Journal of Clinical Virology 64 (2015) 120–127

Contents lists available at ScienceDirect

Journal of Clinical Virology

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

Research efforts to control highly pathogenic arenaviruses: A summary of the progress and gaps

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ARTICLE INFO

Article history:
Received 27 November 2014
Accepted 7 December 2014

Keywords:
Arenavirus
Viral hemorrhagic fever
Lassa virus
Junin virus
Vaccine
Antiviral

ABSTRACT

Significant progress has been made in the past 10 years in unraveling the molecular biology of highly pathogenic arenaviruses that are endemic in several West African countries (Lassa fever virus) and in some regions of South America (Argentine and Bolivian hemorrhagic fever viruses). While this has resulted in proof-of-concept studies of novel vaccine candidates in non-human primates and in the discovery of several novel antiviral small molecule drug candidates, none of them has been tested in the clinic to date. The recent Ebola outbreak in West Africa has demonstrated very clearly that there is an urgent need to develop the prophylactic and therapeutic armamentarium against viral hemorrhagic fever viruses as part of a global preparedness for future epidemics. As it pertains to this goal, the present article summarizes the current knowledge of highly pathogenic arenaviruses and identifies opportunities for translational research.

1. Lassa fever: advances in epidemiology, diagnosis, and therapy

Lassa fever (LF) is a rodent borne viral hemorrhagic disease that is endemic across many areas in western Africa and caused by the Lassa virus (LASV), which belongs to the old world serogroup of the genus arenaviruses. Infection occurs through exposure to excreta of infected rodents, or less often, person-to-person via body fluids. The case fatality rate of endemic Lassa fever is only around 1%, but the disease claims more lives than Ebola fever because its incidence is much higher. However, in nosocomial outbreaks the case fatality may be as high as 50% and it has also been high in the small number of infected expatriates to date.

The true public health burden of LF is still not fully elucidated. Since 1969 when the first cases were seen in North Eastern Nigeria, followed by the identification and isolation of Lassa virus in 1972, several outbreaks (community and nosocomial) have been reported especially in Guinea, Liberia, Sierra Leone and Nigeria, where the disease is considered endemic [1]. Exported LF cases and evidence from serological surveys in human and rodents indicate that LASV or serologically related viruses also exist in Cote d'Ivoire, Mali, Democratic Republic of Congo, Central Africa Republic, Ghana, and Burkina Faso [2–4]. In the past ten years novel arenaviruses of unknown pathogenicity have regularly been detected in various rodent species in West and East Africa, and recently a highly pathogenic novel arenavirus named Lujo virus was isolated from a Zambian patient in South Africa [5]. It can be anticipated that with generally increased awareness of hemorrhagic fevers and improved molecular diagnostics the number of pathogenic arenaviruses found on the African continent will continue to grow.

Estimates of the annual number of LF cases in West Africa vary widely, with conservative figures putting the former at several hundred thousand and the later at up to ten thousand for the endemic countries. Recently, risk maps for LF based on climatic conditions, vegetation, distribution of rodent host and reported LF cases have been published which considerably expand the potentially endemic areas throughout much of West Africa [1]. For practical purposes, the differential diagnosis of LF should be considered in febrile patients returning from travel in rural areas of West

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http://dx.doi.org/10.1016/j.jcv.2014.12.004
1386-6532/

