Arenaviruses

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Abstract  The Arenaviridae family contains 22 recognized virus species, each of them strongly associated with a rodent species (except Tacaribe virus which is associated with a species of bat), suggesting an ancient co-evolutionary process. Although the concept of co-evolution between rodents and arenaviruses is now largely accepted, little has been uncovered in terms of dating the phenomenon and the mechanisms of evolution, including speciation and pathogenicity. These questions are targeted in the present chapter. Old World arenaviruses are associated with the Eurasian rodents in the family Muridae. New World arenaviruses are associated with American rodents in the subfamily Sigmodontinae. The correlation between the rodent host phylogeny and the viruses suggests a long association and a co-evolutionary process. Furthermore, three distinct New World arenaviruses share a common ancestor, demonstrating a unique recombination event that probably occurred in that ancestor. This shows that recombination among arenaviruses of different lineages might occur in nature. Recombination and co-evolutionary adaptation appear as the main mechanisms of
arenavirus evolution, generating a high degree of diversity. The diversity among rodent host reservoir and virus species and the potential to exchange genomic material provide a basis for the emergence of new viruses and the risk of these becoming pathogenic for humans.

1 Introduction

The Arenaviridae family consists of a unique Arenavirus genus that currently contains 22 recognized virus species (Salvato et al. 2005). Arenaviruses are enveloped single-stranded RNA viruses, with a genome consisting of two RNA segments, designated large (L) and small (S). The L genomic segment (~7.2 kb) encodes the viral RNA-dependent RNA polymerase and a zinc-binding protein. The S genomic segment (~3.5 kb) encodes the nucleocapsid protein and envelope glycoproteins in nonoverlapping open reading frames of opposite polarities. The genes on both S and L segments are separated by an intergenic noncoding region with the potential of forming one or more hairpin configurations. The 5’ and 3’ untranslated terminal sequences of each RNA segment possess a relatively conserved reverse complementary sequence spanning 19 nucleotides at each extremity. Nucleocapsid antigens are shared by most arenaviruses, and quantitative relationships show the basic split between viruses of Africa and viruses of the Western Hemisphere. Individual viruses are immunologically distinct by neutralization assays, which depend on the specificity of epitopes contained in the envelope glycoproteins (Salvato et al. 2005).

Virions are spherical to pleomorphic with a diameter of 50–300 nm (average diameter for spherical particles is 120 nm). They possess a dense lipid-containing envelope covered with 8-10-nm-long club-shaped projections. Host cell ribosomes present in the viral particles, are responsible for the sandy appearance of the virus by electron microscopy, hence the name arenavirus (Latin: arena, sand). Buoyant density is 1.17–1.18 g/cm³ in sucrose and 1.19–1.20 g/cm³ in CsCl. Virus is rapidly inactivated at 56°C, at pH below 5.5 or above 8.5, or by exposure to UV and gamma irradiation (Table 1).

Lymphocytic choriomeningitis virus (LCMV) was first isolated in the 1930s (Armstrong and Lillie 1934) but it is only in the late 1960s that LCMV was found to be related to the already existing Tacaribe group, which then led to the creation of the Arenaviridae family (Murphy et al. 1969). The arenaviruses have been classified into two groups according to their antigenic properties: (1) the Tacaribe serocomplex (including viruses indigenous to rodents of the New World) and the prototype Tacaribe virus (TCRV) isolated from Artibeus bats in Trinidad (Downs et al. 1963), and (2) the Lassa-lymphocytic choriomeningitis (LCM) serocomplex (including the viruses indigenous to rodents of Africa and the ubiquitous lymphocytic choriomeningitis virus (LCMV), recognized as the Old World group) (Fig. 1).
### Table 1 The Arenaviridae family

