Chapter 19
Arenaviruses

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Core Message As research models, arenavirus infections such as those induced by Junín virus and lymphocytic choriomeningitis virus (LCMV) have been central to the discovery and characterization of many features of the immune system. In addition, these models have been used to study the establishment of persistent viral infections and relationships between viruses and rodent reservoirs. From the human perspective, several arenaviruses are important as zoonotic pathogens with significant consequences, causing viral encephalitis and meningitis and severe and often fatal hemorrhagic disease.

1 Introduction

In a general sense, geographic distribution may be used to separate the arenaviruses into Old World (OW) and New World (NW) viruses. With the exception of Tacaribe virus (TCRV), a NW arenavirus possibly associated with bats, all currently classified arenaviruses have a natural rodent reservoir ("mammarenaviruses"). The geographic distribution of these reservoirs generally correlates to a restriction of the distribution of the

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viruses and endemic disease. Recently, several novel arenaviruses were identified in snakes ("reptarenaviruses"), and whether an intermediate rodent or mite is involved in their transmission is not known (Tables 19.1, 19.2, and 19.3 and references within).

Arenaviruses were originally characterized ultrastructurally through electron micrographs of lymphocytic choriomeningitis virus (LCMV) particles and LCMV-infected cells about 45 years ago [53]. Virions were found to be of variable size and shape, budding from the plasma membranes with visible spikes and ribonuclease-resistant electron-dense bodies within the particles (also shown with Lassa particles in Fig. 19.1). On the basis of these morphological features, in 1969 researchers initially suggested that LCMV, Machupo virus (MACV), and TCRV should be reorganized in a single taxonomic group with LCMV as the prototype virus [54]. This was quickly followed by serological studies confirming cross-reactivity between LCMV, TCRV, MACV, Amaparí virus, Junín virus (JUNV), Paraná virus, Pichindé virus (PICHV), Tamiami virus, and Latino virus, but not other arthropod-borne viruses or mouse viruses [55]. Several biological properties of arenaviruses were also listed as evidence for their separation from arthropod-borne viruses: (1) arenaviruses are RNA and not DNA viruses, (2) rodent vectors play a role in arenaviral disease transmission, (3) arenaviruses produce persistent carrier state in rodents, and (4) they do not require arthropods in their life cycle. A more formal naming proposal was presented in 1970 [56] naming this virus group "Arenoviruses," from the Latin word "arena" (= sand) based on the characteristic electron-dense granules in arenavirions. This name was later changed to Arenavirus (and later to *Arenavirus*), ostensibly to prevent confusion with "Adenovirus." Lassa virus (LASV) was classified as an arenavirus in 1970 after in vitro characterization of several isolates [2, 57].

Smaller arenavirions tend toward being spherical, whereas larger particles are pleomorphic or "cup-shaped" [53, 54, 58]. The typical mean particle size is approximately 110–130 nm in diameter, although individual particles may range from 50 to over 350 nm in diameter. Particles are spotted with electron-dense granules of approximately 20 nm in diameter, later determined to be host ribosomes. Often, the formation of large intracytoplasmic inclusion bodies is observed in vitro in tissue culture and in vivo [53, 54, 56, 59–61]. These tubuloreticular inclusion structures (shown in Fig. 19.2) are also seen in cells infected with other viruses, such as Epstein Barr virus or Ebola virus [62], and have recently been the starting point of the discovery of a novel group of arenaviruses in snakes associated with inclusion body disease (IBD) [50, 51, 63–66].

2 Genome Organization, Viral Proteins, and Replication Strategy

2.1 Genome Structure

Arenaviruses have bisegmented, single-stranded ambisense RNA genomes. These segments are designated by their length: small, S (approximately 3.5 kb) and large, L (approximately 7.3 kb) [67, 68]. The L segment encodes a viral RNA-dependent

Table 19.1 Old World arenaviruses ("Old World Mammarenaviruses")

Virus	Abbreviation	Distribution	Reservoir species (reservoir(s))	Year identified	Human disease	Reference(s)
Classified Old World arenaviruses						
Ippy virus	IPPYV	South Africa	*Arvicanthis* sp. (unstriped grass rats)	1970		[1]
Lassa virus	LASV	Guinea, Liberia, Mali, Nigeria, Sierra Leone	*Mastomys natalensis* (Natal mastomys)	1969	Lassa fever	[2, 3]
Lujo virus	LUJV	South Africa, Zambia	Unknown (isolated from human)	2008	Viral hemorrhagic fever	[4]
Luna virus	LUNV	Zambia	*Mastomys natalensis* (*Natal mastomys*)	2009		[5]
lymphocytic choriomeningitis virus	LCMV	Worldwide?	*Mus musculus* (house mouse)	1933	lymphocytic choriomeningitis, aseptic meningitis	[6–10]
Mobala virus	MOBV	Central African Republic	*Praomys* sp. (soft-furred mice)	1983		[11]
Mopeia virus	MOPV	Mozambique, Zimbabwe	*Mastomys natalensis* (Natal mastomys)	1977		[12]
Morogoro[a]	MORV	Tanzania	*Mastomys natalensis* (Natal mastomys)	2004		[13]
Unclassified Old World arenaviruses						
Dandenong virus	DANV	Australia	Unknown (isolated from human)	2008	Possibly	[14]
Gbagroube[a]		Côte d'Ivoire	*Mus setulosus* (Peters's mouse)	2005		[15]
Jirandogo		Ghana	*Mus baoulei* (Baoule's mouse)	2011		[16]
Kodoko virus	KDKV	Guinea	*Mus minutoides* (African pigmy mouse)	2006		[17]
Lunk virus	LNKV					
Menekre virus[b]		Côte d'Ivoire	*Hylomyscus sp*. (African wood mice)	2005		[15]
Merino Walk Virus	MRWV	South Africa	*Myotomys unisulcatus* sp. (Busk Karoo rat)	1985		[18]

HF hemorrhagic fever, *sp*. species

[a]Only sequence and seroprevalence data available, not virus isolation

[b]Only sequence data available, not virus isolation

Table 19.2 New World arenaviruses ("New World Mammarenaviruses")

Virus	Abbreviation	Distribution	Reservoir species (reservoir(s))	Year identified	Human disease	Reference(s)
Classified New World arenaviruses, Clade A						
Allpahuayo virus	ALLV	Peru	*Oecomys bicolor* (white-bellied oecomys) and *Oecomys paricola* (Brazilian oecomys)	1997		[19]
Flexal virus	FLEV	Brazil	*Oryzomys* sp. (rice rats)	1975		[20]
Paraná virus	PRAV	Paraguay	*Oryzomys angouya* (Angouya oryzomys)	1965		[21]
Pichindé virus	PICHV	Colombia	*Oryzomys albigularis* (white-throated oryzomys)	1965		[22]
Pirital virus	PIRV	Venezuela	*Sigmodon alstoni* (Alston's cotton rat)	1997		[23, 24]
Classified new world arenaviruses, Clade A/B (aka. A/rec, or North American Tacaribe Serocomplex)						
Bear Canyon virus	BCNV	USA: California	*Peromyscus californicus* (California deermouse) *Neotoma macrotis* (big-eared woodrats)	1998		[25]
Big Brushy Tank virus	BBTV	USA: Arizona	*Neotoma albigula* (white-throated woodrat)	2002		[26]
Catarina virus	CTNV	USA: Texas	*Neotoma micropus* (southern plains woodrat)	2007		[27]
Skinner Tank virus	SKTV	USA: Arizona	*Neotoma mexicana* (Mexican woodrat)	2002		[28]
Tamiami virus	TMMV	USA: Florida	*Sigmodon alstoni* (Alston's cotton rat)	1963		[29, 30]
Tonto Creek virus	TTCV	North America (USA: Arizona)	*Neotoma albigula* (white-throated woodrat)	2001		[26]
Whitewater Arroyo virus	WWAV	USA: New Mexico, Oklahoma, California, Colorado, Utah	*Neotoma albigula* (white-throated wood rats)	1993	Controversial	[31–33]
Classified New World arenaviruses, Clade B						
Amaparí virus	AMAV	Brazil	*Neacomys guianae* (Guianan neacomys)	1964		[20, 34]
Chapare virus	CHAPV	Bolivia	Unknown (isolated from human)	2004	Viral hemorrhagic fever	[35]

