Antiviral Research 141 (2017) 48–61

Contents lists available at ScienceDirect

Antiviral Research

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

Review

Filovirus proteins for antiviral drug discovery: Structure/function bases of the replication cycle

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ARTICLE INFO

Article history:
Received 19 November 2016
Received in revised form
12 January 2017
Accepted 7 February 2017
Available online 10 February 2017

Keywords:
Ebola virus
Marburg virus
Filovirus
Antiviral therapy
Mononegavirales

ABSTRACT

Filoviruses are important pathogens that cause severe and often fatal hemorrhagic fever in humans, for which no approved vaccines and antiviral treatments are yet available. In an earlier article (Martin et al., *Antiviral Research*, 2016), we reviewed the role of the filovirus surface glycoprotein in replication and as a target for drugs and vaccines. In this review, we focus on recent findings on the filovirus replication machinery and how they could be used for the identification of new therapeutic targets and the development of new antiviral compounds. First, we summarize the recent structural and functional advances on the molecules involved in filovirus replication/transcription cycle, particularly the NP, VP30, VP35 proteins, and the "large" protein L, which harbors the RNA-dependent RNA polymerase (RdRp) and mRNA capping activities. These proteins are essential for viral mRNA synthesis and genome replication, and consequently they constitute attractive targets for drug design. We then describe how these insights into filovirus replication mechanisms and the structure/function characterization of the involved proteins have led to the development of new and innovative antiviral strategies that may help reduce the filovirus disease case fatality rate through post-exposure or prophylactic treatments.

Contents

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http://dx.doi.org/10.1016/j.antiviral.2017.02.004
0166-3542/

1. Introduction

Filoviruses are filamentous, enveloped, non-segmented, negative-sense RNA viruses (NNS) that belong to the order *Mononegavirales*. The family *Filoviridae* includes the genera *Ebolavirus* and *Marburgvirus* that comprise highly pathogenic viruses, responsible for hemorrhagic fevers for which there are no approved therapies. In addition, in 2002, Lloviu virus (LLOV), a new filovirus that so far has only been identified in bats, was discovered and proposed to be classified in the novel genus *Cuevavirus* (Ascenzi et al., 2008; Negredo et al., 2011). The filovirus classification and nomenclature have recently been overhauled (Bukreyev et al., 2014). Accordingly, the genera *Marburgvirus* and *Cuevavirus* each include a single species: *Marburg marburgvirus* (Marburg virus – MARV) and LLOV, respectively. In contrast, the genus *Ebolavirus* includes five virus species: *Zaire ebolavirus* (Ebola virus – EBOV), *Sudan ebolavirus* (Sudan virus – SUDV), *Taï Forest ebolavirus* (Taï Forest virus - TAFV), *Bundibugyo ebolavirus* (Bundibugyo virus - BDBV) and *Reston ebolavirus* (Reston virus - RESTV).

Filoviruses share a common genome organization with seven open reading frames that encode all viral proteins (Fig. 1): a nucleoprotein (NP), the viral proteins VP35 and VP40, the surface glycoprotein (GP), the viral proteins VP30 and VP24, and the "large" polymerase (L) (Ascenzi et al., 2008; Negredo et al., 2011). GP is the protein that mediates filovirus entry into host cells. This step is a key point in the viral life cycle and an attractive target for antiviral strategies (Martin et al., 2016). After entry by macropinocytosis, the viral nucleocapsid (i.e., the viral genome encapsidated by NP and associated with other viral proteins) is released into the host cell cytoplasm, allowing the synthesis of new viral proteins and genomes. Then, nucleocapsid and progeny virion assembly and budding are orchestrated by NP, VP24 and VP40, and enhanced by GP (Hartlieb and Weissenhorn, 2006; Noda et al., 2006). VP24 condenses the ribonucleoprotein (RNP) complex (e.g. the NP-bound RNA genome) that may fix L at the 3′ end of genomes, thus blocking the transcription/replication cycle (Watt et al., 2014). Whole viral particle assembly is then driven by VP40 (assisted by NP in the case of MARV) that recruits host proteins important for efficient virus egress and spread (Hartlieb and Weissenhorn, 2006; Noda et al., 2006; Silva et al., 2012; Mittler et al., 2013).

In an earlier article, we provided a structure/function analysis of filovirus surface glycoproteins and viral entry into cells (Martin et al., 2016). In this review, we summarize the current knowledge about the structure/function relationships of the viral proteins that drive and regulate filovirus genome transcription/replication. We detail the complexes in which viral proteins are involved and their structural features. We then describe their role in the viral cycle and compare their functionalities with those of homolog proteins from prototype viruses within the order *Mononegavirales*. Finally, we show how these insights can help developing new and innovative antiviral strategies, with a specific focus on small organic compounds.