| Virus       | Acronym | Country of prototype virus isolate | Human significance<sup>a</sup> | Historical reference |
|-------------|---------|------------------------------------|------------------------------|----------------------|
| 1 Allpahuayo| ALLV    | Peru                              | NE                           | Moncayo et al. 2001  |
| 2 Amapari   | AMAV    | Brazil                            | NE                           | Pinheiro et al. 1966 |
| 3 Bear canyon | BCNV | USA, California                    | NE                           | Peters et al. 1996   |
| 5 Cupixi    | CPXV    | Brazil                            | NE                           | Charrel et al. 2002  |
| 6 Flexal    | FLEV    | Brazil                            | LI                           | Pinheiro et al. 1977 |
| 7 Guanarito | GTOV    | Venezuela                         | HF, LI                       | Salas et al. 1991    |
| 8 Ippy      | IPPYV   | Central African Republic          | NE                           | Swanepoel et al. 1985|
| 9 Junin     | JUNV    | Argentina                         | HF                           | Parodi et al. 1958   |
| 10 Lassa    | LASV    | Nigeria                           | HF                           | Buckley et al. 1970  |
| 11 Latino   | LATV    | Bolivia                           | NE                           | Webb et al. 1973     |
| 12 Lymphocytic chorion meningitis | LCMV | Europe, USA                      | NS                           | Armstrong and Lilly 1934 |
| 13 Machupo  | MACV    | Bolivia                           | HF, LI                       | Johnson et al. 1965  |
| 14 Mobala   | MOBV    | Central African Republic          | NE                           | Gonzalez et al. 1983 |
| 15 Mopeia   | MOPV    | Mozambique                        | NE                           | Wulff et al. 1977    |
| 16 Oliveros | OLVV    | Argentina                         | NE                           | Mills et al. 1996    |
| 16b Pampa   | MOBV    | Argentina                         | NE                           | Lozano et al. 1997   |
| 17 Parana   | PARV    | Paraguay                          | NE                           | Webb et al. 1970     |
| 18 Pichinde | PICV    | Colombia                          | LI                           | Trapido and Sammartin 1971 |
| 19 Pirital  | PIRV    | Venezuela                         | NE                           | Fulhorst et al. 1997 |
| 20 Sabia    | SABV    | Brazil                            | HF, LI                       | Lysier et al. 1994   |
| 21 Tacaribe | TCRV    | Trinidad                          | LI                           | Downs et al. 1963    |
| 22 Tamiami  | TAMV    | USA Florida                       | NE                           | Calisher et al. 1970 |
| 23 Whitewater Arroyo | WWAV | USA, south West                  | NE                           | Fulhorst et al. 1996 |

Acronyms are attributed by the ICTV (Salvato et al. 2000). Countries are where the virus was first isolated and the associated reference is also the first report of the prototype virus. For arenaviruses known to be human pathogens virus, the primary clinical syndrome is indicated.

<sup>a</sup> BSL biosafety level
<sup>b</sup> HF hemorrhagic fever; NS neurological syndrome; LI laboratory infection; NE No evidence of natural human infection

<sup>c</sup> Pampa virus should be considered as a genotype of Oliveros virus
Fig. 1 Arenavirus phylogeny and rodent reservoir
Genetic studies of arenaviruses are congruent with comparative serological analyses. Both methods indicate that the 22 arenaviruses represent four phylogenetic lineages. The Old World (Lassa-LCM serocomplex) lineage comprises five viruses: LCMV, Lassa (LASV), Mopeia (MOPV), Mobala (MOBV) (Buckley et al. 1970; Wulff et al. 1977; Gonzalez et al. 1983), and Ippy (IPPYV) (Swanepoel et al. 1985) and is deeply rooted to the three New World (Tacaribe serocomplex) lineages, designated A, B, and C. Lineage A includes five South American viruses, Pirital (PIRV), Pichinde (PICV) (Fulhorst et al. 1997; Trapido and Sanmartin 1971), Flexal (FLEV), Parana (PARV), and Allpahuayo (ALLV) (Pinheiro et al. 1977; Webb et al. 1970; Moncayo et al. 2001). Lineage B includes seven South American viruses including Sabia (SABV), Junin (JUNV), Machupo (MACV), Guanarito (GTOV), Amapari (AMAV) (Lisieux et al. 1994; Parodi et al. 1958, Johnson et al. 1965; Salas et al. 1991; Pinheiro et al. 1966), Tacaribe (TCRV) (Downs et al. 1963), and Cupixi (CPXV) (Charrel et al. 2002). Lineage C comprises three South American viruses: Oliveros (OLVV) (Mills et al. 1996), Latino (LATV) (Webb et al. 1975), and Pampa (PAMV), which is a genotype of OLTV and does not represent a taxonomic species (Salvato et al. 2005). Phylogenetic studies conducted with complete gene sequences recently demonstrated that discrepancies observed in the topology of phylograms reconstructed from nucleoprotein and envelope glycoprotein genes are attributed to the recombinant nature of the S RNA segment of the three North American viruses: Whitewater Arroyo (WWAV), Tamiami (TAMV), and Bear Canyon (BCNV) (Fulhorst et al. 1996; Calisher et al. 1970; Fulhorst et al. 2002) (Table 2).