Classified New World arenaviruses, Clade A						
Cupixi virus	CUPXV	Brazil	*Oryzomys megacephalus* (Azara's broad-headed oryzomys)	1970		[36]
Guanarito virus	GTOV	Venezuela	*Zygodontomys brevicauda* (short-tailed zygodont)	1990	"Venezuelan hemorrhagic fever"	[37]
Junín virus	JUNV	Argentina	*Calomys musculinus* (drylands laucha)	1958	Junín/Argentinian hemorrhagic fever	[38, 39]
Machupo virus	MACV	Bolivia	*Calomys callosus* (big laucha)	1963	Machupo/Bolivian hemorrhagic fever	[40, 41]
Sabiá virus	SABV	Brazil	Unknown (isolated from human)	1990	"Brazilian hemorrhagic fever"	[42]
Tacaribe virus	TCRV	Trinidad, West Indies	*Artibeus jamaicensis trinitatis* (Jamaican fruit-eating bat)	1956		[43]
Classified New World arenaviruses, Clade C						
Latino virus	LATV	Bolivia	*Calomys callosus* (big laucha)	1973		[44, 45]
Oliveros virus	OLVV	Argentina	*Necromys benefactus* (Argentine akodont)	1990		[46, 47]
Unclassified new world arenaviruses						
Ocozocoautla de Espinosa[a]	OCEV	Mexico	*Peromyscus mexicanus* (Mexican deermouse)	2000		[48]
Real de Catorce[a]	RCTV	Mexico	*Neotoma leucodon* (White-toothed woodrat)	2005		[49]

HF hemorrhagic fever, *sp.* species
[a]Only sequence data available, not virus isolation

Table 19.3 Newly detected or isolated arenaviruses ("Reptarenaviruses") from snakes

Unclassified arenaviruses from snakes					
Virus	Abbreviation	Distribution	Reservoir species (reservoir(s))	Year identified	Reference(s)
CAS virus[a]	CASV	USA: California	*Corallus annulatus* (annulated tree boa)	2012	[50]
Collierville virus[a]	CVV	USA: California	*Boa constrictor* (boa constrictor)	2012	[50]
Golden Gate virus	GOGV	USA: California	*Boa constrictor* (boa constrictor)	2012	[50]
ROUT virus[a]	ROUTV	Netherlands	*Boa constrictor* (boa constrictor), *Corallus caninus* (emerald tree boa)	2013	[51]
University of Helsinki virus	UHV	Germany, UK, Costa Rica	*Corallus annulatus* (annulated tree boa), *Corallus hortulanus* (common tree boa), *Boa constrictor* (boa constrictor)	2012	[52]

ROUTV was previously known as Boa Av NL B3
[a]Only sequence data available (no virus isolate)

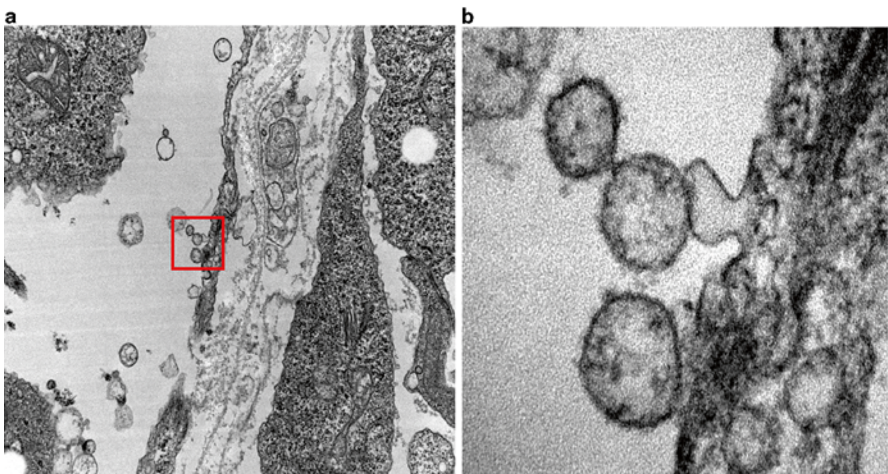

Fig. 19.1 Lassa virus particles budding from a stellate cell of a crab-eating macaque. Electron micrographs of virions (90–100 nm in diameter) budding from a presumed dendritic cell from an inguinal lymph node of a crab-eating macaque. Tissue was harvested 10 days following aerosol exposure to Lassa virus, Josiah strain. (**a**) Low magnification at 25,000× and (**b**) *inset*, shown at high magnification at 150,000×

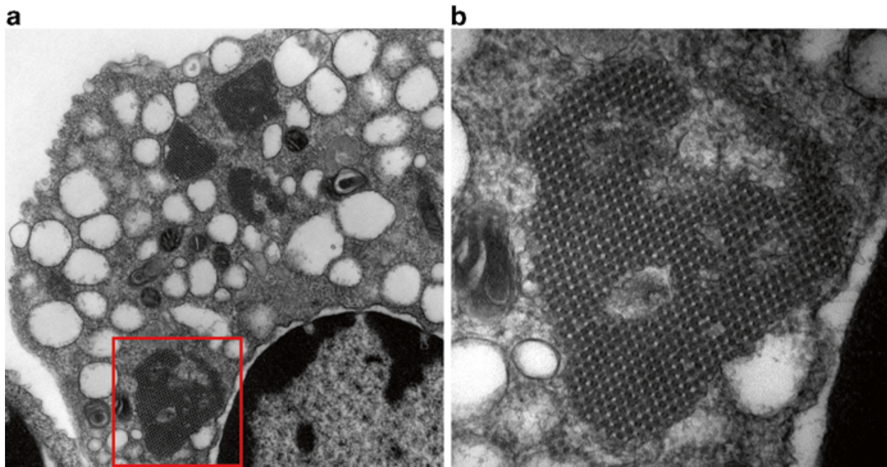

Fig. 19.2 Tubuloreticular structures in Lassa virus-infected circulating lymphocytes from a crab-eating macaque. Electron microscopy reveals burlap-like tubuloreticular structures (TRS) in a circulating lymphocyte collected 8 days following aerosol exposure to Lassa virus, Josiah strain. (**a**) Low-magnification (30,000×) shows multiple, highly ordered TRS in the cytoplasm. (**b**) Higher magnification (80,000×) of *boxed area*, showing cross-sectional detail of a single TRS

RNA polymerase (L), as well as the matrix protein Z. The S segment encodes the nucleoprotein (NP) and the glycoprotein precursor (GPC) [69]. With such limited genome coding capacity, each expressed viral protein must play more than one role in the virus life cycle and suppression of the host immune response.

2.2 *Role of Viral Proteins*

2.2.1 NP

During viral infection, NP is the most abundantly produced viral protein. NP is involved in genomic RNA encapsidation and formation of viral ribonucleoprotein complexes (RNPs). NP binds to both genomic and antigenomic RNA and has immunosuppressive effects via the C-terminal domain [70, 71] that contains 3′–5′ exoribonuclease activity [72]. NP is encoded by the S segment, and translated from the subgenomic viral complementary mRNA [73]. The interaction of NP and L may be involved in the transient release of the RNA template from the nucleocapsid and in the movement of L during transcription [74].

2.2.2 L

Based on sequence [75] and mass (greater than 200 kDa), researchers presumed that the L protein was an RNA-dependent RNA polymerase consisting of multiple domains, which was later confirmed by mutational analysis and crystallographic

studies [76–80]. L has at least four conserved regions with separate transcription, cap-snatching, and genome replication functions [76, 78, 80, 81]. L also interacts with Z and NP. The interaction of NP and L may be required for the release of template RNA during transcription [74].