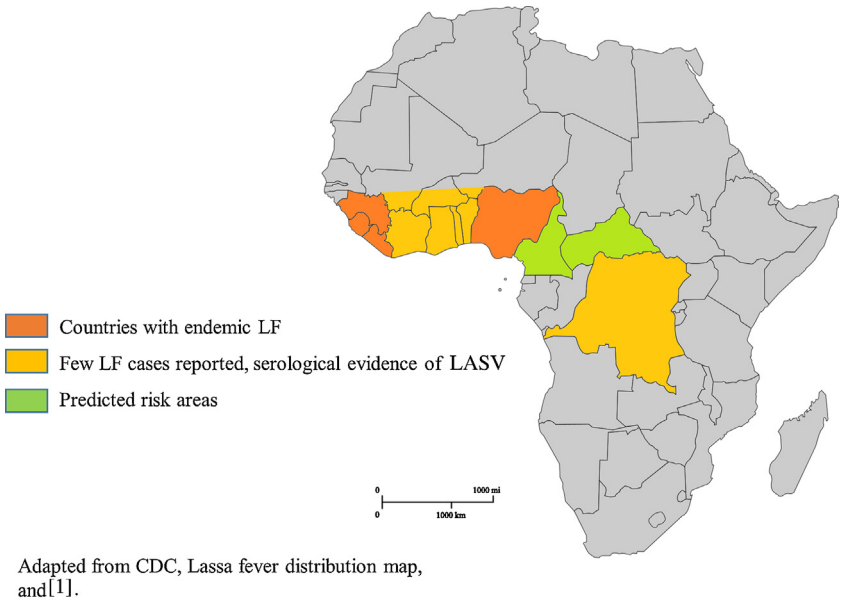

Fig. 1. Lassa fever distribution in West Africa.

Africa, where LF is endemic or sporadic cases have previously been reported, as well as predicted risk areas (Fig. 1).

The natural host of LASV has recently been genetically determined as the small rodent *Mastomys natalensis*, which occurs throughout sub-Saharan Africa [6]. Infected rodents shed LASV in the urine and not unexpectedly, increased risk of LF occurs under all conditions which bring humans into closer contact with *Mastomys*, such as substandard living conditions in refugee camps, hunting rodents for human consumption, and massive ecological perturbation, e.g., deforestation [7,8].

The incubation period for LF is 6–21 days, the clinical course is highly variable and the illness to infection ratio in endemic areas presumably 20% [9,10]. LF is difficult to distinguish clinically from other common febrile illnesses such as malaria, typhoid fever and influenza. For instance, at Irrua Specialist Teaching Hospital in Nigeria, LF is suspected in patients with:

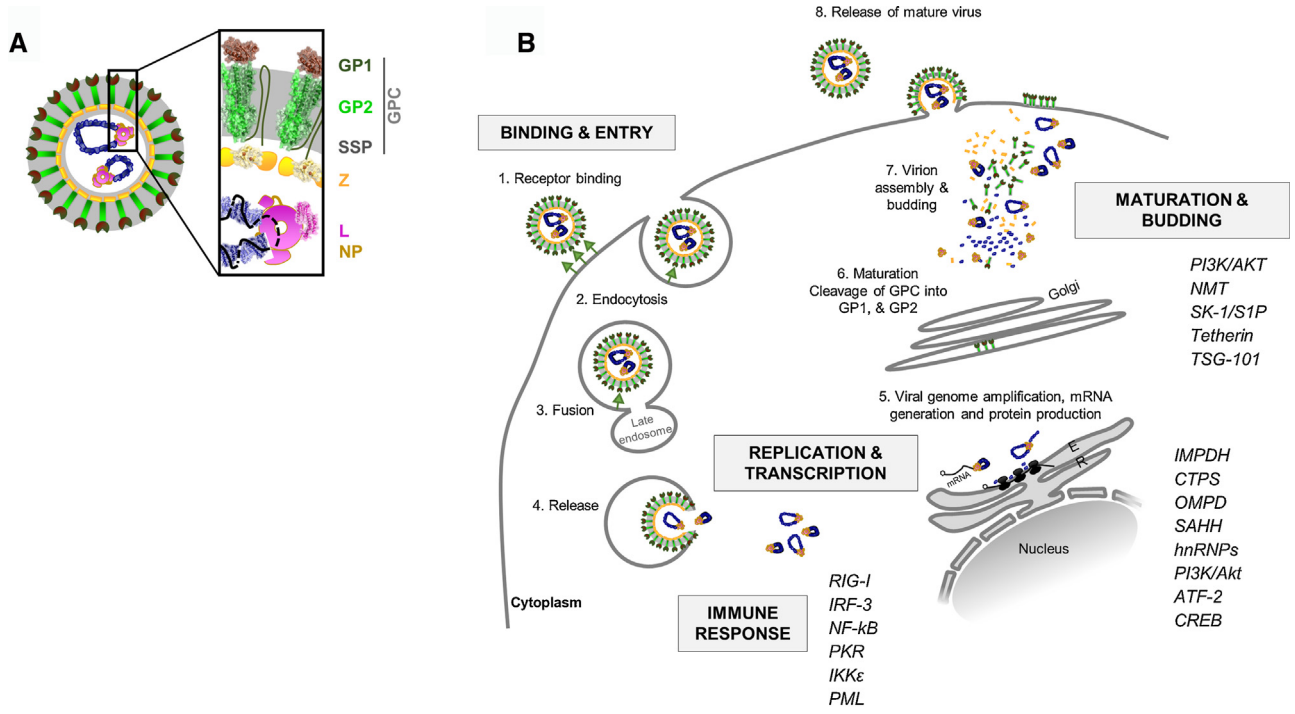

Fig. 2. The arenavirus life cycle and antiviral drug targets.
Arenavirus structure, the viral life cycle and tragets for antiviral research. (A): Arenavirus particles consist of four proteins: L and N proteins form a ribonucleoparticle together with the genome segments. They are packed in a lipid bilayer containing the G protein and lined on the inside by the Z protein. Proteins or protein domains with known atomic structures are shown in cartoon/surface representation in the close-up. (B): The steps of the arenaviral life cycle are depicted with the four main targets for antiviral research: 'binding and entry', 'replication and transcription', 'immune response' and 'maturation and budding'. Cellular host factors that play a significant role for virus propagation are listed in italic at the equivalent position. Adapted from (Linero et al., 2012, McLay et al., 2013).

(1) Fever (temperature ≥ 38 °C) for at least 2 days, with typhoid fever having been excluded and malaria negative or just 1+ in thick smear, and some or one of the following symptoms: chest pain, sore throat, headache, muscle pain, vomiting, and diarrhea, or (2) patients with fever who show bleeding or facial edema, or (3) patients with fever who do not respond to anti-malarials or antibiotics after 2 days of treatment, or (4) patients with fever who had contact with a confirmed Lassa fever case within the last three weeks [11].

Recent evaluation of these criteria revealed that among fatal cases of LF seen at the hospital, a significant proportion did not have fever at presentation or recorded low temperature at the terminal stage of illness [11]. This finding warrants review of the existing case definition for improved sensitivity, especially in the advanced stage of the disease.

Onset of illness is insidious, starting with fever, general weakness, and malaise. After a few days, headache, sore throat, muscle pain, chest pain, nausea, vomiting, diarrhea, cough, and abdominal may follow. Severe cases may progress to show facial swelling, pleural and pericardial effusion, bleeding from mucosal surfaces, low blood pressure, shock and renal failure. LF has been diagnosed among surgical patients who presented with acute abdomen, characterized by extensive intra-operative bleeding and oozing of blood from suture sites postoperatively [12]. Although LF is referred to as hemorrhagic fever, a review of previous reports suggests that bleeding is not a sensitive clinical sign of LF, as only a small proportion of patients show hemorrhagic signs and furthermore the degree of bleeding is often not significant enough to explain the shock commonly seen in the terminal stage of the disease [9]. The pathophysiology of LF is still incompletely understood but recent experimental data from animal models point to an inflammatory condition, which is possibly driven by activation of the monocyte/macrophage system and a detrimental T-cell response [13,14].

Neurological complications such as confusion, tremor, seizures, ataxia, neuropsychiatric syndrome and coma may occur in 41% of LF cases, especially at the terminal stage. Detection of LASV in CSF but not in serum has been reported [15]. Sensorineural hearing loss is a common neurological sequel of LF, occurring in 15–20% of confirmed cases and is likely due to VIII cranial nerve or cochlear damage resulting from immune response to LASV [16].

Vertical transmission of LASV in pregnancy leads to fetal loss and neonatal death in 90% of cases. Maternal mortality is about 29% with up to 80% in the 3rd trimester. Chances of survival are improved by evacuation of the uterus and administration of Ribavirin [17].