LCMV, JUNV, MACV, GTOV, and SABV are known to cause a severe hemorrhagic fever, in western Africa, Argentina, Bolivia, Venezuela, and Brazil, respectively (Peters et al. 1996), and were first recovered during investigations of human disease in 1969 (Buckley et al. 1970), 1958 (Parodi et al. 1958), in 1963 (Johnson et al. 1965), 1989, (Salas et al. 1991), and 1990 (Coimbra et al. 2002), respectively. They are included in the Category A Pathogen List as defined by the CDC, and listed as Biosafety Level 4 (BSL-4) agents. The family prototype, LCMV, was first isolated in 1933 during serial monkey passage of human material obtained from a fatal infection in the first documented epidemic of St. Louis encephalitis. LCMV is an agent of acute central nervous system disease (Barton and Hyndman 2000) and is also responsible for congenital malformations (Barton et al. 1993). FLEV and TCRV viruses have caused febrile illnesses in laboratory workers. WWAV has been associated with three fatal cases of infection in California in 2000 (CDC 2000), but further cases have not been documented since.

LCMV, LASV, and related viruses from the Old World are associated with rodents from the family Muridae, subfamily Murinae. New World arenaviruses are associated with New World rodents in the family Muridae, subfamily...
| Acronym | Evolutionary lineage<sup>a</sup> | Distribution<sup>b</sup> | Biogeographic domain | Reservoir |
|---------|---------------------------------|--------------------------|----------------------|-----------|
| **Old World arenaviruses** | | | | |
| LASV    | OW                              | Nigeria, Guinea, Liberia, Sierra Leone<sup>c</sup> | Palearctic | *Mastomys huberti* |
| MOBV    | OW                              | Central African Republic | Palearctic | *Praomys* spp. |
| MOPV<sup>d</sup> | OW                              | Mozambique, Tanzania | Palearctic | *Mastomys natalensis* |
| IPPYV   | OW                              | Central African Republic | Palearctic | *Arvicanthus niloticus* |
| LCMV    | OW                              | Eurasia, USA, Canada | Holoartic | *Mus musculus* |
| **New World arenaviruses (North Central America)** | | | | |
| BCNV<sup>e</sup> | NW-rec-A/B                       | USA, California | Neartic | *Peromyscus californicus* |
| TAMV<sup>e</sup> | NW-rec-A/B                       | USA, Florida Everglades | Neartic | *Sigmodon hispidus* |
| WWAV<sup>e</sup> | NW-rec-A/B                       | Southwestern USA | Neartic | *Neotoma albigula* |
| **New World arenaviruses (South America)** | | | | |
| ALLIV<sup>e</sup> | NW-A                            | Peru | Neotropic | *Oecomys bicolor* |
| FLEV    | NW-A                            | Brazil | Neotropic | *Oryzomys capito* |
| PARV    | NW-A                            | Paraguay | Neotropic | *Oryzomys bicucnatus* |
| PICV    | NW-A                            | Colombia | Neotropic | *Oryzomys albigularis* |
| PIRV    | NW-A                            | Venezuela | Neotropic | *Sigmodon alstoni* |
| **Lineage A** | | | | |
| AMAV    | NW-B                            | Brazil | Neotropic | *Oryzomys capito* |
| CPXV    | NW-B                            | Brazil, northeastern | Neotropic | *Oryzomys capito* |
| JUNV    | NW-B                            | Argentina | Neotropic | *Calomys musculus* |
| GTOV    | NW-B                            | Venezuela | Neotropic | *Zygodontomys brevicauda* |