2.2.3 Z

Z is a self-associating protein forming dimers that can form virion-like particles (VLPs) with myristoylation sites for membrane targeting. The primary function of Z is to serve as a viral matrix protein, recruiting NP and the GP to the site of budding particles at the plasma membrane [71, 82, 83]. The release of viral particles from the cell requires the intracellular cargo receptor ERGIC-53 and its associated machinery [84], and the budding process has been modeled in vitro [85]. Also, Z appears to have an immune-modulatory role, as a domain was identified in NW arenaviruses (but not LASV or LCMV) that inhibited type I interferon (IFN) induction of the retinoic acid-inducible gene 1 (RIG-I) signaling pathway [86]. Z inhibits viral RNA synthesis by directly binding to L [71] and exerts inhibitory effects on polymerase activity.

2.2.4 GPC

GPC is expressed as a single polypeptide precursor that is cleaved in the lumen of the endoplasmic reticulum. The cleaved stable signal peptide (SSP) remains stably associated with the GP spike complex. SSP plays essential roles in endosomal trafficking and pH-mediated fusion and interacts with Z [87–89]. Further proteolytic processing cleaves GP to separate GP1 and GP2, producing a globular head domain, a transmembrane region, and spontaneous trimer formation [90, 91].

The trimeric GP spike complex on the virion surface mediates cell entry of arenavirions; GP1 mediates cell attachment and receptor binding, whereas GP2 mediates membrane fusion within the endosome [92, 93]. GP2 is typical class I fusion protein and, during fusion, undergoes a conformational change involving a characteristic six-helix bundle [94]. The association of GP with membrane microdomains and Z promotes efficient budding at the plasma membrane [95].

2.3 Receptor Usage, Attachment, Entry, and Uncoating

Cellular entry of arenavirions is mediated by at least two defined receptors. The primary OW cellular receptor is the highly conserved cell surface protein α-dystroglycan (α-DG). This receptor is the entry receptor for LCMV, LASV, Mobala virus, Mopeia virus, Ippy virus, Oliveros virus, and Latino virus [92, 96]. Transferrin receptor 1 (TfR1) was first identified as the cellular receptor for the pathogenic NW arenaviruses JUNV, MACV, Guanarito virus, and Sabiá virus (SABV) [93]. Later studies

examined and compared arenavirus usage of TfR1 from hosts of different species [74, 97, 98], and preference of virion binding to human TfR1 correlated directly with pathogenicity. Lujo virus (LUJV) appears to enter cells via both α-DG- and TfR1-independent mechanisms, suggesting the existence of a third arenavirus receptor [99].

Following attachment, virion internalization occurs via clathrin-dependent or clathrin-independent mechanisms depending on receptor usage and virus. Similarly, differences in endosomal trafficking are also observed. However, a pH-dependent fusion step of the viral and cellular membrane is required [100–102]. Once virions are internalized and uncoated, virus replication is restricted to the cytoplasm where L initiates transcription at the 3′ end of each genomic RNA segment.

2.4 Ambisense Coding Strategy and Replication

Arenaviruses use an ambisense coding strategy, whereby each single-stranded RNA genome segment has two open reading frames in opposite orientation (viral genomic sense versus the viral complementary sense). The noncoding intergenic regions (IGR) between the two open reading frames of each segment of most arenaviruses are predicted to form one- or two-stem-loop hairpin structures (SABV segments are predicted to have three-stem loop structures [103]). This G:C rich hairpin configuration was first identified in the S segment of PICHV [104, 105], and its role as a putative terminator of L was suggested [105]. Both the L and S segments also have terminal noncoding untranslated regions (UTRs) at their extremities; these conserved regions of reverse complementary sequence promote the circularization of each genome segment into “panhandle” structures via base pairing [106]. The coiled, circular filaments of viral RNA genome have been made visible by electron microscopy using purified TCRV nucleocapsid [107]. The 3′ UTR of each segment also serves as a conserved promoter for L.

Arenavirus RNA synthesis is initiated after delivery of each of the two genomic segments, each associated with L, into the cytosol. Primary transcription from the 3′ end of each genomic template results in mRNA transcribed from the NP and L genes in antigenomic orientation, terminating at nonspecific sites within the distal end of the stem loop in the IGR. As an example of the ambisense strategy for the S segment, NP mRNA would be transcribed directly in this fashion from the viral genome. However, transcription of GPC gene would not occur until the replication intermediate step of viral complementary RNA has been completed. Regulation of the switch from transcription to replication is controlled by the local abundance of particular viral proteins. At early times after uncoating, gene expression of NP and L is favored as the limiting amounts of NP reduce the read-through capability of L. Viral RNA synthesis is also promoted at this time, when low concentrations of Z protein are present. As the intracellular concentrations of Z increase following transcription and translation, the functions of Z might be modulated to increase the inhibition of viral RNA synthesis by directly interacting with L [71]. Z directly binds to L and exerts inhibitory effects on the polymerase activity in a dose-dependent

manner, potentially driving the shift from viral replication to virus assembly and budding. This interaction of Z with L would also ensure that L is packaged into virions prior to release.

The arenavirus ambisense coding strategy is hypothesized to play a role in the establishment of persistence in the rodent host, as well as immune evasion by limiting and regulating transcription and replication at critical times during the arenavirus replication cycle.

3 Human Disease

3.1 Transmission

Humans usually become infected via direct contact with rodents by inhaling dried excreta (feces, urine) during occupational exposure (laboratory workers, rodent sellers, farm workers) or from keeping rodents as pets [108]. Destruction of natural habitat due to human expansion increases the potential for human contact with infected rodents and may be a factor in zoonotic transmission.

3.2 Clinical Presentation and Pathogenesis

The incubation period for human arenavirus infections ranges from 7 to 21 days followed by onset of influenza-like clinical signs and symptoms, including general malaise, sore throat, high fever, headache, myalgia, and lymphadenopathy. Progression of disease typically includes gastrointestinal symptoms such as nausea, vomiting, and diarrhea [109–113]. Disease presentation may range widely, from very mild to severe disease. More severe disease and poorer prognosis is generally associated with higher viral loads [114].

In cases that resolve, recovery typically occurs within 8–10 days of disease onset and is usually concomitant with appearance of circulating antibody and measurable cellular responses [112]. Severe disease is characterized by deterioration in the patient's condition that includes facial edema, severe pulmonary effusion, and bleeding from mucosal surfaces. Neurological signs, including tremors, disorientation, hyporeflexia, and ataxia may also present. Patients who succumb to disease (approximately 15–30 % of cases of viral hemorrhagic fever-causing arenaviruses) may experience respiratory distress, as a result of pulmonary edema, and/or encephalopathy, which sometimes results in seizures and coma, followed by shock [115]. In the case of Lassa fever, nosocomial outbreaks are sometimes associated with higher incidence of fatality, ranging from 36 to 65 % [116]. Survivors of Lassa fever may experience diffuse hair loss and changes in nail beds. Sensorineural deafness, a common clinical feature that occurs during convalescence and late stage of disease, is noted in approximately 15 % of cases [117].

Unlike other highly virulent hemorrhagic fever viruses, such as Ebola virus, arenaviruses are not distinguished by causing prominent hemorrhagic features or

disseminated intravascular coagulation (DIC) [111]. However, viral infection of endothelia and disruption of vascular function plays a prominent role in pathogenesis caused by hemorrhagic fever-causing arenaviruses, particularly in the case of LASV. Impaired vascular regulation is the causative underlying mechanism of facial erythema or edema, conjunctivitis, hypotension, pulmonary and pericardial edemas, and shock. In some cases, petechial or macular rash likely results from increased vascular permeability [116].

LASV and JUNV are perhaps the best characterized of the OW and NW hemorrhagic fever viruses, respectively, and diverge in their histological and pathological features of disease. Lassa fever is characterized by a viral hepatitis [118] that is not as prominent in patients with Junín hemorrhagic fever. Renal necrosis is more pronounced in patients with Junín hemorrhagic fever than in patients with Lassa fever, and these necrotic sites correspond to presence of high viral replication [113]. Other OW arenaviruses, such as LUJV, and NW arenaviruses, such as Chapare virus, MACV, GTOV, and SABV, cause diseases with very similar presentation.

