Antiviral Research 97 (2013) 81–92

Contents lists available at SciVerse ScienceDirect

Antiviral Research

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

Review

Targeting virulence mechanisms for the prevention and therapy of arenaviral hemorrhagic fever

Lisa McLay [a], Aftab Ansari [a], Yuying Liang [b], Hinh Ly [a,b,*]

[a] Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA 30322, United States
[b] Department of Veterinary and Biomedical Sciences, University of Minnesota, Twin Cities, MN 55108, United States

ARTICLE INFO

Article history:
Received 27 October 2012
Revised 28 November 2012
Accepted 7 December 2012
Available online 20 December 2012

Keywords:
Arenavirus
Lassa virus
Viral hemorrhagic fever
Virulence mechanisms
Antiviral therapy

ABSTRACT

A number of arenaviruses are pathogenic for humans, but they differ significantly in virulence. Lassa virus, found in West Africa, causes severe hemorrhagic fever (HF), while the other principal Old World arenavirus, lymphocytic choriomeningitis virus, causes mild illness in persons with normal immune function, and poses a threat only to immunocompromised individuals. The New World agents, including Junin, Machupo and Sabia virus, are highly pathogenic for humans. Arenaviral HF is characterized by high viremia and general immune suppression, the mechanism of which is unknown. Studies using viral reverse genetics, cell-based assays, animal models and human genome-wide association analysis have revealed potential mechanisms by which arenaviruses cause severe disease in humans. Each of the four viral gene products (GPC, L polymerase, NP, and Z matrix protein) and several host-cell factors (e.g., α-dystroglycan) are responsible for mediating viral entry, genome replication, and the inhibition of apoptosis, translation and interferon-beta (IFNβ) production. This review summarizes current knowledge of the role of each viral protein and host factor in the pathogenesis of arenaviral HF. Insights from recent studies are being exploited for the development of novel therapies.

Contents

* Corresponding author. Address: Department of Veterinary and Biomedical Sciences, University of Minnesota, 1988 Fitch Ave., Ste 295, Saint Paul, MN 55108, United States. Tel.: +1 612 625 3358; fax: +1 612 625 0204.
E-mail address: hly@umn.edu (H. Ly).

0166-3542/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.antiviral.2012.12.003

1. Introduction: arenaviral diseases of humans

The *Arenaviridae* family consists of a large group of single-stranded ambisense RNA viruses that are separated phylogenetically, serologically, and geographically into Old World (OW) and New World (NW) viruses. Some viruses from both groups cause significant morbidity and mortality in humans. Lassa virus, found in West Africa, causes severe hemorrhagic fever (HF), while the other principal OW arenavirus, lymphocytic choriomeningitis virus (LCMV), produces only mild illness in immunocompetent humans. In contrast, Junin virus (JUNV) and the other NW arenaviruses found in South America, cause severe hemorrhagic fever (HF). There are currently limited prevention and treatment measures against these pathogenic arenaviruses. The only available vaccine (Candid #1) has been developed and used extensively to prevent Argentine hemorrhagic fever (AHF) caused by JUNV (Maiztegui et al., 1998). Ribavirin, the only licensed antiviral for the treatment of arenaviral hemorrhagic fevers, has had mixed success and significant toxicity in treating arenaviral HF (Günther and Lenz, 2004).

A major question is why some arenaviruses cause severe disease in humans, while others do not. Many factors have been proposed to explain the differential degrees of pathogenicity, such as host genetic polymorphism, routes and doses of infection, and viral virulence factors. It has been postulated that virulent arenaviruses are able to replicate to high levels and can effectively suppress host immunity. Recent studies using viral reverse genetics, cell-based assays, animal models, and human genome wide association analyses have revealed potential mechanisms that arenaviruses utilize to cause virulent infections in the hosts. Understanding viral virulence mechanisms is expected to facilitate the development of appropriate preventive and therapeutic strategies against these deadly viral hemorrhagic fevers. This paper summarizes current progress in understanding the roles of viral factors in mediating efficient viral entry, enhanced viral RNA synthesis, inhibition of cellular apoptosis, translation and host innate immunity, all of which contribute to the virulence of pathogenic arenaviruses for humans.