2. Nucleocapsid structural and functional organization

Filoviruses share the replication/transcription strategy of NNS RNA viruses of the order *Mononegavirales* (Fig. 1) (Whelan et al., 2004). Briefly, upon host cell entry through virus

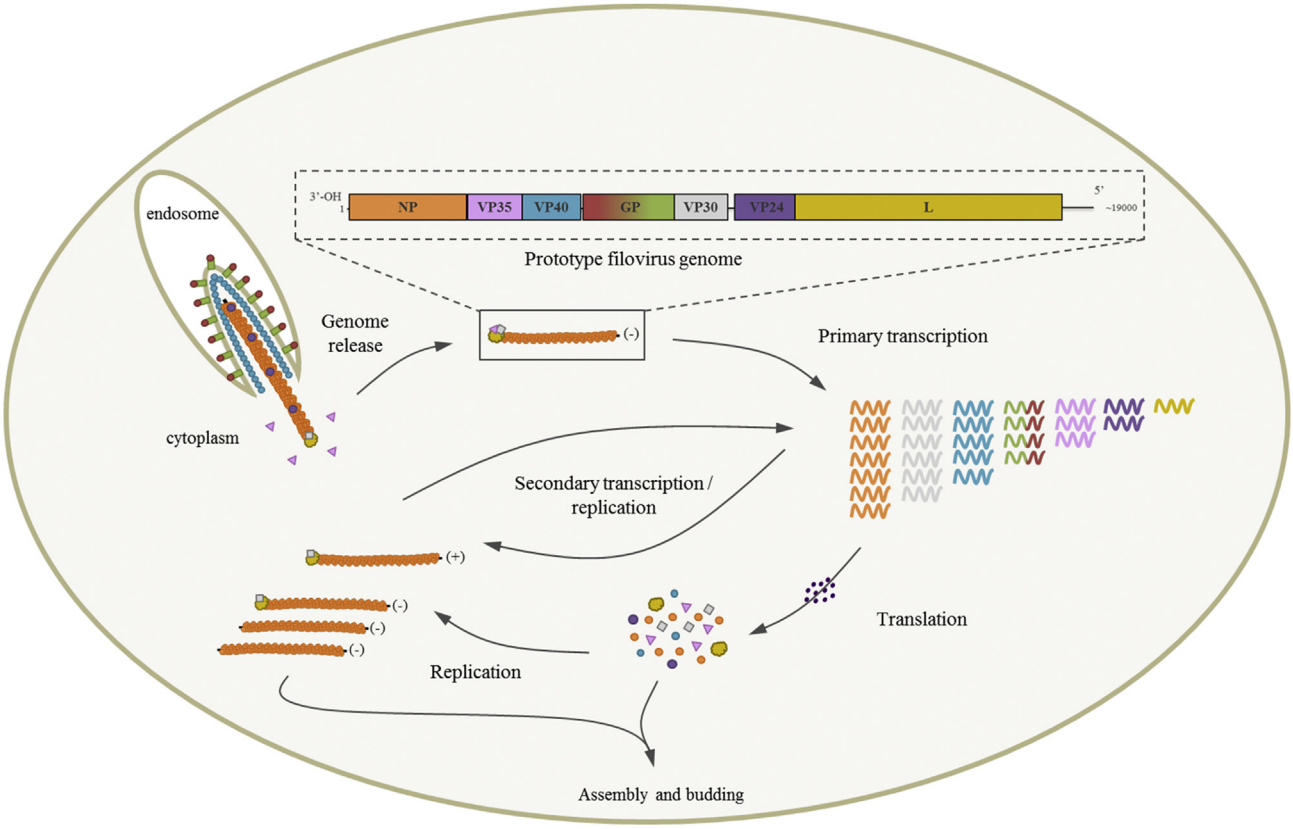

Fig. 1. Filovirus replication cycle. After entry into the host cell (reviewed in Martin et al., 2016), the filovirus genome is released in the cytoplasm. The negative-sense, single-stranded RNA genome is first sequentially transcribed (primary transcription) and then mRNAs are translated into viral proteins. With the increase of viral protein concentration and host cell factor regulation, the polymerase complex switches to replication mode to generate anti-genomes and new genomes. Finally, a balance between secondary transcription and replication leads to the assembly and budding of progeny virions.