Prominent differences in OW and NW arenavirus infections become more readily apparent in regard to the immune response. Lassa fever results in generalized immune suppression [119, 120], whereas Junín hemorrhagic fever promotes development of a deregulated systemic inflammation resulting from uncontrolled cytokine production [121–123]. Survival from Lassa fever is dependent on a strong cellular response whereas humoral immunity is less important [114]. Conversely, neutralizing antibodies are much more important for controlling NW arenavirus disease. Results from animal modeling of arenavirus infection suggest that complement fixation is a critical component of the effectiveness of the humoral immune response, although cellular immunity is important [124].

Pathogenesis is thought to partially result from virus damage to the endothelial system. Endothelial cells support high levels of virus replication without causing cell death, as arenaviruses do not undergo lytic cell replication. This replication initiates release of inflammatory mediators such as prostaglandins and nitric oxide, which promote vascular permeability [125]. Additionally, arenaviruses are known to cause thrombocytopenia as a result of abnormal platelet aggregation [126] and reduced complement activity [127], both of which contribute to coagulopathy and tissue edema. Generally, severity of arenaviral disease is proportional to concentrations of IFN-α, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), particularly in Junín hemorrhagic fever [121–123].

4 Animal Models of Highly Pathogenic Arenaviruses

4.1 Rodents

4.1.1 Laboratory Mice

Since the almost simultaneous discovery of LCMV by three groups [6–10], the use of LCMV in vitro and in laboratory mice as a research model [128–133] has been critical to the fundamental understanding of the immune system, particularly in

regard to cellular immunity. LCMV models have allowed investigators to study all aspects of the T lymphocyte response. These aspects include early interactions of T cells with dendritic cells in the context of major histocompatibility complex (MHC) restriction, the determination of immunodominant peptides and development of tetramer reagent systems, the phases of T cell expansion and contraction, and establishment of memory cells that occur following infection. Most of this research compared the dynamics of the murine immune response induced by the LCMV Armstrong isolate, which results in an acute infection of 7–10 days, to the clone 13 isolate, which establishes a chronic infection (≥3 months) of laboratory mice.

For the pathogenic arenaviruses, rodent models of disease provide an economical way to characterize pathogenesis, vaccine immunogenicity, host-range restriction, and therapeutic drug evaluation. Infection of laboratory mice with arenaviruses generally leads to a transient or persistent infection without characteristic pathogenesis seen in primates and requires extensive virus adaptation to promote virulence. As a result, most mouse models of highly pathogenic arenavirus infections typically rely on gene-knockout variants that produce mice with an immune-compromised status rendering them more susceptible to viral infections in general.

Two gene knockout models utilize either signal transducer and activator of transcription 1 (STAT1) or type I interferon (IFNαβR) receptor knockout mice to cripple the IFN response and establish a pathogenic model without the requirement for virus adaptation to the host. The STAT1 gene family is activated in response to type I IFN triggered by viral infection and regulates expression of a variety of genes important for cell viability and immune function regulation.

STAT1 knockout mice have previously been utilized for both wild-type LASV [134] and MACV [135] exposures resulting in lethal disease characterized by weight loss, disseminated infection, high serum and tissue viral titers, and death. Additional models have also been developed with similar results by eliminating the gene for IFN-α- and IFN-β-receptors, effectively disabling the IFN response. IFNαβR knockout mice have been used for a variety of both OW and NW arenaviruses with success [136, 137].

Laboratory mice that are typically not susceptible to LASV infection become unable to control viral replication and present with severe Lassa fever-like disease when murine MHC class I is replaced with a humanized ortholog. Depletion of T cells revokes the conferred lethality and development of significant disease, despite the ability of the virus to maintain high-level replication, suggesting an important role for T-cells in LASV pathogenesis. The absence of T cells may lead to an abolition of appropriate activation of antigen-presenting cells, i.e., T cells may be contributing to deleterious inflammatory responses mediated by monocytes/macrophages [138].

T cells are also important for JUNV pathogenesis. Murine models that make use of athymic mice persistently infected with JUNV have been described. The neurovirulence of JUNV in laboratory mice has been previously hypothesized to depend on the presence of T lymphocytes [139]. To achieve virulence in suckling mice, splenocytes from persistently infected athymic animals were passively transferred

via the intracranial route. Transfer of virus-infected cells results in brain lesions and establishment of acute disease, followed by death within 25 days [140]. Normal splenocytes did not affect viral burden in the brain nor result in pathology. Results of these studies highlight the role for T cells in neurovirulence and pathogenesis, at least in the murine model. The establishment of persistent infection is also critical for pathogenesis as splenocytes taken from athymic mice just after infection were unable to confer disease, whereas those harvested 30–45 days postinoculation produced a lethal outcome [141].

4.1.2 Guinea Pigs

Guinea pig models of arenavirus infections have been widely used to study pathogenesis and to evaluate the efficacy of potential vaccines and therapeutics. Current guinea pig models of arenavirus infection caused by both NW and OW hemorrhagic fever-causing arenaviruses appear to closely resemble human disease, but do not epitomize its neurological aspects. Strain 13 guinea pigs have been the primary animal model to date, presumably because they are more susceptible to arenavirus infections than Hartley guinea pigs [142]. Both LUJV and LASV infection of strain 13 guinea pigs results in uniform susceptibility and high lethality with similar pathological features [142, 143]. Animals rapidly develop high fever and weight loss progressing to lethargy, reduced grooming, and death. Viremia and tissue titers are consistent with disseminated viral disease involving most visceral and lymphatic organs. Histologic findings from animals infected with LUJV include hepatic infarction with associated necrosis and fibrin deposition, whereas the most prominent histologic feature in LASV infection is interstitial pneumonia.

JUNV infection models utilizing strain 13 guinea pigs are characterized by prominent hematologic and lymphatic involvement including necrosis and cellular depletion and hemorrhage [144, 145]. Further study of the hematological changes of bone marrow during the course of infection revealed a significant increase in cells with abnormal morphology [145, 146].

4.2 Nonhuman Primates

4.2.1 Common Squirrel Monkey

Walker et al. first described a nonhuman primate model of Lassa fever in the common squirrel monkey (*Saimiri sciureus*) [147]. Four monkeys were inoculated intramuscularly and serially sampled post-exposure on days 7, 12, 14, and 28 to both evaluate the clinical course and characterize progression of disease pathology. Animals exhibited a variable clinical course with an incubation period between 8 and 18 days. Early clinical signs included development of anorexia, polydipsia, and lassitude. Early presence of detectable virus in the tissues involved lymph nodes,

liver, and kidneys followed by dissemination through various other organs in a pantropic manner. Histopathological findings suggested similarities between the common squirrel monkey model and human disease pathology that included germinal necrosis in lymphoid organs, myocarditis, acute arteritis, renal tubular necrosis, hepatocytic regeneration, and chronic inflammation of the choroid plexus, ependymal, and meninges with cerebral perivascular cuffing.

4.2.2 Tufted Capuchins

Intracerebral JUNV infection of tufted capuchins (*Cebus apella*) [148] results in clinical signs after a 2-week incubation period, including weight loss and mild-to-moderate central nervous system involvement that resolves in most animals. Despite resolution, some animals still have detectable viral antigen in the brain as long as 5 months post exposure. Hemorrhagic manifestations do not develop. The clinical response to infection is not uniform, though all animals develop high antibody responses. Although the model does not reproduce the human disease faithfully, it may have utility to study effects of the virus on the central nervous system or to evaluate viral persistence.