To date, there is no commercially available diagnostic assay for LF and laboratory diagnosis is performed at the level of research laboratories, which are very few in endemic regions. Various improved RT/PCR protocols using conserved primers to account for virus variability (e.g., targeting the 5′ region of the S-RNA) have been published recently [18–21]. Some of these methods have been validated with a large number of field isolates representing various LASV strains. Historically, LF has also been diagnosed using antibody detection assays such as indirect immunofluorescence (IIF) and ELISA. IIF is fraught with false positive results, especially for detection of IgM antibodies that in addition may persist for months to years and are therefore of limited value. IgM detection by ELISA has recently been shown not to be a reliable diagnostic test for LF compared to RT/PCR [22,23]. ELISA tests for detection of LASV antibodies or antigen have not been brought into standardized formats, despite the availability of various recombinant antigens and monoclonal antibodies, and are usually perform reliably only in the research laboratories which are using them [23–27]. Isolation of the virus can only be performed in biosafety level 4 laboratories.

No specific therapeutic drug is currently available for treatment of LF but the broad spectrum antiviral Ribavirin was shown to reduce mortality by 90% if given within six days of the onset of illness [28]. Its direct antiviral effects comprise interference with RNA capping, polymerase inhibition and lethal mutagenesis [29,30]. A number of experimental antiviral drugs have been tested for anti-LASV activity in vitro or in small animal models, e.g., the RNA polymerase inhibitor Favipiravir (T-705), the viral entry inhibitor ST-193 and small interfering RNAs, but none has progressed into clinical trials for LF [31–33].

2. South American arenaviral hemorrhagic fevers: advances in epidemiology, diagnosis and therapy

South and North American arenaviruses belong to the New World serogroup of the genus arenaviruses. They generally infect rodents of the family *Muridae*, subfamily *Sigmodontinae,* which represent their reservoir hosts [34]. The viruses show circumscribed geographical distribution patterns related to the distribution of their hosts, and humans may occasionally be infected with aerosolized rodent excreta containing infectious virus that may enter the body through skin, respiratory tract, or gastrointestinal mucosa. Junin virus causes Argentine Hemorrhagic fever (AHF), Machupo virus Bolivian hemorrhagic fever, Guanarito virus Venezuela HF and Sabia virus has been isolated from a single case of HF in Brazil [35]. A number of new arenaviruses have recently been discovered, some of which are associated with human disease, such as Whitewater Arroyo virus in the USA and Chapare virus in Bolivia [36]. Most cases of HF occur during the harvest season in male workers, and their emergence can be linked to environmental modifications made by humans for agricultural production or settlements that favor contact with rodents or their excreta [37].

Since the first description of AHF in the 1950s, uninterrupted annual outbreaks have been observed in a progressively expanding region in north-central Argentina (humid Pampa), to the point that almost five million individuals are considered today to be at risk for AHF [38]. Because several hundred thousand persons in the endemic areas have meanwhile been vaccinated, the annual incidence of up to 300 cases/100.000 male workers in endemic areas with high virus activity has been greatly reduced since the 1990s. Bolivian hemorrhagic fever (BHF) currently occurs sporadically throughout rural areas in Bolivia, with a marked reemergence during 2007–2008, and a novel arenavirus named Chapare was isolated during a small outbreak in 2003 [36,39]. Venezuelan hemorrhagic fever is endemic in a relatively circumscribed area of central Venezuela [34].

AHF is the best studied of the South American HF and is similar in clinical presentation to the others. The incubation period ranges from 6 to 12 days, usually associated with a flu-like syndrome that may include myalgia, arthralgia, headache, relative bradycardia, conjunctivitis, nausea, vomiting, and diarrhea, with little central nervous system (CNS) or hematological involvement during the first week. In the second week of the disease, around 75% of infected individuals begin to improve, while the remaining 25% manifest neurological disorders or severe bleeding. Overlapping shock and bacterial infections appear 6–12 days after the onset of symptoms. Fever persists, while petechiae in the oral mucosa and the axillary region as well as gingival bleeding can be observed. Less commonly, bleeding from other mucosal surfaces may occur. CNS involvement can also be present during the second week in the form of hyporeflexia and mental confusion. In severe cases, it can progress to include areflexia, muscular hypotonia, ataxia, increased irritability and tremors, followed by delirium, generalized seizures, and coma. Fatality rate is as high as 30% among untreated AHF patients.

