The emergence of Ebola and Marburg viruses

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Introduction

An emerging pathogen is defined as either a hitherto unknown agent or a pathogen whose incidence has increased considerably in susceptible populations; Ebola and Marburg fulfill the two criterions of this definition. These viruses are members of the *Filoviridae* family and the most virulent species induce acute hemorrhagic fevers and death within a few days in up to 90% of symptomatic individuals.

Goals

- The first goal of this project is to know what the causes of the emergence of these viruses are, for this reason, we have to know what the reservoirs and the interaction with the guest are.
- The second goal is to see what the epidemiology and the mechanisms of control and prevention are.

Epidemiology

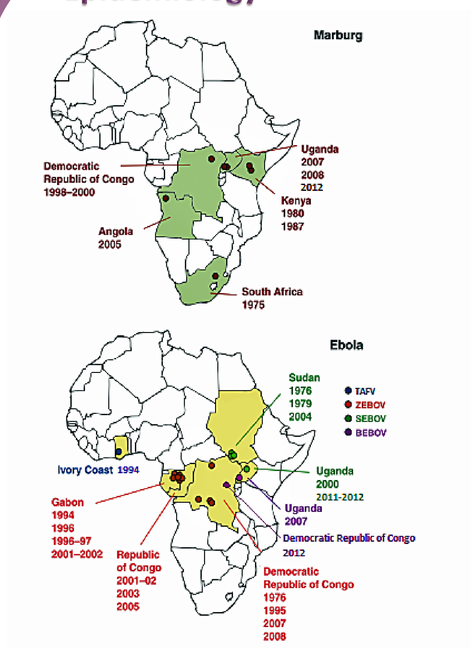

Fig.1. Filovirus outbreaks in Africa. Reported outbreaks or isolated cases of hemorrhagic fever caused by *Marburg* virus (MARV) and *Ebola* virus (EBOV).

The virus family *Filoviridae* has been known since 1967, when *Marburg* virus caused an outbreak of hemorrhagic disease in Frankfurt, Belgrade and Marburg, and later in 1976 when there was an outbreak of *Ebola* in Sudan and in DRC (Democratic Republic of Congo). Since then, five species of *Ebola* virus and only one of *Marburg* virus have been discovered (Table 1); all these species show clear geographic patterns.

These viruses have been responsible for a few outbreaks (Fig.1), resulting in thousands of confirmed deaths. Hence, the disease burden of filovirus infection in Africa is extremely small compared with other infectious diseases and malnutrition.

Species of *Ebolavirus*	Species of *Marburgvirus*
• *Bundibugyo* (BEBOV) • *Zaire* (ZEBOV) • *Sudan* (SEBOV) • *Taï Forest* (TAFV) • *Reston* (REBOV)	• *Marburg Marburgvirus* (MARV)

Table 1. Species of *Ebola* and *Marburg.*

Reservoirs

Despite numerous epidemiologic analyses of the disease, laboratory tests of effects of infection on potential hosts and searches for natural virus infections among animals in localities where outbreaks have occurred; the source of these viruses in nature has remained obscure. Conclusive evidence that bats are natural hosts for filoviruses has been recently obtained. Antibodies and nucleotide sequences specific for *Ebola* and *Marburg* were detected in the liver and spleen of four fruit bat species (Fig.2). This would indicated that these viruses are transmitted from wildlife to people through contact with infected fruit bats, or through intermediate hosts, such as monkeys, apes, or pigs that would become infected themselves through contact with bat saliva or faeces (Fig.3).

Fig.2. Bat species that act as a reservoirs.

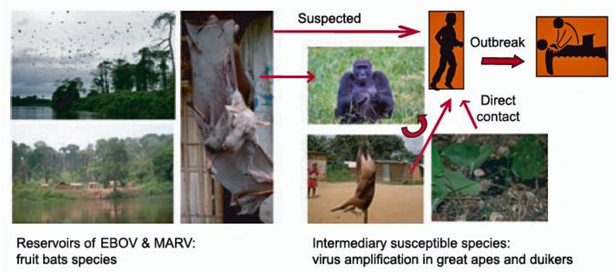

Fig.3. Model of the natural cycle of filovirus. The diagram shows animal-to-human transmissions leading to outbreak appearance.

Filoviruses structure

Protein	Function
VP24	Formation of the ribonucleoprotein complex/ Viral uncoating
VP30	Activation and modulation of RNA transcription
VP35	Tipe I IFN antagonist / Viral RNA synthesis
VP40	Assembly of lipid envelope/Budding
Nucleoprotein NP	Virus nucleocapsid assembly/ Budding
Glycoprotein GP	Virus attachment and entry in the host cell
RNA-dependent RNA polymerase (L)	Gene transcription

Table 2. Protein composition and their function.

The *Filoviridae* family comprises three genera, *Marburgvirus*, *Ebolavirus* and *Cuevavirus*, and belongs to the order *Mononegavirales*, a group of viruses characterized by a genome consisting of a linear, non-segmented and single-strand negative RNA genome. The *Filoviruses* genomes are about 19.000 nucleotides long and are transcribed into seven major subgenomic mRNAs, which encode seven structural proteins: nucleoprotein (NP), virion protein 35 (VP35), VP40, VP30, VP24, glycoprotein (GP) and RNA-dependent RNA polymerase (L)-5' (Table 2). These viruses are long filamentous particles that have about 14.000 nm long and 80 nm wide (Fig.4).