4.2.3 Common Marmoset

Both JUNV and LASV infection models utilizing the common marmoset (*Callithrix jacchus*) have been described [149–154]. Except for microscopic neurological irregularities [155], JUNV infection in common marmosets shares pathological and hematological characteristics with human disease. Common marmosets infected with JUNV intramuscularly developed characteristic disease [156]. Animals initially presented with anorexia, lassitude, weight loss, thrombocytopenia, and leukocytopenia, followed by progression to severe fatal neurological and hemorrhagic disease approximately 3 weeks after exposure. Histologically, development of multifocal hemorrhage, microscopic lesions of the central nervous system, interstitial pneumonia, lymphocytic depletion, hepatocytic necrosis, and loss of bone marrow cellularity correlate with high virus concentrations [155].

Further evaluation of the hematological values of JUNV-infected marmosets revealed anemia and alteration of blood coagulation as evidenced by reduction of platelets and disruption of enzymatic activation of thrombin. These alterations ultimately led to a state of DIC [157, 158]. Complement activation was independent of clotting abnormalities, though this finding is inconsistent with what is known about human disease and remains to be further evaluated in nonhuman primate models.

A later study also described LASV infection in experimentally infected common marmosets that echoed human disease [149]. Following subcutaneous inoculation with LASV strain Josiah, common marmosets developed a systemic illness including fever, weight loss, high viremia and viral tissue loads, liver damage, and substantial morbidity. Virus tissue tropism was extensive as indicated by extremely

high viral titers in the spleen, lymph nodes, lung, liver, kidney brain, and adrenal glands. The most prominent microscopic features included hepatic necrosis, interstitial nephritis, and depletion of lymphoid cells. Additionally, these histologic findings suggested impairment of adaptive immune responses by depletion of T and B cells and ablation of macrophage expression of MHC class II. The common marmoset therefore appears to be a suitable model for further characterization of Lassa fever pathogenesis.

4.2.4 Rhesus Monkey

The disease caused by LASV in rhesus monkeys (*Macaca mulatta*) shares many striking similarities with human Lassa fever, including onset of high fever, general weakness and malaise, pleural and pericardial effusion, hemorrhagic manifestations (e.g., bleeding from mucosal surfaces), shock, and death [116]. Several authors reported on LASV Josiah exposure of rhesus monkeys via the subcutaneous route of exposure with very similar findings [159–162]. Animals developed clinical signs (high fever, anorexia, reduced responsiveness) 4–12 days post exposure. This model was not uniformly lethal, and survivors tended to present with signs of disease later than their moribund counterparts. As disease progressed, animals became increasingly lethargic and presented with petechial skin rash, recumbency, elevated liver enzyme concentrations, and weakness. Although not ubiquitously reported, some cases involved aphagia, constipation, conjunctivitis, and hiccups. End-stage disease involved hypotension and hypothermia just prior to death.

Gross pathology and histological studies of LASV-infected rhesus monkeys resembled human disease, including pulmonary congestion, pleural effusion, pericardial edema, fibrin deposition, and gross visceral hemorrhage. The most prominent histological findings included necrotizing hepatitis and interstitial pneumonia [161]. While coagulopathy consistent with DIC was not observed, increased time for sample clotting was observed occasionally, suggesting a clotting abnormality consistent with viral hemorrhagic diseases with associated platelet aggregation [160, 162]. High virus titers in tissues were consistently reported in excess of serum viremia and included liver, lung, adrenal glands, pancreas, spleen, kidneys, lymph nodes and neurological tissues, with liver, spleen, and lungs generally yielding the highest virus titers. With the exception of a single animal that developed hind leg paralysis following apparent recovery from clinical signs at day 58 [162], no other neurological findings were reported. This finding is in contrast to the smaller primate models described previously (such as common marmosets and common squirrel monkeys). Intravenous inoculation of LASV strain Josiah into rhesus monkeys led to similar clinical presentation and pathological findings as those recorded after subcutaneous inoculation [163].

JUNV infection in rhesus monkeys can be established by the intramuscular and aerosol routes of exposure. McKee et al. compared several strains of JUNV (Romero, Espindola, Ledesma, and P-3551) in rhesus monkeys to characterize differences in disease course and outcome [164, 165]. Animals initially presented with similar

onset independent of strain, including progressive anorexia, lassitude, and diarrhea or constipation. JUNV infection in macaques infected with the Romero strain spontaneously resolved without developing more substantial illness.

In macaques infected with the other three strains (i.e., Espindola, Ledesma, P-3551), JUNV infection progressed to debilitating illness and, in most cases, death. These strains induced a pronounced loss of body weight, facial erythema developing into macular rash, conjunctivitis, oral ulcerations, and in some cases hypothermia precluding death by 24–48 h.

All three strains evolved into distinct disease phenotypes. Espindola strain infection induced a primarily hemorrhagic disease, including widespread petechial rash, mucous membrane and/or nasal bleeding prior to death, and was associated with severe bacteremia [164–166]. In contrast, animals infected with the Ledesma strain developed early bacteremia and a prominent neurological disease, including encephalopathy, tremors, spontaneous and isolated limb paralysis, and balance disturbances. Animals infected with the P-3551 strain presented with a disease that shared components of both JUNV Espindola and Ledesma strain infections, but disease was generally milder (all animals infected with the Espindola strain succumbed to disease, whereas infection with the other two strains did not necessarily have a lethal outcome).

Investigators of a study assessing the aerosol route of exposure used the Espindola strain of JUNV but induced disease was similar to disease seen in intramuscularly inoculated animals [167]. All macaques developed acute signs 2–3 weeks post exposure, including anorexia, malaise, and weight loss, followed by development of rash, thrombocytopenia, lymphadenopathy, oral hemorrhage, and mucosal bleeding. Animals surviving beyond 3 weeks experienced a wasting illness prior to death. Interestingly, no distinct neurological signs were noted following aerosol exposure in rhesus monkeys.

MACV, the causative agent of Machupo/Bolivian hemorrhagic fever in humans, was also studied in rhesus monkeys. Initials signs were present within a week of subcutaneous inoculation and included depression, progressive anorexia followed by constipation, and intermittent diarrhea [168, 169]. Animals generally either succumbed to disease in this initial phase or progressed to develop neurological manifestations (tremors, nystagmus, lack of coordination, paresis, coma). Most animals succumbed during this neurological phase of disease, but some recovered. Animals that survived the first phase of disease typically developed neutralizing antibodies [168]. The mean time to death was also partially dependent on age and weight, with younger animals succumbing earlier. The mean time to death for smaller and larger rhesus monkeys was 19.3 days and 30.5 days, respectively.

Viremia in animals exposed to MACV was highest during the initial 2 weeks of infection but was still present in animals that had neurological signs. Interestingly, in an experiment in which complement was selectively depleted, viremia increased overall, highlighting the importance of complement fixation for clearance of the virus by antibodies [168]. These findings indicate that clinicians should exercise caution when passive transfer of convalescent serum is considered to treat human disease.

Gross and microscopic lesions included lymphocytic infiltrates in brain, spinal cord, pancreas, intestine, liver, kidneys, adrenals, heart, and skeletal muscle. Additional lymphocytic inflammation was noted in the nervous system [170].

Disease in rhesus monkeys, unlike NW monkeys, appears to correlate well with human disease induced by both the OW and NW arenaviruses (specifically LASV, JUNV, and MACV). Progression of the clinical phase for the rhesus monkey model is well mirrored in human case reports, making these models particularly well suited for studies exploring pathogenesis or evaluating medical countermeasures, including both vaccine and therapeutic approaches.

4.2.5 Crab-Eating (Cynomolgus) Macaque

Crab-eating macaques (*Macaca fascicularis*) have been used as models for infection caused by highly virulent arenaviruses, including LASV and MACV. As with rhesus monkeys, arenavirus disease in crab-eating macaques caused by LASV and MACV share major defining characteristics with human disease.

Following intramuscular inoculation of LASV, animals develop high fever, anorexia, mild-to-moderate depression, and dehydration between days 3 and 10. Facial edema occurs in some animals. Progressive anorexia and severe dehydration are followed by development of neurological signs, including convulsions and seizures, which rapidly increase in duration and severity until death [171].