The pathogenesis of AHF including the causes of the bleeding is still poorly understood. However, it is generally accepted that these are associated to some degree with impaired hemostasis, endothelial cell dysfunction and low platelet counts or function [40].

Table 1
Most advanced Lassa fever vaccine candidates.

Vaccine candidates for LASV	Preclinical efficacy data	Considerations for development	Reference
Alphavirus replicon expressing LASV-GPC	Full protection in guinea pig, transient viremia	Alphavirus replicon based vaccines have been tested in clinical trials for other indications	[53]
Recombinant vesicular stomatitis virus expressing LASV-GPC (VSV-G deleted)	Full protection in NHP, transient viremia	A recombinant VSV vaccine expressing Ebola-GP has been given safely as post-exposure prophylaxis to a laboratory worker	[54,55]
Live attenuated Lassa/Mopeia virus reassortant ML29 (NP and GPC of LASV, L and Z protein of MOPV)	Full, sterilizing protection in guinea pig and NHP. Safe in normal and SIV infected monkeys Effective post-exposure treatment 48 h post challenge	Mopeia virus is classified as BSL2 or BSL3 agent, according to European or CDC guidelines. ML29 is genetically stable over 12 passages in Vero cells	[56]
Recombinant vaccinia virus expressing LASV-GPC and NP	86% protection in NHP, transient viremia	Not safe for HIV infected persons	[57]
Recombinant yellow fever 17D vaccine virus expressing LASV-GPC	83% protection in guinea pig, transient viremia	Stability issues, low immunogenicity in NHP	[58]

NHP: non-human primates.

In contrast to Lassa fever, immune plasma therapy reduces mortality in AHF to less than 1%, although this specific therapy is effective only when started during the first week of illness [38,41]. Unfortunately, it is unknown if a similar approach can be applied to the other HF, with limited positive evidence generated in BHF. Ribavirin may be used alone or together with the immune treatment to reduce mortality further [38]. Without treatment, over 80% of patients improve after the second week although bacterial infection is a frequent complication. Approximately 10% of cases treated with immune plasma develop a late neurologic syndrome (LNS). After a symptom-free period, LNS onset is characterized by fever, cerebellar signs, and cranial nerve palsies. Interestingly, LNS had never been registered among AHF patients recovering without specific treatment. Novel potentially therapeutic antiviral molecules are being tested preclinically, e.g., T-705 [42].

AHF diagnosis is based on clinical and laboratory data. Platelet counts below 100,000 /mm^3 in combination with white blood cell counts under 2500/mm^3 detected in patients in endemic areas can be indicative of JUNV infection [38]. Reverse transcriptase PCR-based assay have been established for rapid diagnosis of South American arenaviruses [20]. Recombinant proteins and monoclonal antibodies are used for antibody and antigen detection assays, but none of these has been standardized [43–46].

