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Equine arteritis virus

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ABSTRACT

Equine arteritis virus (EAV) is the causative agent of equine viral arteritis (EVA), a respiratory and reproductive disease of equids. There has been significant recent progress in understanding the molecular biology of EAV and the pathogenesis of its infection in horses. In particular, the use of contemporary genomic techniques, along with the development and reverse genetic manipulation of infectious cDNA clones of several strains of EAV, has generated significant novel information regarding the basic molecular biology of the virus. Therefore, the objective of this review is to summarize current understanding of EAV virion architecture, replication, evolution, molecular epidemiology and genetic variation, pathogenesis including the influence of host genetics on disease susceptibility, host immune response, and potential vaccination and treatment strategies.

1. Introduction

Equine arteritis virus (EAV) was first isolated from the lung of an aborted fetus following an extensive outbreak of respiratory disease and abortion on a Standardbred breeding farm near Bucyrus, Ohio, USA, in 1953 (Doll et al., 1957a,b). After isolation of the causative virus and description of characteristic vascular lesions, equine viral arteritis (EVA) was identified as an etiologically distinct disease of the horse (Doll et al., 1957a). EAV is a small enveloped, positive-sense, single-stranded RNA virus that is the prototype virus in the family *Arteriviridae* (genus: *Arterivirus*), order *Nidovirales*, a taxonomic grouping that includes porcine reproductive and respiratory syndrome virus (PRRSV), simian hemorrhagic fever virus (SHFV), and lactate dehydrogenase-elevating virus (LDV) of mice (Cavanagh, 1997). Pioneering work on the distinctive replication strategy utilized by EAV originally led to the taxonomic designation of the Order *Nidovirales* (Cavanagh, 1997), a grouping of morphologically distinct viruses included in the families *Arteriviridae*, *Coronaviridae*, and *Roniviridae* that all utilize a similar replication strategy that involves the generation of a nested set of subgenomic RNAs (de Vries et al., 1997; den Boon et al., 1991; Gorbalenya et al., 2006; Snijder and Spaan, 2006). The order *Nidovirales* has been expanded recently to include several newly identified plus-stranded RNA viruses including wobbly possum disease virus (WPDV), a close relative to the other members of the family *Arteriviridae* and the cause of neurologic disease among free-ranging Australian brush-tail possums (*Trichosurus vulpecula*) in New Zealand (Dunowska et al., 2012). Similarly, two new genetically divergent SHFV variants (SHFV-krc1 and SHFV-krc2) were recently identified in a single male colobus monkey (*Procolobus rufomitratus tephrosceles*; Lauck et al., 2011). Both SHFV-krc1 and SHFV-krc2 are highly divergent from the prototypic LVR 42-0/6941 strain of SHFV (52.0% and 58.1% nucleotide diversity, respectively) and, interestingly, the two variants are also significantly different from one

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another and share only 51.9% nucleotide sequence identity. Subsequently, two additional highly divergent variants of SHFV (SHFV-krtg-1a/b and SHFV-krtg-2a/b [79.4% nucleotide identity]) were isolated from African red-tailed (guenon) monkeys (*Cercopithecus ascanius*) from Kibale National Park, Uganda (Lauck et al., 2013). These two variants were also genetically distinct from the prototypic LVR 42-0/6941 strain of SHFV (54.1%) and the SHFV-krc1 and SHFV-krc2 (50.1%) variants. Additional novel nidoviruses have also been isolated recently from mosquitoes, including Cavally virus (CAVV) and Nam Dinah virus (NDiV). These newly identified arthropod-borne nidoviruses are provisionally placed in a new family *Mesoniviridae*, which is an intermediate between the families *Arteriviridae* and *Coronaviridae* and more closely related to the family *Roniviridae* (Lauber et al., 2012). The recent recognition of these related but distinct viruses that share similar replication strategies indicates an increasing need for reclassification of the order *Nidovirales*.