Significant clinical parameters of LASV infection included increases in D-dimer and protein C plasma concentrations followed by elevation of liver enzyme and blood urea nitrogen concentrations in late stages of disease. Viremia occurred early in disease, starting as early as day 3, and peaked at approximately 2 weeks prior to death.

Increases in peripheral cytokine concentrations were significant for IL-6, IL-1β, eotaxin, and monocyte chemoattractant protein-1 (MCP-1) [171]. Baize et al. demonstrated that production of large quantities of IL-6 was correlative with fatal outcome. Survivors tended to have early and robust cell-mediated immune responses, further supporting the pivotal role of T cells over humoral responses in survival of Lassa fever [120]. Other studies supported these findings by demonstrating substantial increases in chemokines and cytokines in crab-eating macaques following inoculation with LASV, including those associated with immunosuppressive activities [172, 173].

Gross necropsy findings of LASV infection revealed lymphadenopathy with associated congestion, pale and friable livers, enlargement of the adrenal glands and pancreas, renal congestion, and pericardial effusion. Focal, petechial hemorrhage was noted on the mucosal surface of the urinary bladder, and congestion of the ileocecal junction suggested gastrointestinal involvement.

Histology supported gross pathological findings with antigen staining primarily associated with antigen-presenting cells in lymph nodes, spleen, and thymus. Hepatic and renal changes included lymphoplasmacytic and neutrophilic inflammation with substantial immunostaining in animals sacrificed during late-stage disease.

Fibrin deposition was also noted in both tissues. Mild interstitial pneumonia occurred in a single animal, and cardiac involvement was evident by neutrophilic inflammation of the pericardium. LASV antigen staining was present in all tissues evaluated, indicating systemic dissemination of virus. Microscopic examination of neurological tissue indicated meningoencephalitis in the cerebrum, cerebellum and brain stem with neuronal necrosis and gliosis. Endothelial and histiocytic cells were antigen positive in terminal cases [171].

Crab-eating macaques inoculated subcutaneously with MACV (Carvallo strain) exhibited clinical progression and pathogenesis similar to rhesus macaques with a biphasic disease character consisting of initial fever, anorexia, and depression followed by development of neurological symptoms often leading to death. Unlike rhesus monkeys, however, crab-eating macaques succumbed to disease without development of signs equal in severity to those in rhesus monkeys inoculated with an equivalent dose of virus. The mean time to death for MACV-infected crab-eating macaques was 17 days post-exposure [168].

Aerosol and intramuscular exposure of macaques with the Chicava strain of MACV caused a similar disease course as seen with the Carvallo strain in crab-eating macaques [174]. Animals exhibited similar biphasic disease, and death occurred within 3 weeks of exposure. Similar to previous studies, lymphadenopathy with associated congestion, viral hepatitis, and gastrointestinal hemorrhage were present. Histologic findings consisted of necrosis and apoptosis of cells of affected tissues, including liver, pancreas, adrenal glands, lymph nodes, stomach, and intestines. Interstitial pneumonia was also present in some cases. As expected, inflammation within the central nervous system was also histologically confirmed.

4.3 Use of Surrogate Models of Highly Virulent Arenaviruses

Work with OW and NW arenaviruses that cause viral hemorrhagic fevers in humans (LASV, Lujo virus, MACV, JUNV, SABV, GTOV, and Chapare virus), is restricted to biosafety level 4 conditions, limiting the work to a few specialized facilities. As a result, surrogate models utilizing related viruses in both rodent and primates have been developed for disease modeling purposes [175–186]. Several arenaviruses (e.g., TCRV, PICHV, MOPV, LCMV) or attenuated varieties of parental viruses that do not cause substantial disease in humans (except immunocompromised individuals) have been used in the development of both rodent and primate models with less inherent risk to researchers.

While these surrogate models can and have provided a wealth of information in advancing understanding of their highly pathogenic relatives, caution should be exercised with the extent to which these models can be used to identify pathogenic mechanisms and correlates of human disease. Most rodent models are based on gene knockouts that fundamentally alter the immune response, and nonhuman primate models rarely completely recapitulate the disease resulting from more virulent arenavirus members. These models are best suited to be used to specifically explore

pointed questions about aspects of these diseases that the models can faithfully reproduce. Alternatively, surrogate models can be used to ask more general questions about arenavirus replication applicable to all family members.

5 Vaccines and Therapeutics

5.1 Vaccines

5.1.1 Live Attenuated or Nonpathogenic Viruses

Currently, the only licensed, yet not FDA-approved, vaccine for use in the prevention of disease caused by an arenavirus is Candid#1. This vaccine has been clinically demonstrated to be save and efficacious against JUNV infection [187]. Using recombinant viruses in a laboratory mouse model of JUNV infection, the parental JUNV XJ44 strain was shown to be attenuated via a single amino acid change in GPC at position 427 (phenylalanine to isoleucine) [188, 189]. Vaccine safety and immunogenicity were demonstrated in rabbits, guinea pigs, and rhesus monkeys, and finally in randomized clinical trials in humans [190]. The vaccine has been successful in reducing both disease magnitude and severity of Junín hemorrhagic fever and is licensed in Argentina for vaccination of people living in high-risk areas where JUNV virus is endemic [187].

Another live attenuated vaccine candidate with substantial promise is the chimeric virus ML-29 containing the LASV S segment and the MOPV L segment. This recombinant virus was generated by coinfection of Vero cells with both viruses followed by plaque purification of the ML-29 virus clone [191]. In guinea pigs vaccinated with ML-29 and inoculated with LASV, disease did not develop. Immunogenicity was then evaluated in rhesus monkeys, and virus-specific cellular immunity to LASV and MOPV antigens, as well as LCMV, was demonstrated. The rhesus monkeys did not develop overt disease, nor were there histological lesions following vaccination, suggesting that ML-29 could be used for prevention of Lassa fever [192].

Nonpathogenic arenaviruses have also been evaluated as vaccine candidates against disease caused by more virulent arenaviruses. Early studies using MOPV indicated cross-protection against LASV infection in rhesus monkeys, as the monkeys had no signs of disease and survived otherwise fatal infection [193]. However, liver and kidney histological alterations were noted in rhesus monkeys infected with MOPV in the absence of overt clinical signs of disease, indicating that arenaviruses thought to be apathogenic may not be entirely safe [163]. Thus, caution should be exercised when evaluating the safety of closely related viruses thought not to cause disease in humans.

Similar approaches with TCRV have also been used successfully in the common marmoset primate model of JUNV disease [153, 154, 194–196]. Intramuscular or intranasal inoculation of marmosets with TCRV prior to injection with a lethal dose of JUNV provided protection from disease development and death.

Additionally, intrathalamic inoculation of animals with TCRV caused no clinical signs of disease, histopathologic changes, or viremia up to 480 days post-inoculation. Common marmosets developed measurable, protective immune responses as early as 3 weeks following exposure to TCRV. Results of these studies suggest TCRV may be a viable and safe candidate for vaccination against the pathogenic JUNV.

XJC13, an attenuated variant of JUNV derived from the parental XJ strain, was tested for efficacy as a vaccine candidate in common marmosets [151]. Following intramuscular inoculation of XJC13, no fatality or signs of overt illness were observed in animals up to 420 days post-inoculation. The only evidence of pathogenicity was slight weight loss between days 18 and 40 post-inoculation, after which animals' weight rapidly normalized. Viremia was detectable between day 6 and 22 post-inoculation with virus spread limited to lungs, spleen, lymph nodes, and bone marrow. Ganglionic hypertrophy with immunoblast proliferation was detected in animals sampled approximately 3 weeks after inoculation without recovery of virus. Measureable infectious virus could not be isolated at sampling time points greater than 1 year post-inoculation, although viral antigen staining was present in some organs.

All animals developed neutralizing antibody responses from week 3 onward. At days 60 or 380 following XJC13 inoculation, animals were inoculated with a lethal dose of the parental JUNV strain. XJC13 exposure conferred protection to all animals, whereas all control animals died. This study provides evidence that common marmosets may be useful in evaluating attenuated vaccines for JUNV infection.

