Virus Research 139 (2009) 240–252

Contents lists available at ScienceDirect

Virus Research

journal homepage: www.elsevier.com/locate/virusres

Cis-active RNA elements (CREs) and picornavirus RNA replication

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ARTICLE INFO

Article history:
Available online 20 September 2008

Keywords:
Picornavirus
Cis-active RNA element
CRE
RNA replication
VPg
Picornavirales
Virus replication
3D polymerase

ABSTRACT

Our understanding of picornavirus RNA replication has improved over the past 10 years, due in large part to the discovery of cis-active RNA elements (CREs) within picornavirus RNA genomes. CREs function as templates for the conversion of VPg, the Viral Protein of the genome, into $VPgpUpU_{OH}$. These so called CREs are different from the previously recognized cis-active RNA sequences and structures within the 5′ and 3′ NTRs of picornavirus genomes. Two adenosine residues in the loop of the CRE RNA structures allow the viral RNA-dependent RNA polymerase $3D^{Pol}$ to add two uridine residues to the tyrosine residue of VPg. Because VPg and/or $VPgpUpU_{OH}$ prime the initiation of viral RNA replication, the asymmetric replication of viral RNA could not be explained without an understanding of the viral RNA template involved in the conversion of VPg into $VPgpUpU_{OH}$ primers. We review the growing body of knowledge regarding picornavirus CREs and discuss how CRE RNAs work coordinately with viral replication proteins and other cis-active RNAs in the 5′ and 3′ NTRs during RNA replication.

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1. Introduction

Picornavirus RNA genomes are mRNAs that also function as templates for viral RNA replication. Considering the RNA World hypothesis (Gesteland et al., 1999), picornaviruses represent modern day organisms with evolutionarily ancient replication strategies. Picornaviruses replicate via RNA intermediates within replication complexes assembled on lipid membranes in the cytoplasm of eukaryotic host cells. The replication of viral RNA within oligomeric viral protein particles or membranous replication complexes containing oligomerized viral proteins (Kopek et al., 2007) reveals common features of positive-strand RNA viruses, dsRNA viruses, and retroviruses (Ahlquist, 2006). Co-localization of viral proteins and viral nucleic acid templates within replication complexes facilitates interactions between viral proteins and viral RNA templates and also sequesters viral replication intermediates (like dsRNA) from innate antiviral host proteins. When picornavirus RNA genomes like that of poliovirus are introduced into cell-free reactions containing cytoplasmic extracts from uninfected host cells the viral RNA is translated, the viral polyproteins are processed, viral RNA replication complexes are assembled, viral RNA is replicated, and newly synthesized RNA genomes are packaged into progeny virus (Barton and Flanegan, 1993; Molla et al., 1991). Thus, all of the metabolic steps of picornavirus mRNA translation, RNA replication, and virus assembly are faithfully recapitulated in cell-free reactions containing cytoplasmic extracts. In addition to poliovirus, cell-free reactions containing cytoplasmic extracts support the translation and replication of EMCV (Svitkin and Sonenberg, 2003), rhinovirus 14 (Todd et al., 1997b), Aichi virus (Nagashima et al., 2005), and Coxsackievirus B3 RNAs (van Ooij et al., 2006). These data document the incredible ability of picornavirus RNA genomes, via cis-active RNA sequences and structures, to co-opt the cellular translation machinery of the cytoplasm, to express viral proteins, to build viral replication complexes anchored on host lipid membranes, to efficiently replicate viral RNA, and to assemble progeny virus.

Picornaviruses are a family of positive-strand RNA viruses in the order *Picornavirales* (Le Gall et al., 2008). There are nine genera in the *Picornaviridae* family: *Enterovirus*, *Rhinovirus*, *Hepatovirus*, *Parechovirus*, *Kobuvirus*, *Erbovirus*, *Cardiovirus*, *Aphthovirus*, and *Teschovirus* (Fig. 1) (Stanway et al., 2002). Viruses from these genera include many notorious human and agricultural pathogens. Polioviruses, rhinoviruses, and hepatitis A virus are well known human pathogens. Foot and mouth disease virus (FMDV), encephalomyocarditis virus (EMCV), and Theiler's virus are notable non-human pathogens. As exemplified by the four human enterovirus species (HEV-A, HEV-B, HEV-C, and HEV-D) (Fig. 2), each picornavirus genus often includes several species and there are often many individual serotypes of virus within each species. In addition to the viruses mentioned above, there are many new picornaviruses being discovered, including simian enteroviruses (Oberste et al., 2007b), a new genus of human rhinoviruses (Briese et al., 2008; Lau et al., 2007), and new human (Oberste et al., 2007a) and non-human picornaviruses (Hales et al., 2008).