3. Progress in vaccine development against arenavirus infections

Currently there is no licensed vaccine against LASV available. In natural infection neutralizing antibodies appear late in the course of disease and their titers are usually too low to allow use of convalescent serum for passive immunotherapy. Recently, progress has been made in studying T-cell responses in Lassa fever infection. A direct role for T-cells in protection was demonstrated experimentally by showing that monkeys surviving LASV challenge have early and strong innate and adaptive immune responses, i.e., a high number of activated circulating monocytes and LASV-specific CD4 and CD8 T cells, whereas fatal infection is characterized by weak cellular immune responses, and uncontrolled viral replication [14]. However, T-cell depletion experiments in human MHC-I transgenic mice infected with Lassa virus also demonstrated that T lymphocytes might play a key role in Lassa fever pathogenesis by entertaining a cytokine release syndrome [13]. In humans, strong memory CD^{4+} T-cell responses have been detected in both LASV seropositive and seronegative individuals residing in endemic areas and epitopes were mapped to the nucleoprotein and a highly conserved region of glycoprotein 2 [47]. In A*0201 transgenic mice HLA class I-restricted, arenavirus cross-reactive epitopes were identified than can potentially be utilized for immunization [48]. Taking all data into account a LASV vaccine has to provide a balanced T-cell mediated protection, which has not been achieved using past vaccination approaches based on traditional, antibody-inducing technologies (e.g., killed virus, recombinant proteins). However, in the past 10 years encouraging progress has been made showing that recombinant viruses or vector systems can protect guinea pigs or monkeys up to 100% against lethal challenge, which is beyond the approx. 86% protection afforded by a recombinant vaccinia virus expressing LASV-GPC that was described in the 1990s (reviewed by Olschlager et al., 2013) [49]. Notably, recombinant vesicular stomatitis virus expressing Lassa virus GPC, the attenuated Lassa/Mopeia virus reassortant ML29 and an alphavirus replicon system expressing LASV-GPC have shown promise in animal challenge (reviewed by Falzarano et al., 2013; Lukashevich et al., 2012) [50,51]. No phase 1 study with any LASV vaccine candidates has been conducted to date. Since Lassa fever is fairly common in endemic areas and field trials are thus conceptually feasible, it is not clear whether a vaccine against LASV would be licensable based on the FDA “animal rule” alone. This path to licensure would require a correlate of protection, which is currently not known. The three most advanced LASV vaccine candidates are outlined in Table 1.

In contrast to LASV, South American arenaviruses induce high-titered neutralizing antibodies and passive serum therapy has effectively been carried out in humans. Candid #1 is a live attenuated vaccine against Junin virus, which is licensed in Argentina for adults >15 years and has been administered to several hundred thousand persons in endemic areas, with a major impact on the incidence of the disease [52]. Even though neutralizing antibodies clearly are important, data from heterologous challenge experiments suggest that T-cells can also mediate protection. To this end, Candid #1 was shown to protect non-human primates from a challenge with Machupo virus, the etiological agent of Bolivian hemorrhagic fever. Development of a temperature stable formula-

Table 2
Important research milestones of the past 10 years.

- Development of highly sensitive rapid diagnostics using real time RT/PCRs with broad strain coverage.
- Prediction of risk areas for LF occurrence based on epidemiological and ecological information.
- New insights into the molecular biology of arenavirus infections using replicon systems.
- Development of several preclinical Lassa virus vaccine candidates with excellent safety and efficacy in non-human primates.

Table 3
Research roadmap for the next 10 years.

- Development of simple diagnostic tools for LF and South American HF and transfer to the field.
- Clinical development of the most promising LV vaccine candidate.
- Clinical development of Favipiravir (T-705) and possibly other antivirals for LF and AHF.
- High-throughput discovery of novel antiviral drugs using non-infectious arenavirus replicon systems.

- Development of human monoclonal antibodies for passive immune therapy for all South American HF.

tion of Candid #1 for use in rural vaccination campaigns would be desirable.

Based on biological and technological probability of success the most promising LASV vaccine candidate should be chosen for clinical development (Table 1). As there is no commercial interest in a Lassa fever vaccine and the governments of endemic regions are unlikely to contribute any funding, the only realistic way of bringing a vaccine to licensure seems through a multi-partner consortium involving research organizations as well as not for profit organizations. Specifically, the following activities should be pursued:

– Identification of a correlate or at least surrogate of protection against Lassa virus through immunization/challenge studies in NHP and GP. This set of biomarkers is required to license a vaccine based on the FDA "animal rule" and to support clinical development.
– Head-to-head comparison of the most advanced candidates in NHP challenge studies, investigating cross-protection against genetically divergent LASV virus strains.
– Exploration of a path to licensure for a Lassa fever vaccine with regulatory authorities and conduction of phase 1 and 2 (and possibly phase 3) trials in endemic areas. The endpoints of these trials need to be defined (clinical disease, infection, correlates of protection) and local infrastructure to conduct trials in endemic areas needs to be generated.