5.1.2 Recombinant Vaccine Vector Approaches

More targeted approaches for the development of recombinant vaccine virus vectors have also been used. Vaccinia virus vectors modified to express LASV NP or GPC successfully protected guinea pigs against lethal LASV infection [197, 198]. Multiple vaccinia virus vaccines expressing different LASV antigens were tested in nonhuman primates, including vectors expressing only N-terminal (GP1) or C-terminal (GP2) parts of GPC, whole GPC or NP. Only whole GPC or administration of both GP1 and GP2 provided significant protection against disease and death in both rhesus monkey and crab-eating macaque models [199]. All animals receiving either GP1 or GP2 vaccines succumbed to disease, and 80 % of NP-vaccinated animals died despite development of high antibody titers. In comparison, all animals receiving both the GP1 and GP2 vaccines simultaneously survived, and 90 % of the animals receiving whole GPC survived even in the absence of significant antibody responses. The results of these studies suggest that a predominant cellular response is important in conferring protection and that whole GPC of LASV is necessary in eliciting a protective outcome.

A similar strategy was used for the development of a candidate vaccine against JUNV infection. A recombinant vaccinia virus expressing either GPC or NP of TCRV or GPC of JUNV was used to vaccinate guinea pigs. This approach resulted in partial protection of guinea pigs following lethal JUNV injection in both groups (50 % for TCRV GPC and 72 % for JUNV GPC) [200]. Interestingly, while recombinant

vaccinia virus expressing NP protein elicited a neutralizing antibody response, the vaccine was not protective. Conversely, both GPC vaccines were protective in the presence of low or undetectable neutralizing antibodies. Protection with recombinant vector vaccines against LASV and JUNV infection without appreciable antibody responses suggest that cell-mediated immunity (e.g., T cell responses) may play a prominent role in protection of animals from arenavirus infection.

Vesicular stomatitis Indiana virus (VSV) has also been used as a recombinant vaccine vector. Replication-competent VSV expressing LASV GPC protected nonhuman primates from lethal LASV infection. Transient viremia developed following inoculation, but no outward clinical signs of disease were noted [201, 202]. As was seen with the vaccinia virus vector, the VSV vaccine elicited strong cellular immune responses in vaccinated monkeys. In contrast to other vaccines, however, rVSV expressing LASV GP also induced a humoral response, although the contribution of this response to the positive outcome was impossible to determine.

Vaccination with the well-described yellow fever virus 17D backbone modified to express LASV GP1 and GP2 has resulted in partial protective efficacy in guinea pigs. Approximately 6 weeks post vaccination, five of six guinea pigs inoculated subcutaneously with 1,000 PFU of LASV survived; however, all animals developed clinical signs of disease (e.g., fever, loss of body weight and viremia) [203]. The vaccine also successfully elicited CD8+ T-cell responses in both CBA/J+ mice and strain 13 guinea pigs. As the vaccine failed to protect common marmosets from lethal LASV infection, the likelihood of efficacy in humans may be questionable [204].

A Venezuelan equine encephalitis virus replicon particles (VRP)-based vaccine has also been tested and found effective in protecting guinea pigs from lethal LASV infection [205]. Both individual vaccine strategies, VRPs expressing LASV GP or NP, were protective, as was vaccination with both vaccines simultaneously. None of the vaccinated animals developed signs of disease, and the majority of guinea pigs did not develop viremia as a consequence of LASV inoculation. Unlike previous vaccine strategies in which the use of NP did not lead to protection, results of this study provide evidence that an NP vaccine strategy may be viable. None of the vaccinated animals developed significant neutralizing antibody responses following vaccination, again suggesting a central role for cellular immunity in prevention of arenavirus disease.

Perhaps one of the most interesting approaches to development of a vaccine against LASV infection has been the expression of LASV NP in *Salmonella* Typhimurium. Mucosal immunization of mice elicited both virus NP-specific humoral and T cell responses [206]. Further evaluation of efficacy in an LCMV laboratory mouse model suggested that protection against LCMV infection could be achieved with the strategy. Experiments using this strategy with LASV, both in rodents and nonhuman primates, remain to be performed [207].

5.1.3 Inactivated and Virion-Like Particle Vaccines

Inactivated vaccine strategies for the prevention of arenavirus disease are underexplored. Virion-like particles (VLPs) containing LASV GP1, GP2, Z, and NP have been evaluated for their ability to induce antibody responses [208]; however, they have

yet to be evaluated for efficacy. LASV particles inactivated by gamma-irradiation failed to protect rhesus monkeys from lethal infection with live LASV, despite development of a humoral antibody response. This failure is attributed to a lack of an adequately induced cellular immunity following vaccination [209]. Likewise, guinea pigs vaccinated with formalin-inactivated JUNV developed neutralizing antibodies, but these animals were not protected from lethal disease [210]. Taken together, results of these studies suggest that non-replicating approaches are unlikely to provide protective immunity against arenaviral infections.

5.1.4 DNA Vaccines

Electroporation of DNA plasmids encoding viral genes and uptake by host cells can induce immunity to targets by promoting host cell expression of viral proteins. Cross-presentation of these antigens by antigen-presenting cells thus may elicit a potentially protective immune response. To evaluate this approach for vaccination against LASV infection, both the immunogenicity and efficacy of electroporation of DNA plasmid vaccine expressing LASV NP was evaluated in mice using LCMV or PICHV inoculant. A single inoculation induced cellular CD8+ immune responses and resulted in lower viral titers in vaccinated mice euthanized 4 days post-virus inoculation as compared to non-vaccinated controls [211]. While these results are encouraging, it remains to be demonstrated that these vaccines can provide protection against LASV infection. Furthermore, DNA vaccines are known to elicit rather weak immune responses and often require multiple dosing in prime-boost strategies or additional adjuvants to provide both protection and durability. As mice were inoculated with virus 3 weeks post-vaccination, the duration of protection with this DNA vaccine approach is unclear.

A DNA plasmid expressing LASV GPC was efficacious in protecting both guinea pigs [212] and nonhuman primates [213] from otherwise lethal LASV infection. In initial studies, 5/6 guinea pigs were protected, although the vaccine did not provide sterilizing immunity. Subsequent improvements in delivery and codon optimization of the GPC gene resulted in complete protection, and no viremia developed in vaccinated animals. Similarly, this strategy also completely protected crab-eating macaques.

5.2 Therapeutics

5.2.1 Passive Transfer Using Immune Sera

Multiple studies have highlighted the protective value of immune sera treatment to counter JUNV infection in both common marmoset and guinea pig models. Guinea pigs were protected from illness as many as 6 days post-challenge, though development of viremia and neurological complications (encephalitis, meningitis detected

at necropsy) did occur [214, 215]. Similar results were seen in common marmosets inoculated with JUNV—a 75 % survival rate following treatment with immune sera 6 days post-inoculation [152]. All animals developed clinical signs. Some survivors also developed neutralizing antibody titers following convalescence. Collectively, these studies suggest that passive immune therapy may be a promising approach for treatment of NW arenavirus infections.

The effectiveness of passive immune treatment has also been shown in nonhuman primate and guinea pig models of LASV infection. Multiple methods were used to characterize the neutralizing antibody components of animal or human convalescent serum, including immunofluorescent and standard plaque reduction neutralization titer techniques. The quality and concentration of neutralizing antibodies was clearly correlated with favorable outcome [216–218], and therapeutic cut-off values predictive of a favorable outcome were established. Treatment with neutralizing antibodies coupled with ribavirin therapy resulted in enhanced protection in the crab-eating macaque models of LASV and JUNV infections, underlining the advantages of combinational therapy approaches [219, 220]. A single study assessed the role of complement in neutralization of JUNV [221]. Presence of complement was critical for neutralization of virulent JUNV strains, but not for attenuated strains, suggesting that complement activation may play an important role in the quality of the neutralizing antibody response.