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0168-1702/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.virusres.2008.07.027

Family *Picornaviridae*

Genus ***Enterovirus***	Polio, Coxsackie, Echo, & Enteroviruses
Genus ***Rhinovirus***	Rhinoviruses
Genus ***Hepatovirus***	Hepatitis A virus
Genus ***Parechovirus***	Human Parechoviruses 1 & 2
Genus ***Kobuvirus***	Aichi virus — Human Pathogens
Genus ***Erbovirus***	Equine Rhinitis B viruses 1 & 2
Genus ***Cardiovirus***	EMCV, Theiler's viruses
Genus ***Aphthovirus***	FMDV
Genus ***Teschovirus***	Porcine teschoviruses 1-10

Fig. 1. The *Picornaviridae* family.

RNA recombination between more than one member of a particular picornavirus species leads to viable recombinants, providing a biologically meaningful relationship between individual viruses within each species (Brown et al., 2003; Oberste et al., 2004a,b,c). RNA recombination between individual viruses within a species occurs in the regions of the genome encoding for picornavirus replication proteins (Brown et al., 2003). Replication genes within this region of the genome have a high degree of identity (80–95% identity between viruses within a species) which allows for viable chimeric virus. Recombination between viruses in alternate species is restricted because the chimeric viral proteins are too unrelated to function effectively with the chimeric RNA genome. While RNA recombination can occur within intratypic capsid genes (i.e., the same serotype), the degree of variation between different (intertypic) serotypes, even those within a species, restricts the production of viable progeny. RNA recombination during viral RNA replication in co-infected cells is important in the poliovirus eradication campaign, where Sabin strains of the live-attenuated oral poliovirus vaccine recombine with non-polio group C enteroviruses in vaccinees and their contacts leading to progeny vaccine-derived polioviruses that have the capacity to circulate in human populations and cause paralytic poliomyelitis (reviewed in Kew et al., 2005). Thus, the production of viable chimeric progeny from RNA recombination helps define picornaviral species and is also biologically relevant in nature.

Although there are many different picornaviruses with various degrees of relatedness, all picornaviruses share several common features. All picornaviruses have single-stranded RNA genomes of positive polarity covalently linked to 5′ terminal viral proteins. The RNA genome contains a 5′ nontranslated region (NTR) with an internal ribosome entry site (IRES), an open reading frame encoding the viral capsid proteins and the viral replication proteins, a 3′ NTR and a 3′ poly(A) tail. The contribution of particular cis-active RNA elements to viral mRNA stability (Kempf and Barton, 2008), viral mRNA

Genus Enterovirus **Species: HEV-A through HEV-D**

Recombination within replicase genes is characteristic of members in same species.
50 to 65% amino acid identity of replicase genes between viruses in different species.
80 to 95% amino acid identity between viruses within a species.

***Human enterovirus A* (HEV-A)**
Coxsackieviruses A2, A3, A4, A5, A6, A7, A8, A10, A12, A14, A16.
Enteroviruses 71 and 76.

***Human enterovirus B* (HEV-B)**
Coxsackieviruses B1, B2, B3, B4, B5, B6, A9.
Echoviruses 1, 2, 3, 4, 5, 6, 7, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 24, 25, 26, 27, 29, 30, 31, 32, 33.
Enteroviruses 69, 73, 74, 75, 77 and 78.

***Human enterovirus C* (HEV-C)**
Polioviruses 1, 2, and 3.
Coxsackieviruses A1, 11, 13, 15, 17, 18, 19, 20, 21, 22 and 24.

***Human enterovirus D* (HEV-D)**
Enteroviruses 68 and 70.

Fig. 2. Virus in the genus *Enterovirus*: human enterovirus species A–D.

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