Filovirus

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Filoviruses are among the deadliest infectious agents known to man, causing severe hemorrhagic fever, with up to 90% fatality rates. The 2014 Ebola outbreak in West Africa resulted in over 28,000 infections, demonstrating the large-scale human health and economic impact generated by filoviruses. Zaire ebolavirus is responsible for the greatest number of deaths to date and consequently there is now an approved vaccine, Ervebo, while other filovirus species have similar epidemic potential and remain without effective vaccines. Recent clinical success of REGN-EB3 and mAb-114 monoclonal antibody (mAb)-based therapies supports further investigation of this treatment approach for other filoviruses.

Keywords: Filovirus ; AAV Vectored Immunoprophylaxis ; Zaire ebolavirus ; marburg

1. Introduction

Infectious diseases have had profound and long-lasting impacts on the human race throughout history. Epidemic threats are deepened by the emergence of new and uncharacterized infectious diseases, coupled with the ability to impact human health and the economy at a global scale. Although our understanding and surveillance of infectious disease has advanced, the pursuit of effective methods for preventing the spread of these infections at times remains elusive. Filovirus disease outbreaks showcase these concerns, due to their high pathogenicity, zoonotic transmission efficiency, and spontaneity of spillover. Although Ebola hemorrhagic fever (EHF) and Marburg hemorrhagic fever (MHF) are highly pathogenic viral diseases, the global burden of EHF and MHF is minor in comparison to other infectious diseases [1]; however, as we observed with the 2014 West Africa outbreak, EHF has the potential to cause large, multi-nation outbreaks resulting in significant mortality and economic devastation. In this review, we will discuss the history and pathogenesis of filoviruses, highlight the role of antibodies in protection against filovirus infections, and examine the potential of viral vector-mediated expression of monoclonal antibodies (mAbs) as an alternative prophylactic strategy to enable long term passive immunity against filovirus infections.

1.1. A Brief History of Filovirus Outbreaks

Filovirus outbreaks have been reported since 1967, with the first outbreak of Marburg virus (MARV) occurring simultaneously in Germany and Yugoslavia, when laboratory workers imported African green monkeys (Chlorocebus aethiops) from Uganda and were exposed while working with the tissues of infected animals [2]. The second outbreak of Marburg virus disease (MVD) occurred in 1975 in South Africa, where it was determined that the index patient had visited caves in Rhodesia (now Zimbabwe) and had come in contact with bats [3]. A subsequent Marburg outbreak occurred in Kenya in 1987, where the index case had also visited a cave and contracted the virus; however, in this case the disease was caused by a new strain of Marburgvirus; Ravn virus (RAVV). In total, there have been 13 recorded MARV outbreaks (MARV and RAVV) with over 460 confirmed cases and 370 reported deaths [4].

Shortly after the discovery of MARV, there were three outbreaks of Sudan ebolavirus (SUDV) and Zaire Ebolavirus (EBOV) in 1976, across Sudan, the Democratic Republic of Congo (DRC) (formerly Zaire), and England [5]. Since the identification of Ebola virus in 1976, there have been a total of 38 Ebola virus disease (EVD) outbreaks, including the recent EBOV outbreak in the DRC, which was announced 1 June 2020 [6]. The largest filovirus outbreak occurred from December 2013 to March 2016, shedding light on the true epidemic potential of EBOV. Epidemiological and genomic analyses suggest that the index case was a 2-year old boy in Meliandou, Guinea, who had been infected through exposure to bats [7]. By the time multiple cases of fatal diarrhea were reported and the Pasteur Institute had confirmed EBOV was the cause, the disease had already spread to the capital of Guinea, Conakry [8], as well as to neighboring countries, Sierra Leone and Liberia. On 23 March 2014, the WHO officially declared an outbreak of EVD. Inadequate disease surveillance, poor public health infrastructure, the ravages of civil war, extreme poverty, and local customs, such as washing a dead body prior to burial, aided in the spread of EBOV [9][10]. After more than two years, the outbreak was declared over in June of 2016, claiming the lives of more than 11,320 people and infecting a staggering 28,600 individuals [11]. The unprecedented scale of this outbreak left many survivors suffering from post-Ebola syndrome [12], orphaned more

than 17,000 children [13], and devastated economies. Moreover, the EVD outbreak reduced the availability of treatments and monitoring for other serious infectious diseases, including HIV, tuberculosis, and malaria leading to increased mortality [14]. Despite the fact that previous filovirus outbreaks had highlighted the potential for efficient transmission and high case fatality rates, there were no U.S Food and Drug Administration (FDA)-approved vaccines or therapeutics for EBOV prior to the 2014 West Africa Ebola outbreak.