Passive transfer of immune sera has also been tested experimentally in rhesus monkeys or crab-eating macaques inoculated with MACV [222]. Immunoglobulin of human origin was given either pre- or post-virus inoculation. Animals receiving sera were protected from developing initial clinical illness; however, some survivors later developed neurological signs and subsequently succumbed to disease. Neurological development may have had a greater association with high doses of immunoglobulin, suggesting that neurological pathology may be at least in part mediated by delivery of treatment.

5.2.2 Drugs Targeting Viral Entry

Preventing virion cell entry in theory prevents a virus from establishing infection and therefore subsequent replication. Cell entry begins with engagement of attachment factors present on the target cell surface by arenaviral GP1, leading to internalization, endosomal trafficking, and virus uncoating. Thus, targeting cell-surface receptors involved in engagement of arenaviral glycoproteins and host pathways involved in permitting access of virus to the cell following attachment is an attractive therapeutic strategy.

Virulent NW arenaviruses (all of which belong to clade B) utilize human hTfR1 by recognition of structures distinct from the transferrin-binding site [74, 93, 223]. Understanding the binding site necessary for arenavirion attachment presents the possibility of targeting the site for therapeutic intervention. Using a monoclonal antibody to hTfR1 targeting the region necessary for arenavirus GP1 binding, but dispensable for transferrin binding, Helguera et al. successfully blocked infection of

HEK293 cells by all NW arenaviruses. The antibody may be promising for studies in nonhuman primates as the antibody is cross-reactive with transferrin receptor orthologs of primates belonging to several species.

OW arenaviruses are thought to utilize extracellular matrix ligands for attachment and entry, presenting a more difficult challenge for inhibiting entry at the cell surface. Despite this possible hurdle, phosphorothioate DNA oligonucleotides can potently inhibit LCMV infection by interfering with the virus–αDG interaction, thus preventing viral entry by steric blockade [224].

Small molecule inhibitors are capable of blocking entry by preventing pH-mediated fusion of the arenaviral GP1 with cellular entry receptors that are relatively specific to arenaviruses in multiple cell types [225]. High-throughput screening of various compounds yielded lead candidate small molecule inhibitors, ST-193 and ST-294, which are effective at blocking LASV, JUNV, MACV, and GTOV GP-mediated entry by inhibiting membrane fusion [226, 227]. ST-193 tested in the guinea pig model of LASV infection significantly reduced fatality [228].

Lassa virus GPC is proteolytically cleaved by cellular site 1 protease (S1P) to generate the attachment protein GP1 and the fusion-active transmembrane protein GP2. PF-42942, a small molecule inhibitor of S1P, had no impact on transcription, translation, or budding of LCMV and LASV, but had a modest effect on virus cell entry [229]. Thus, the anti-arenavirus activity of PF-42942 is primarily related to inhibition of S1P-mediated processing of GPC. More recent studies indicate that PF-42942 may work against NW arenaviruses as well [230]. Using small molecule inhibitors of S1P may therefore hold promise as a novel antiviral strategy in preventing arenavirus infection.

Imidazothiazole carbohydrate derivatives also have potential utility in blockade of JUNV at the point of infection [231]. Cells were preincubated with varying concentrations of these compounds, compounds were premixed and incubated with virions prior to cell infection, or cells were treated at time of infection. Preincubation with virions yielded little reduction in infectivity, but both pretreatment of cells or simultaneous addition of drug and virions reduced infection.

Trifluoperazine and chlorpromazine, both drugs in the phenothiazine class, proved efficacious in vitro against JUNV, TCRV, and PICHV. These effects were achieved at IC_{50} concentrations ranging from 7.7 to 23 μM. Time-of-addition experiments revealed that the drugs acted early in the replicative cycle, likely by modulating actin microfilaments and affecting viral entry [232].

5.2.3 Drugs Targeting Viral Replication

Ribavirin, the only off-label drug for treatment of arenavirus infections, is a nucleoside analogue and still remains the treatment drug of choice, despite its well-known toxicity [233–237]. Ribavirin reduces morbidity and fatality in both clinical and experimental conditions of Old and New World arenavirus infections when provided early in course of clinical disease [161, 219, 238–242]. Ribavirin is thought to exert its antiviral activity by negatively regulating RNA synthesis. While the

precise mechanism remains elusive, ribavirin may inhibit inosine monophosphate dehydrogenase activity, leading to depletion of intracellular GTP pools [243], although results of some studies have challenged this idea [244]. Another possible explanation for ribavirin's antiviral effect may be direct mutagenesis of viral RNA [245]. Other drugs targeting inosine monophosphate dehydrogenase, which may be as efficacious as ribavirin but be less toxic, may be worth investigating.

T705, also known as favipiravir, is a pyrazine derivative that is effective in vitro against arenavirus infections. The mechanism of action involves disruption of the early intermediate phase of virus replication by inhibition of L activity [246, 247]. In vivo studies using PICHV rodent models yielded promising results. Twenty and seventy eight percent of guinea pigs treated with favipiravir by the oral or peritoneal routes, respectively, survived inoculation with PICHV when treatment occurred with 48 h [248]. Those animals who succumbed to disease experienced a prolonged disease course, and surviving animals presented with less severe disease overall. In hamsters, initiating treatment during the most severe stage of disease still altered disease outcome. These results suggest that T705 is an exceptional candidate for further preclinical development to treat arenavirus disease [249, 250]. Most of the studies described above incorporated ribavirin as a comparative treatment control. Not only did T705 outperform ribavirin in direct studies, but it also was significantly less toxic [246, 248, 250].

The antibiotic pyrazofurin was tested both in vitro and in guinea pigs inoculated with PICHV [251]. Results in cell culture were promising as relatively low concentrations of the drug, 2 μg/ml, markedly inhibited plaque formation of multiple arenaviruses. The mechanism of action is attributed to inhibition of de novo synthesis of nucleotides by blocking the activity of orotic acid monophosphate decarboxylase and preventing formation of uridine. Unfortunately, results in guinea pig studies were disappointing as treatment did not prevent lethal outcome or alter viral loads.

A few studies have also evaluated the use of type I IFNs, specifically IFN-α, as a treatment for arenavirus infection. Generally speaking, results of these studies indicated arenavirus infections to be relatively insensitive to IFN treatment [252–255]; however, at least one study suggested that treatment with type I IFNs can reduce LASV replication in HuH7 and Vero cells [256]. Additionally, therapeutic benefit has also been achieved by treating hamsters with IFN alfacon-1 immediately following and up to 2 days after exposure to PICHV [257]. A protective effect in the same hamster model was also achieved using the non-replicating recombinant adenovirus platform DEF201 encoding consensus IFN alfacon-1 in pre- and post-prophylaxis approaches. These results suggest that IFN treatment may be at least partially beneficial to controlling arenavirus infections [258].

Several other compounds, including *S*-adenosyl-L-homocysteine (SAH) hydrolase inhibitors [259–262], brassinosteroids [263], myristic acid [264], carboxamide derivatives [265], and zinc-finger-reactive compounds [266], have anti-arenaviral activity. Zinc-finger-reactive compounds are thought to act via inhibition of Z, presenting yet another viral replication cycle target. To date, none of these compounds have been evaluated in animals or demonstrated to have significant advantages over ribavirin as a therapeutic alternative.

Kinase inhibitors have also been evaluated for efficacy in treating both NW and OW arenavirus infections. Genistein is a general tyrosine kinase inhibitor that blocks infection of cells by PICHV, likely at the step of entry. Activation of transcription factor-2 protein (ATF-2) and cyclic adenosine monophosphate response element binding protein (CREB) in Vero cells by PICHV was inhibited following treatment with genistein, and this inhibition correlated with decreased viral entry [267]. A similar suppression of infection was observed when genistein was paired with tyrphostin, another kinase inhibitor. The drugs both demonstrated individual efficacy and a synergistic effect when combined [268]. Genistein was also tested in the Syrian golden hamster model of PICHV infection with successful reduction in fatality and improved clinical profile [269].

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