Like the other arteriviruses, EAV infection is highly species-specific and exclusively limited to members of the family *Equidae*, which includes horses, donkeys, mules, and zebras (Stadejek et al., 2006; Timoney and McCollum, 1993). The EAV associated disease, EVA, is a respiratory and reproductive disease of horses that occurs worldwide (Bell et al., 2006; Glaser et al., 1996; Timoney and McCollum, 1993). Although there is only one known EAV serotype, field strains of the virus differ in their virulence and neutralization phenotype (Balasuriya et al., 1999b, 2002a, 2007; Balasuriya and Maclachlan, 2004; Go et al., 2012; MacLachlan et al., 1996; McCollum et al., 1998; Patton et al., 1999; Pronost et al., 2010; Vairo et al., 2012; Zhang et al., 2010b, 2012). The clinical signs exhibited by individual EAV-infected horses depend on a variety of factors including the age and physical condition of the animal, challenge dose and route of infection, strain of virus, and environmental factors. With the sole and notable exception of the experimentally derived and highly horse-adapted, virulent Bucyrus strain, other strains and field isolates of EAV very rarely cause fatal infection in adult horses (McCollum and Timoney, 1998; Pronost et al., 2010). The vast majority of EAV infections are subclinical, but acutely infected animals may develop a wide range of clinical signs including pyrexia, depression, anorexia, dependent edema (scrotum, ventral trunk, and limbs), stiffness of gait, conjunctivitis, lacrimation and swelling around the eyes (periorbital and supraorbital edema), respiratory distress, urticaria, and leukopenia (Timoney and McCollum, 1993). The incubation period of 3–14 days (typically 6–8 days following venereal exposure) is followed by pyrexia of up to 41 °C (105.8 °F) that may persist for 2–9 days. The virus can cause abortion of pregnant mares, with abortion rates during field outbreaks varying from approximately 10% to 70%, depending on the virus strain (Timoney and McCollum, 1993). EAV-induced abortions can occur at any time between 3 and 10 months of gestation. Infection of neonatal foals can cause a severe fulminating interstitial pneumonia, and in 1–3 months old foals a progressive "pneumo-enteric" syndrome (Vaala et al., 1992). A variable proportion of acutely infected stallions (10–70%) become persistently infected and shed the virus exclusively in their semen (Timoney and McCollum, 1993 and references therein). There is no evidence of EAV causing persistent infection in mares, geldings, or foals. The virus persists mainly in the ampulla of the stallion's reproductive tract, and the establishment and maintenance of the carrier state in the stallion is testosterone-dependent.

Serologic surveys have shown that EAV infection has occurred among horses in North and South America, Europe, Australia, Africa, and Asia (Echeverria et al., 2003; Eichhorn et al., 1995; Szeredi et al., 2005; Timoney and McCollum, 1993). Other countries such as Iceland and Japan are apparently free of the virus. Recent studies have shown that New Zealand is also free of active EAV infection (McFadden et al., 2013). However, the seroprevalence of EAV infection of horses varies between countries and among horse breeds within a country. For example, the seroprevalence of EAV infection varies among horses of different breeds and ages in the United States (US), with marked disparity between the prevalence of infection of Standardbred and Thoroughbred horses (Timoney and McCollum, 1993). EAV infection is considered endemic in Standardbred but not Thoroughbred horses in the US, with 77.5% to 84.3% of all Standardbreds but only up to 5.4% of Thoroughbreds being seropositive to the virus (Hullinger et al., 2001; McCollum and Bryans, 1973; McCue et al., 1991; McKenzie, 1996; Moraillon and Moraillon, 1978; Timoney and McCollum, 1988, 1993). Similarly, the seroprevalence of EAV infection of Standardbred horses in California was 68.5% in 1991, *versus* less than 2% in all other breeds tested (McCue et al., 1991). The 1998 National Animal Health Monitoring System (NAHMS) equine survey showed that only 0.6% of the US American Quarter Horse (AQH) population was seropositive to EAV (Anonymous, 2000). However, the extensive US outbreak of EVA in 2006–2007 mainly involved AQHs and this very likely significantly increased the seroprevalence of EAV within this breed. The seroprevalence of EAV infection of Warmblood stallions is also very high in a number of European countries, with some 55 to 93% of Austrian Warmblood stallions being seropositive to EAV (Burki et al., 1992). Similarly, there is high seroprevalence among mares and stallions of Hucul horses in Poland, 53.2% and 68.2%, respectively (Rola et al., 2011).

Transmission of EAV between horses occurs *via* either the respiratory or venereal route (Cole et al., 1986; Doll et al., 1957b; McCollum et al., 1971; Timoney and McCollum, 1993; Timoney et al., 1986, 1987). Horizontal respiratory transmission occurs after aerosolization of infected respiratory tract secretions from acutely infected horses; high titers of EAV are present in respiratory secretions for some 7–14 days during acute infection (McCollum et al., 1971). However, direct and close contact is necessary for aerosol transmission of EAV between horses (Collins et al., 1987; Timoney and McCollum, 1988). EAV can also be transmitted by aerosol from urine and other body secretions of acutely infected horses, aborted fetuses and their membranes, and the masturbates of acutely or chronically infected stallions (Burki et al., 1992; Glaser et al., 1996, 1997; Guthrie et al., 2003; McCollum, 1981; McCollum et al., 1971, 1995). Venereal transmission