4. Progress in drug development against arenavirus infections

Arenavirus structure and a summary of the life cycle are shown in Fig. 1. Arenaviruses consist of two ribonucleoprotein particles (RNPs – viral proteins bound to the viral RNA genome) surrounded by a lipid envelope. The genome consists of two single-stranded RNA segments, called S (small) and L (large) with an ambisense coding strategy. The viral RNA per se is not infectious. The S RNA encodes the nucleocapsid protein (NP) and the glycoprotein precursor (GPC), which is posttranslationally cleaved to produce the stable signal peptide (SSP), the transmembrane protein GP2, and the most external glycoprotein GP1. The L RNA encodes the viral polymerase (L protein) and a small, zinc-binding (Z) protein. The genes encoded by each RNA segment are separated by an intergenic region with predicted stable secondary structure. Due to this structure the IGR is thought to play a role in viral mRNA transcription termination [59,60]. The terminal 19 nucleotides (nt) of the untranslated regions (UTRs) at the 5′ and 3′ ends of the two RNA segments are highly conserved among arenaviruses, complementary to each other and form a specific binding site for the viral polymerase [61].

Numerous unique small molecules were identified as inhibitors of arenavirus infection using a high throughput screening of synthetic combinatorial libraries and pseudotyped virion particles bearing the glycoproteins (GPs) of highly pathogenic arenaviruses [62–64]. It was shown that small-molecule compounds inhibit arenavirus entry and protect against lethal infection in animal models, acting on the glycoprotein (GP) spikes [65,66]. The pH-sensing interface of GP spikes is a highly vulnerable target for antiviral intervention. The small molecules ST-366, ST-294 and ST-193 are potent entry blockers inhibiting host cell infection with several new world arenaviruses. Treatment with ST-294 caused both reduced and delayed mortality of Tacaribe virus infected newborn mice. ST-193 tested in guinea pig model for Lassa virus infections resulted in less severe clinical signs of disease and in enhanced survival of infected animals [32,63,64,66,67]. Virus entry is a process that was intensively studied in the past and will remain in the focus of basic research for the development of antiviral targets, as it is the first crucial step in the viral life cycle. Patients with advanced infections; however, might be more efficiently treated with compounds aiming at later processes in the viral life cycle.

The RNA-dependent RNA-polymerase (RdRp) active site of the L protein is clearly a drug target and the known broad-spectrum inhibitors of RNA viruses are thought to inhibit this viral polymerase. The current standard therapy for Lassa fever in man is the broad-spectrum nucleoside analogue Ribavirin. Despite some side effects, it is the only approved drug for treatment of Lassa virus infections and also used to combat infections with RNA viruses like Hepatitis C Virus (HCV) and Crimean Congo Hemorrhagic Virus (CCHFV) [29,68]. For arenaviruses the mode of action has not been clearly determined. From recent data on LCMV it is assumed that incorporation of Ribavirin into the nascent RNA strand during replication leads to an increased mutation rate, a process called lethal mutagenesis or error catastrophe [69,70]. T-705 is another broad-spectrum inhibitor. It was demonstrated to exert antiviral activity against arenaviruses in vitro and in vivo, probably through direct inhibition of the viral polymerase and initiation of a lethal mutagenesis [31,71]. Other well-known replication inhibitors are the acridon-derivative 3f (e.g., 10-allyl-9(10*H*)-acridones or 10-allyl-6-chloro-4-methoxy-9(10H)-acridone), whose mechanism of action is not yet clearly understood, and peptide-conjugated phosporodiamidate morpholino oligomers (PPMOs). PPMOs are single-stranded nucleic acid analogs targeting a sequence at the genomic 5′ end and thus preventing association of the viral polymerase and promotor [72,73]. The replication and transcription machinery is a very attractive target for drug development. For influenza A for example, whose polymerase complex is related to the arenavirus L protein, several inhibitors targeting the endonuclease domain involved in cap-snatching could be identified. In a similar way the active site of the L protein endonuclease may serve as attractive target for drug development [74]. The determination of protein structures of the other regions of the L protein would be a crucial step towards the development of specific inhibitors of replication and transcription activities.