2. Filovirus Taxonomy and Filovirus Molecular Biology and Pathogenesis

2.1. Filovirus Taxonomy

Filoviruses are a family of non-segmented, negative-sense RNA viruses belonging to the order Mononegavirales. Filovirus taxonomy has been frequently updated during the past decade, where the most recent update by the International Committee on Taxonomy of Viruses in July of 2019 listed six genera and eleven species in the family [15]. The six genera within the Filoviridae family include: Ebolavirus, Marburgvirus, Cuevavirus, Thamnovirus, and Striavirus, and the most recently classified, Dianlovirus [16][17]. The Ebolavirus genus contains six species: the highly pathogenic Zaire ebolavirus (EBOV, Ebola virus) and Sudan ebolavirus (SUDV, Sudan virus), the less prevalent Taï forest ebolavirus (TAFV, Taï Forest virus), Bundibugyio virus (BDBV, Bundibugyio virus), Reston ebolavirus (RESTV, Reston virus), and the recently discovered Bombali ebolavirus (BOMV, Bombali virus) [18]. The genus Marburgvirus contains a single species, Marburg marburgvirus (MARV, Marburg virus); however, two distinct strains with less than 30% genetic divergence, Marburg virus (MARV) and Ravn virus (RAVV), make up this species [19]. Lloviu cuevavirus (LLOV, Lloviu virus), isolated from insectivorous bats located in Northern Spain, is the only species confirmed in the Cuevavirus genus [20]. Of the members in the Filoviridae family, seven species have been confirmed to infect humans, including EBOV, SUDV, TAFV, BDBV, MARV, RESTV, and RAVN, albeit with different severity [21]. The most virulent is EBOV, followed closely by MARV with fatality rates ranging from 25–90% and 24–88%, respectively, whereas, BDBV and SUDV are less severe with fatality rates of ~30% and 50%, respectively [21][22][23]. Though RESTV does cause infections in humans, these have only ever been reported as asymptomatic; however, it can be fatal in non-human primates (NHP) [24]. Limited information is known about TAFV infections in humans as there has only been one documented case, with that person recovering after a severe illness [25].

2.2. Filovirus Molecular Biology and Pathogenesis

Filoviruses are filamentous enveloped particles 80 nm in diameter and up to 14,000 nm in length [26]. The negative-sense, single stranded RNA genome is approximately 19 kb in length and encodes seven open reading frames (ORF) orientated in a 3′-5′ direction: the nucleoprotein (NP), viral protein (VP) 35, VP40, glycoprotein (GP), VP30, VP24, and the RNA-dependent RNA polymerase (L) [27]. Each ORF is flanked by non-translated regions including conserved transcriptional start and stop signals crucial for protein expression [28][29]. The GP for filoviruses is the only protein “studded” on the surface of the virion and is the sole determinant of viral entry into host cells [30]. In addition to the fundamental role of the GP in viral entry, ebolavirus GPs appear to have multiple auxiliary functions, likely contributing to the complex pathogenesis of the virus [31].

As humans are not the natural reservoir hosts for filoviruses, spillover occurs through contact with the virus’s natural reservoir hosts, which in the case of EBOV is likely to be a species of bat [32]. Alternatively, transmission can occur through contact with intermediate hosts, for instance when hunting bushmeat, or through secondary transmission by infected humans. In patients with disease, acute EBOV and MARV virus shedding occurs and can be found in blood or other bodily fluids including: urine, saliva, sweat, feces, vomit, breast milk, and semen [33]. Once an individual becomes infected there is a 2–21 day incubation period, with calculated mean incubation periods of 5.3–12.7 days for EBOV, 3.35–12 days for SUDV, and 6.3–7 days for BDBV, characterized by onset of non-specific flu-like symptoms [34][35][36][37][38][39][40]. Following this incubation period, disease occurs rapidly in lethal cases, with high fever, severe hemorrhage, shock, followed by death, due to systemic viral replication, immunosuppression, and abnormal inflammatory responses with extensive organ distribution [41][42][43]. Upon entering the host, filoviruses preferentially infect antigen presenting cells (APCs) including dendritic cells (DCs), monocytes, and macrophages [44][45][46][47]. Infected APCs fail to activate and mature and are therefore unable to present antigens to T cells in the lymph nodes. Upregulation of co-stimulatory molecules (i.e., CD40, CD80, CD86, and MHC class II) is inhibited in infected APCs, which subsequently interferes with their ability to initiate adaptive immune responses [48][49]. Additionally, studies have shown that infection of EBOV and MARV results in lymphopenia, affecting CD4+ and CD8+ T cells, as well as B cells and natural killer cells [50][51][52]. Loss

of B cells, as well as helper T cells, leads to impairment in humoral responses, as there is an absence of specific IgG and barely detectable IgM in fatal infections [53]. Conversely, Ebola survivors have revealed significant activation of both B and T cells, proliferating plasmablasts, as well as circulating Ebola virus-specific IgG [54][55].

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