7 to 21.6% of individuals throughout various regions of Greece (Mavrouli et al., 2007). An analysis of a French-Canadian population in Montreal showed a seroprevalence as high as 60–80% for some strains of CV (Payment, 1991). In a region of China, the seroprevalence for a single serotype of CV was shown to be greater than 50% in groups aged 15 years or more (Tao et al., 2013). The wide distribution of CV, their genetic variability, and ability to persist in the human host make it challenging for epidemiologists to link previous viral infection and subsequent pathology, suggesting a potential role for these viruses in chronic human idiopathies (Victoria et al., 2009) in addition to recognized illnesses. Vaccine design against CVs and EVs remain challenging for a number of reasons which include their remarkable genetic variability and inconsistent pathology in humans.

Spontaneous abortions, fetal myocarditis, and neurodevelopmental delays in the newborn remain serious outcomes if CV infection occurs during pregnancy (Ornoy and Tenenbaum, 2006; Euscher et al., 2001). Infants infected with CV have a higher likelihood of developing myocarditis, meningitis and encephalitis; and the mortality rate may be as high as 10%. Also, many chronic diseases may be the end result of a previous CV infection. These chronic diseases include chronic myocarditis (Chapman and Kim, 2008), schizophrenia (Rantakallio et al., 1997), encephalitis lethargica (Cree et al., 2003), and amyotrophic lateral sclerosis (Woodall et al., 1994; Woodall and Graham, 2004). The molecular mechanisms determining the tropism of CVs and their ability to persist in the host remain unclear. The lasting consequences of CV infection upon surviving individuals remain largely unknown despite clear dangers associated with infection and the cytolytic nature of the virus.

Many publications have suggested a link between early CV infection and insulin-dependent diabetes (IDDM) (Laitinen et al., 2014; Jaidane and Hober, 2008; Christen et al., 2012), although additional data is needed to support these correlative studies. In addition, a mouse model has shown the development of insulin-dependent diabetes (IDDM) to be associated with CV-induced pancreatitis and replication efficiency (Drescher et al., 2004), although the factors determining viral tropism and mechanism of disease are not well understood (Tracy et al., 2011; Kanno et al., 2006).

Type B coxsackieviruses (CVB) include six serotypes, each being associated with acute disease in humans, including acute viral myocarditis and pancreatitis. While CVB is generally regarded as a lytic virus, emerging evidence suggests that persistent infection can be established which may be responsible for chronic inflammation within target organs. Moreover, latency and episodic reactivation could also contribute to the disease process (Feuer et al., 2002; Ruller et al., 2012; Feuer and Whitton, 2008). Previously, we described the nature of the CVB viral genome in quiescent cells whereby a viral state similar to latency was established (Feuer et al., 2002, 2004). Following stimulation of quiescent cells by injury, or by the addition of growth factors, viral protein expression was detected and infectious virus was produced, suggesting that latent CVB may be reactivated in response to cellular activation. In parallel, CVB has evolved to modulate cell-signaling networks to evade host antiviral immunity, enter cells, and undergo replication even as the host cell suffers the consequences of a cytolytic viral infection (Esfandiarei et al., 2004; Jensen et al., 2013; Esfandiarei and McManus, 2008).

Our review will cover recent progress specifically in CVB research, while acknowledging advances in other areas of EV investigation which have contributed to a greater understanding of CVB replication and pathogenesis.

Molecular biology of CVB

CVBs, and EVs in general, are non-enveloped viruses which have the ability to survive harsh environments. Infection proceeds via the fecal/oral route, and hence virion stability in the acidic environment of the stomach becomes a necessity for efficient transmission. The virion structure exhibits an icosahedral symmetry with a diameter size of approximately 30 nm (Jiang et al., 2014). Four capsid proteins (VP1-VP4) comprise the virion structure, and these viral proteins are major antigenic determinants following the activation of the host humoral response. The positive-strand viral RNA genome ranges in size ~7 to 8 kb and is covalently linked at the 5′ end with a viral protein called VPg (the Viral Protein of the genome). VPg, one of the viral proteins 3B, plays an essential role in both positive and negative-strand RNA synthesis by covalently attaching to the 5′ end of the viral genome and acting as a primer for RNA synthesis. It remains unclear how