Several host factors involved in arenaviral replication have been shown to be potentially promising antiviral targets. Metabolism of nucleosides is a very well-known target site for antiviral treatment. In particular, purine biosynthesis depends on inosine monophosphate dehydrogenase (IMPDH), which is crucial for de novo synthesis of guanosine nucleotides. In addition to the above described role in replication, Ribavirin likely targets other steps of the virus life cycle like the blockage of the IMPDH leading to a decrease in the GTP pool in host cells [30,75]. Other promising candidates are acridone derivatives, which in addition to the anti IMPDH activity also inhibit DNA topoisomerase II [73,76]. In contrast, inhibitors of biosynthesis of pyrimidine nucleotides, e.g., analogs of cytidine inhibit cytosine triphosphate synthetase (CTPS), analogs of adenosine inhibit S-adenosylhomocysteine hydrolase (SAHH) or carbanucleoside analogs inhibit orotidylic acid decarboxylase (OMPD), showed no advantage compared to Ribavirin [77,78].

5. Conclusions

During the past years, an impressive progress has been made towards our understanding of the basic molecular and cellular biology of arenaviruses (Table 2). In particular, the development of a reverse genetics system for several arenaviruses represented an important breakthrough and provided a powerful tool to precisely address questions of fundamental biology and pathogenicity as well as novel vaccine candidates [79–83]. The studies on early molecular events of arenavirus infection involving viral GP spikes and cell surface receptors as well as virion and cell membrane fusion provided the basis for the development of novel therapeutic strategies [62,66]. All other steps specific for virus entry, processing and replication are being explored as potential therapeutic targets [42,72,76,84–86]. In addition, cellular proteins interacting with viral components are being explored as drug targets (Fig. 2). T-705 is a promising pyrazine derivative (6-fluoro-3-hydroxy-2-pyrazinecarbox- amide) with broad antiviral activity against RNA viruses. So far, animal models of acute arenaviral disease have demonstrated that T-705 can be used effectively to treat advanced infections [42]. T-705 is currently in late stage clinical development for the treatment of influenza [87].

Based on the success of treating AHF with convalescent plasma, passive immune therapy should be investigated for all South American HF viruses and human plasma should be replaced by neutralizing human monoclonal antibodies [88]. In the past ten years several vaccine approaches using viral vector systems have been employed to successfully protect non-human primates against a lethal LASV challenge and these vaccines have proven safe in immunosuppressed non-human primates. While the absence of a correlate of protection against LASV still complicates development of a vaccine that will mainly rely on T-cell mediated immunity, the time is ripe to move one or two of the most promising LASV vaccine candidates into clinical trials.

Lastly, the recently developed nucleic-acid based detection methods need to be brought into a “low-tech” format which can be deployed in the field for early detection of suspected patients. Until vaccines become available, early detection of arenavirus infection and treatment of patients under strict isolation is the only way to prevent potentially disastrous hospital or community outbreaks. In summary, a number of translational research activities should urgently be addressed to improve the prospects of controlling highly pathogenic arenaviruses in the near future (Table 3).

Funding

Stephan Günther, Romy Kerber and Sophia Reindl – DFG GU 883/4-1 “Pathophysiology, treatment, and epidemiology of Lassa fever in Nigeria” DFG GU 883/3-1. “Ecology of Lassa virus and related arenaviruses in the natural host *M. natalensis*”.

Jan ter Meulen – Not applicable.

Gomez RM – Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT) PICT 2012-0434 (R.M.G.).

Víctor Romanowski – Universidad Nacional de La Plata (UNLP), Argentina) Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT / FONCyT), Argentina.

Competing interests

The authors declare no competing interests.

Ethical approval

No ethical approval is required for this review article.

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