Infection, Genetics and Evolution 11 (2011) 1514–1519

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

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

Review

Current perspectives on the phylogeny of *Filoviridae*

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ARTICLE INFO

Article history:
Received 9 March 2011
Received in revised form 24 June 2011
Accepted 25 June 2011
Available online 30 June 2011

Keywords:
Filoviridae
Ebola
Marburg
Phylogeny
Virus
Reston

ABSTRACT

Sporadic fatal outbreaks of disease in humans and non-human primates caused by Ebola or Marburg viruses have driven research into the characterization of these viruses with the hopes of identifying host tropisms and potential reservoirs. Such an understanding of the relatedness of newly discovered filoviruses may help to predict risk factors for outbreaks of hemorrhagic disease in humans and/or non-human primates. Recent discoveries such as three distinct genotypes of *Reston ebolavirus*, unexpectedly discovered in domestic swine in the Philippines; as well as a new species, *Bundibugyo ebolavirus*; the recent discovery of Lloviu virus as a potential new genus, *Cuevavirus*, within *Filoviridae*; and germline integrations of filovirus-like sequences in some animal species bring new insights into the relatedness of filoviruses, their prevalence and potential for transmission to humans. These new findings reveal that filoviruses are more diverse and may have had a greater influence on the evolution of animals than previously thought. Herein we review these findings with regard to the implications for understanding the host range, prevalence and transmission of *Filoviridae*.

Published by Elsevier B.V.

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1. Introduction

1.1. Types of filoviruses

Filoviruses are associated with acute fatal hemorrhagic diseases of humans and/or non-human primates. The family consists of the two classic genera: *Marburgvirus*, discovered in 1967 (Siegert et al., 1967), comprised of various strains of the *Lake Victoria marburgvirus* including Marburg virus and Ravn virus, and the antigenically distinct genus *Ebolavirus* discovered in 1976 (Emond et al., 1977), comprised of five species partially including *Sudan ebolavirus*, *Zaire ebolavirus*, *Ivory Coast ebolavirus* also known as *Cote d'Ivoire Ebolavirus* or the *Taï Forest ebolavirus*, and the *Reston ebolavirus* (Towner et al., 2008). The fifth and most recent member of the *Ebolavirus*

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1567-1348/$ - see front matter Published by Elsevier B.V.
doi:10.1016/j.meegid.2011.06.017

genus is the *Bundibugyo ebolavirus* identified in an outbreak of human disease in Uganda, Africa. In addition, a tentative, third genus of *Filoviridae* has been recently identified in Spain, in bats, with formal publication of the discovery and full genome characterization anticipated (Kuhn et al., 2010).

1.2. Classification of filoviruses

Filoviruses are large filamentous viruses, 80 nm in diameter and may vary in length from several hundred nm to as long as or longer than 1 μm. Their linear forms are pleomorphic and may be unbranched, branched, curved or straight. Indeed, genomic similarities between filoviruses and other negative-sense RNA viruses are pronounced, and are the basis for the current classification of filoviruses within the order *Mononegavirales*, proximal to *Paramyxoviridae*, *Rhabdoviridae* and *Bornaviridae* families.