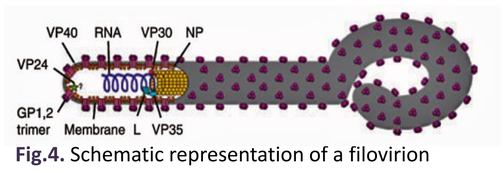

Fig.4. Schematic representation of a filovirion

Interaction virus-host

Filovirus haemorrhagic fevers are typical zoonotic diseases transmitted accidentally by direct contact with infected blood and body fluids of animals or people. In general, they infect a wide range of cell types (Fig.5), but the sequence of infection is largely unknown. Recent studies suggest that monocytes, macrophages and dendritic cells are early and preferred targets of these viruses, whereas endothelial cells are infected much later during the course of disease, proximal to death. The entry mechanisms of filoviruses into host cells have not been well characterized, but entry is not thought to occur by direct fusion with the plasma membrane. Instead, it is thought that these viruses exploit the host cells endocytic machinery to access the cytoplasm. Different types of cell- surface receptors have been proposed to participate in the entry of these viruses (Table 3).

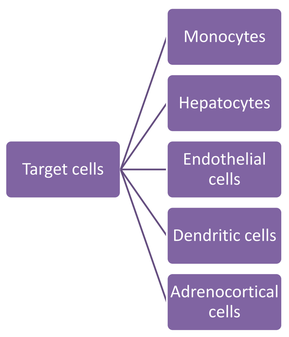

Fig.5. Target cells

Possible filovirus receptors
• Asialoglycoprotein receptor (ASGP-R) • Dendritic cell-specific ICAM-3 grabbing non-integrin (DC-SIGN) • Folate receptor-α (FR-α) • Tyro-3 (tyrosine kinase family) • T-cell immunoglobulin and mucin domain1(TIM-1) • Niemann–PickC1(NPC1) • C-tipe lectin

Table 3. Molecules that have been proposed to be filovirus receptors

Pathogenesis

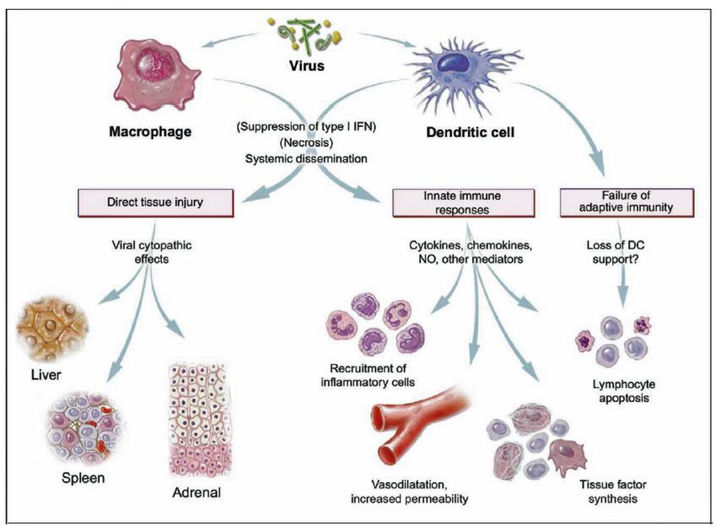

Fig.6. Pathogenic mechanisms of EBOV and MARV.

The viruses spread from the initial site of infection to secondary lymphoid organs and liver where intense replication takes place. The inhibition of type I interferon (IFN) production by viral proteins leads to relentless viral replication in most organs. The extensive infection of antigen-presenting cells (APC) leads to altered inflammatory response, uncontrolled release of mediators and the massive apoptosis of T lymphocytes. This 'cytokine storm' contributes to the pathogenesis by attracting inflammatory cells towards infected tissues, inducing coagulopathy and increasing endothelial permeability and vascular leakage (Fig.6). Together, these events lead to multiorgan failure, impairment of the vascular system, terminal shock and death.

Control and prevention

Outbreak control and prevention is not complex, at least in theory. It requires recognition of the illness, early isolation of suspect cases, personal protective equipment to prevent exposure of healthcare workers and other careers to blood and body fluid (Fig.7). In practice, however, outbreak recognition is usually delayed, such that index cases are usually identified retrospectively. Reporting is hampered by lack of training in surveillance and diagnosis, by poor communications systems and underfunding. The contact of cases with the health care system is as likely to result in the amplification of the outbreak as in control of transmission. For this reason, attempts are being made to develop treatments and vaccines to prevent outbreaks in susceptible populations.

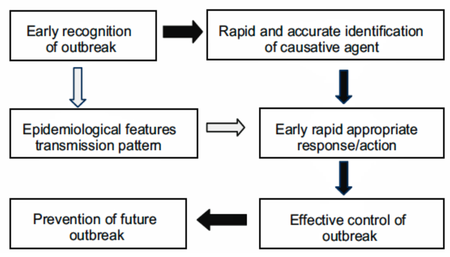

Fig.7. Generic approach to emerging infectious disease outbreak response.

Conclusions

- The different species of the *Filoviridae* family show clear geographic patterns, a possible explanation for this is that the distinct filoviruses have likely coevolved with their specific host species.
- It is thought that the principal reservoir of filoviruses could be fruit bats.
- The pathogenesis would entail the suppression of the immune response, high inflammatory response and unleashing of the coagulopathy.
- Macrophages, monocytes and dendritic cells are early targets of viral infection.
- The mechanisms of control and prevention are simple to implement, but the poor health conditions would be behind the amplification of the outbreaks.
- The expansion of the human population, the intrusion into the habitat of the species that are potential reservoirs and the contact with animals infected with the viruses are the main causes of the emergency.

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