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Review

Astrovirus infections in humans and animals – Molecular biology, genetic diversity, and interspecies transmissions

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ABSTRACT

Astroviruses are small, non-enveloped, positive sense, single-stranded RNA viruses first identified in 1975 in children suffering from diarrhea and then described in a wide variety of animals. To date, the list of animal species susceptible to astrovirus infection has expanded to 22 animal species or families, including domestic, synantropic and wild animals, avian, and mammalian species in the terrestrial and aquatic environments. Astrovirus infections are considered among the most common cause of gastroenteritis in children, second only to rotavirus infections, but in animals their association with enteric diseases is not well documented, with the exception of turkey and mink astrovirus infection. Genetic variability has been described in almost all astrovirus species sufficiently examined infecting mammals and birds; however, antigenic variability has been demonstrated for human astroviruses but is far less investigated in animal viruses. Interestingly, there is an increasing evidence of recombination events occurring in astroviruses, which contributes to increase the genetic variability of this group of viruses. A wide variety of species infected, the evident virus genetic diversity and the occurrence of recombination events indicate or imply either cross-species transmission and subsequent virus adaptation to new hosts or the co-infection of the same host with different astroviruses. This can also favor the emergence of novel astroviruses infecting animals or with a zoonotic potential. After more than 30 years from their first description in humans, there are many exciting streams of research to be explored and intriguing questions that remain to be answered about the relatively under-studied *Astroviridae* family. In the present work, we will review the existing knowledge concerning astrovirus infections in humans and animals, with particular focus on the molecular biology, interspecies transmission and zoonotic potential of this group of viruses.

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1. Introduction

Astroviruses are small, non-enveloped RNA viruses first identified in 1975 by electron microscopy (EM) in children suffering from diarrhea (Appleton and Higgins, 1975; Madeley and Cosgrove, 1975b; Matsui and Greenberg, 1996). Since then, enteric infections in humans caused by astrovirus have been reported worldwide mainly in infants and young children. Several studies suggest that astroviruses are the second most common cause of gastroenteritis in children after rotavirus infection (Matsui and Greenberg, 1996).

The name astrovirus derives from the Greek word "astron" (=star) and describes the characteristic five/six pointed star-like projections detectable by negative stained EM of the virions. Although it should be pointed out that the presence of these projections is pH dependent and may only be present in less than 10% of the population (Caul and Appleton, 1982; Koci and Schultz-Cherry, 2002). In fact, in some instances the typical star-like appearance is not easily recognizable in EM preparations and astroviruses could be misidentified as enteroviruses or provisionally named astrovirus-like particles or small round viruses (SRVs) (Guy et al., 2004; Koci and Schultz-Cherry, 2002). This was probably the case of astrovirus infections in ducks, turkeys, and guinea fowl, where picornavirus or enterovirus-like particles were initially described (Cattoli et al., 2005; Guy et al., 2004; Koci and Schultz-Cherry, 2002). For this reason, the advent of more specific tools for virus detection and genome-based identification in the last ten years has allowed the discovery or the confirmation of the presence of astroviruses in a number of different hosts.

Soon after the first description in human beings, astrovirus-like particles were described and reported in domesticated animals. The first reports in animals were from lambs and calves suffering from diarrhea (Snodgrass and Gray, 1977; Woode and Bridger, 1978). Based on clinical and virological observations during acute mortality cases in ducks in the 1980s, the presence of astrovirus was associated with fatal hepatitis (Gough et al., 1984). This was perhaps the first evidence of extra-intestinal localization of astroviruses. Of interest, similar acute duck hepatitis was also reported in the 1960s, one decade before the discovery of astrovirus in humans and 20 years before identification of astroviruses as the cause of hepatitis in ducks (Asplin, 1965a,b). At present, the list of animal species susceptible to astrovirus infection has expanded to include domestic, synantropic and wild animals, avian and mammalian species in the terrestrial and aquatic environments (Table 1). In the last decade, there has been a dramatic increase in the identification of astroviruses in new animal species due to the advent of better molecular assays and pathogen discovery tools. This list is likely to be far from complete and surely more astrovirus-susceptible hosts are going to be added in the near future.

In the present work, we will review the existing knowledge concerning astrovirus infections in humans and animals, with particular focus on molecular biology, interspecies transmission and zoonotic potential of this group of viruses.

2. Etiology and taxonomy

The family *Astroviridae* comprises non-enveloped, positive sense, single-stranded RNA viruses, typically 28–30 nm in diameter (Matsui and Greenberg, 1996). They have been classified into two genera, namely *Mamastroviruses* (MAstVs) and *Avastroviruses* (AAstVs) known to infect mammalian and avian species, respectively (Mendez and Arias, 2007). Few species are officially classified by the International Committee for Taxonomy of Viruses (ICTV). These are: duck astrovirus 1 (DAstV-1), turkey astrovirus 1 and 2 (TAstV-1 and TAstV-2), and avian nephritis virus (ANV) as AAstVs, bovine astrovirus (BoAstV), feline astrovirus (FeAstV), human astroviruses (HAstVs 1–8), ovine astrovirus (OAstV), mink astrovirus (MiAstV), and porcine astrovirus (PoAstV) as MAstrVs.

The genome length is 6.8 to 7.9 kb and includes a 5′ untranslated region (UTR), followed by three open reading frames (ORFs) namely ORF1a, ORF1b, and ORF2, a 3′ UTR and a poly-A tail. There is a frame-shift structure between ORF1a and ORF1b. ORF1 encodes both a protease and an RNA-dependent RNA polymerase. ORF2 is expressed from a subgenomic RNA and encodes for the viral capsid protein (Fig. 1). The length of each of these structures varies between species and serotypes. From a genetic point of view, ORF1b appears to be the least divergent and ORF2 the most divergent among the different ORFs (Strain et al., 2008). This is of course an expected event since the region encoding for the viral capsid protein is more subject to selective pressure if compared to regions encoding for non-structural proteins. Unfortunately, only a minimal number of complete genomic astrovirus sequences are available (Table 2).

To date, *Astroviridae* taxonomy takes into account the species of origin. Serotypes have been defined on the basis of twenty-fold, or greater, two-way cross-neutralization titers. Serotypes assigned to the species are given consecutive numbers (Lee and Kurtz, 1982; Mendez and Arias, 2007). Astroviruses do not easily grow in laboratory host systems and for this reason serological classification is difficult and is generally speculated based on percentage of nucleotide and amino acid similarity of the ORF2 encoding for the capsid protein (Chu et al., 2008; Koci et al., 2000; Reuter et al., 2011). It has been reported that if two strains of HAstVs have less than 95% homology at the nucleotide level, they are serologically distinguishable (Walter et al., 2001). Few documented antigenic classifications have been attempted for animal AstVs. Serological assays confirmed by molecular characterization, suggested the existence of a putative novel serotype of turkey astrovirus, TAstV-3 (Tang and Saif, 2004; Tang et al., 2005); similarly the application of cross-virus neutralization assays indicated the presence of more undefined serotypes of bovine AstV (Woode et al., 1985).

Although official classification is currently based on the species of origin of AstV, the discovery of viruses in species never implicated before and of viruses genetically unrelated to those known to infect the same species has highlighted the need to review classification of those viruses following updated guidelines. Several AstVs have recently been detected in new species, namely guinea fowl, insectivorous bats, dogs, cheetahs, marine mammals,