1.3. Genome structure and content

Filovirus genomes are comprised of linear, non-segmented, negative-sense, single-stranded RNA approximately 19 kb in length (Regnery et al., 1980) (Fig. 1). The gene organization consists of a conserved 3′ non-coding region followed by seven genes that encode structural proteins and concluding in a conserved 5′ non-coding region (Fig. 1). In addition, the viral genes are flanked by extragenic regions containing promoters for transcription and replication (Feldmann et al., 1992) (Fig. 1). The nucleoprotein (NP), viral proteins VP35 and VP30 and the RNA-dependent RNA polymerase or L protein are bound to the viral genome, mediate transcription and replication and together form the nucleocapsid of the virus particle (Muhlberger, 2007). Another viral protein, VP40, serves as a matrix protein and plays a role in virus budding and release from the host cell (Urata et al., 2007). Virus protein VP24 represents yet another matrix protein and is involved in nucleocapsid formation and assembly (Noda et al., 2007). The seventh protein encoded by the virus is the envelope surface glycoprotein or spike glycoprotein (GP), which mediates attachment and entry into target cells and represents a major determinant of virus pathogenicity (Licata et al., 2004). A notable difference between Ebola and Marburg viruses is the use of mRNA editing in the expression of full length GP by Ebola viruses, but not Marburg viruses. As a result of RNA editing in Ebola viruses, two forms of envelope protein are expressed, the more abundant being a smaller soluble protein (sGP) and the less abundant being the full length GP (Fig. 1). The sGP has been shown to have antagonistic effects on TNF-α induced endothelial barrier functions (Falzarano et al., 2006; Sanchez et al., 1996; Volchkov et al., 1995; Wahl-Jensen et al., 2005). Regarding the full length GP, there is a strong correlation between the level of GP expression and severe vascular cell cytotoxicity that is characteristic of filovirus infections. *In vitro*, the mucin domain of GP itself has been found to elicit cytotoxicity of endothelial cells (Yang et al., 2000). In addition, high level expression of full-length GP on host cell surfaces has been shown to not only mask particular immune-reactive epitopes of the GP but also cause the down regulation of host cell surface immune surveillance markers including major histocompatibility complex class I molecules resulting in immune evasion (Reynard et al., 2009). Among the viral proteins, VP35 and VP24 are known to be involved in interference of host cellular antiviral interferon mechanisms by prevention of nuclear accumulation of the phosphorylated signal transduction and transcription activation element, STAT1(Basler et al., 2003; Reid et al., 2006; Valmas et al., 2010). In addition the VP40 of Marburg virus has been shown to inhibit interferon mediated antiviral mechanisms in a manner that is distinct from Ebola viruses through interference with the phosphorylation event of STAT1 and STAT2 and also has effects on Janus kinase dependent interferon pathways (Valmas et al., 2010).

2. Phylogeny of filoviruses

2.1. Newly proposed phylogenetic naming convention

Due to new discoveries, and a better understanding of the phylogeny, revisions have been recently proposed to the standard naming conventions used to describe members of *Filoviridae* (Kuhn et al., 2010). Using this newly proposed naming convention, Marburg viruses, which comprise multiple isolates of a single genus and species, would be written as *Marburg marburgvirus* to describe the genus and species, and Marburg virus (MARV) or Ravn virus (RAVV) to describe distinct viruses within the species (Table 1). Likewise, the genus *Ebolavirus*, comprised currently of multiple isolates of five representative species, would be similarly written and abbreviated to discriminate the genus, species, and individual virus isolate names (Table 1) (Kuhn et al., 2010). As a result of the recent genome characterization of a novel filovirus, Lloviu virus (LLOV), equidistantly related to Marburg and Ebola viruses and discovered in Schreiber's long-fingered bats (*Miniopterus schreibersii*) in the Cueva del Lloviu Principality of Asturias in Spain, a new genus within *Filoviridae*, *Cuevavirus*, has been proposed (Kuhn et al., 2010).

2.2. Host tropisms and transmission

Since the discovery of filoviruses, ostensibly random, sporadic and fatal outbreaks of disease in humans and non-human primates have evoked interest in delineation of host tropisms, potential reservoirs for disease transmission, and persistence in nature (Strong et al., 2008). While pathogenesis seems largely limited to humans and non-human primates, a few other animal species including swine have been found to be susceptible to infection by Ebola viruses (Barrette et al., 2009). Trace RT-PCR evidence and/or serological evidence suggest the potential susceptibility of duiker antelope to infection (Gonzalez et al., 2007; Rouquet et al., 2005). Candidate reservoir hosts for filoviruses are thought to be mammals of small body size, asymptomatic, and not likely to be companion animals (Peterson et al., 2004). Investigations into potential host species have also recently identified African fruit

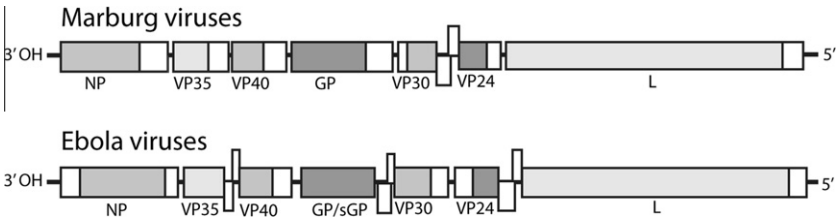

Fig. 1. Genome representations of Marburg viruses and Ebola viruses. Open reading frames and intergenic regions are indicated as shaded and unshaded boxes, respectively. Overlapping intergenic regions are shown as split boxes.