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ORIGINAL ARTICLE

Enterovirus A71 and coxsackievirus A16 show different replication kinetics in human neuronal and non-neuronal cell lines

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Abstract Enterovirus A71 (EV-A71) and coxsackievirus A16 (CV-A16) are closely related enteroviruses that cause hand, foot and mouth disease (HFMD) in children. Serious neurological complications almost always occur in EV-A71 infection, but are rare in CV-A16 infection. Based on the hypothesis that this may be because EV-A71 infects neuronal cells more easily than CV-A16, we compared virus infection, replication and spread of EV-A71 and CV-A16 in SK-N-SH cells. We found that CV-A16 invariably showed significantly lower replication and caused less necrotic cell death in SK-N-SH cells, compared with EV-A71. This was not due to a lower proportion of CV-A16-infected cells, since both viruses showed similar proportions of infected cells at all time points analyzed. Furthermore, reduced replication of CV-A16 in SK-N-SH cells does not appear to be due to limited viral receptor availability, which might limit viral entry, because experiments with viral RNA-transfected cells showed the same results as for live virus infections. On the other hand, no differences were observed between EV-A71 and CV-A16 in RD cells and results were generally similar in RD cells for both viruses. Taken together, our findings suggest that the poor growth of CV-A16 and EV-A71in SK-N-SH cells, compared with RD cells, may be due to cell type-specific restrictions on viral replication and spread. Furthermore, the lower viral replication and necrotic cell death in CV-A16-infected SK-N-SH cells, compared with EV-A71-infected SK-N-SH cells, is consistent with the lower prevalence of neurotropism observed in CV-A16-associated HFMD outbreaks. Nonetheless, *in vivo* data and more extensive comparisons of different viral strains are essential to confirm our findings.

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Introduction

Enterovirus 71 (EV-A71) and coxsackievirus A16 (CV-A16) are human enteroviruses belonging to the species *Enterovirus A*, genus *Enterovirus,* within the *Picornaviridae* family. Both viruses are ~30 nm, each containing a single-stranded, positive-sense RNA genome of approximately 7.5 kbp and they share about 80% of sequence similarity [65]. Furthermore, they use the same Scavenger receptor class B, member 2 (SCARB2) as a receptor for cell entry and possibly other attachment receptors, such as P-selectin glycoprotein ligand-1 (PSGL-1) and heparin sulphate [49, 60–62]. EV-A71 and CV-A16 are known etiological agents for sporadic and epidemic hand, foot and mouth disease (HFMD), a common infectious disease frequently seen in young children aged 5 and below [44, 53, 54]. In recent years, large outbreaks of HFMD have been mainly reported in the Asia-Pacific region [1, 18, 19, 21, 32–34]. HFMD is characterized by lesions on the skin of the hand, foot, buttock and oral mucosa [25].

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