1.1. Old World arenaviruses

Lassa virus (LASV) causes Lassa fever, resulting in approximately 2 million infections and 5–10,000 deaths annually in endemic area of West Africa (McCormick, 1999). LASV infection results in heterogeneity in disease manifestation that ranges from non-symptomatic to multi-organ failure and death. Patients infected with LASV are often misdiagnosed because of the wide range of symptoms they may exhibit. These symptoms include fever, malaise, petechial hemorrhage, edema, nausea, vomiting and diarrhea (Moraz and Kunz, 2010). Up to one third of patients experience sensorineural deafness which remains even after recovery from the illness (Cummins et al., 1990). Fatal cases may display respiratory distress, shock, encephalopathy, seizures, shock, coma, and mucosal bleeding (Moraz and Kunz, 2010).

Lujo virus (LUJV), the only other known hemorrhagic fever-causing OW arenavirus, was identified during an outbreak of the disease in Lusaka (Zambia) and Johannesburg (Republic of South Africa) in 2008 (Briese et al., 2009). Symptoms noted for patients infected with Lujo virus include fever, edema, mild bleeding, elevated liver transaminases, and thrombocytopenia (Paweska et al., 2009).

Lymphocytic choriomeningitis virus (LCMV), which is found worldwide, has also been identified as pathogenic for immunocompromised individuals (Al-Zein et al., 2008; Fischer et al., 2006; MacNeil et al., 2012; Centers for Disease Control and Prevention, 2008). The data at hand suggests that approximately 5% of the human population show evidence of exposure to LCMV, however, most acquired infections are asymptomatic or mild (Table 1) (Peters, 2006; Rousseau et al., 1997). Because the natural host of LCMV, *Mus musculus*, has a worldwide distribution, this virus can likewise be found in most regions. While acquired LCMV infection does not pose a serious threat to the general population, congenital infection with LCMV can be quite serious. This infection can result in spontaneous abortion and fetal death, or leave the infant with brain dysfunction. The incidence of congenital LCMV infection is unknown, as only serious cases are investigated for the cause of infection and reported (Bonthius, 2012). While 35% of reported

Table 1
Human disease caused by Old World arenavirus infection.

	Syndrome produced in humans	Incidence of disease
LCMV (Worldwide)	*Acquired:* most cases are mild or asymptomatic. Symptoms include fever, cough, malaise, myalgia, headache, photophobia, nausea, vomiting, adenopathy, sore throat, thrombocytopenia, and leukopenia. Severe cases may develop meningitis or meningoencephalitis [1,2]	*Acquired:* >5% of humans show evidence of LCMV exposure <1% mortality [1]
	Congenital: spontaneous abortion and fetal death, vision impairment (via chorioretinitis), brain dysfunction (macrocephaly due to inflammation or microcephaly due to lack of growth and immune mediation destruction of brain tissue) [3]	*Congenital:* unknown, only severe cases are investigated and reported
	Transplant associated: severe disease – encephalopathy, coagulopathy, abdominal pain, thrombocytopenia, fever, leukocytosis, graft dysfunction	*Transplant:* 14 cases, 11 fatal [4–6]
Lassa virus (West Africa)	Fever, weakness, malaise, cough, severe headache, sore throat, nausea, vomiting, diarrhea, sensorineural deafness. Facial edema, pleural effusion, thrombocytopenia, and leukopenia are seen in more serious cases. Fatal cases may exhibit pulmonary edema, respiratory distress, shock, encephalopathy, seizures, coma, and bleeding from mucosal surfaces [7]	~2 million infections annually and 5000–10,000 deaths [8]
Lujo virus (South Africa)	Diarrhea, vomiting, fever, chest pain, sore throat, rash, myalgia, facial swelling, respiratory distress, cerebral edema, thrombocytopenia, elevated liver transaminases, fever, mild bleeding in 3 patients, leukopenia [9]	Cases, 4 fatal

[1] Peters (2006); [2] Rousseau et al. (1997); [3] Bonthius (2012); [4] Fischer et al. (2006); [5] MacNeil et al. (2012); [6] Centers for Disease Control and Prevention (2008); [7] Moraz and Kunz (2010); [8] McCormick (1999); [9] Paweska et al. (2009).