(Continued)
Table 2  Phylogeny and rodent vector reservoir ——cont’d.

| Acronym | Evolutionary lineage | Distribution | Biogeographic domain | Reservoir |
|---------|---------------------|--------------|----------------------|-----------|
| MACV    | NW-B                | Bolivia      | Neotropic            | Calomys callosus |
| SABV    | NW-B                | Brazil       | Neotropic            | unknown   |
| TCRV    | NW-B                | Trinidad     | Neotropic            | Artibeus spp. (bat) |
| LATV    | NW-C                | Bolivia      | Neotropic            | Calomys callosus |
| OLVV    | NW-C                | Argentina    | Neotropic            | Bolomys obscurus |

* List: OW Old World; NW New World

*b Listed countries are included on the basis of virus isolation only, no serology

*c One case was probably generated between Ivory Coast and Burkina Faso; the place of origin remains unknown

*d Morogoro virus, which is a genotype of Mopeia virus, has recently been isolated from Mastomys rodents in Tanzania and is under study (Gunter et al., unpublished data)

*e Recombinant lineage as previously reported (Charrel et al. 2001)

Sigmodontinae Wilson and Reeder 2005). The correspondence between the phylogeny of the hosts and of the viruses suggests a long association and co-evolution (Gonzalez 1986a, 1986b; Bowen et al. 1998). TCRV isolated from bats is the only member of the family that is not known to be a chronic, inapparent infection of rodents (Fig. 2).

2  Arenaviruses and Their Natural Hosts

Arenavirus species and rodent species are strongly associated in a specific manner, suggestive of a possible co-evolutionary process. Although the concept of co-evolution between rodents and arenaviruses is now largely accepted within the scientific community, little information has been found in terms of dating the phenomenon and detailed leading mechanisms (Gonzalez et al. 1986b; Bowen et al. 1997, 1998; Charrel et al. 2001) (Table 3).
Cumulated number of new Arenavirus species

![Graph showing the time scale of Arenavirus emergence.](image)

**Fig. 2** The time scale of *Arenavirus* emergence. Each red circle represents the time of the first isolation of a new arenavirus; stars are those pathogenic for humans.

**Table 3** Arenaviruses and their natural reservoir hosts

| Virus   | Place of isolation                  | Primary host, Hp | Secondary host, Hr | Hr, main biotope                  |
|---------|-------------------------------------|------------------|--------------------|-----------------------------------|
| LCMV    | Worldwide                           | *Mus musculus*   | *Apodemus sylvaticus; Mus domesticus* | Domestic environment              |
| LASV    | Nigeria                             | *Mastomys huberti* | *Mastomys erythropleucus* | Savannah and forest galleries     |
| IPPYV   | Central African Republic (north)    | *Arvicanthis niloticus* | *Lemniscomys striatus* | Sudanese dry savanna              |
| MOBV    | Central African Republic (south)    | *Praomys jacksoni* | *Mastomys erythropleucus* | Sub-Sudanese wet savanna          |
| MOPV    | Mozambique, Tanzania                 | *Mastomys natalensis* | *Mastomys huberti* | Dry savanna                        |
| BCNV    | USA, California                      | *Peromyscus californicus* | *Neotoma fuscipes, Peromyscus boylii* | Marshes                           |
| TAMV    | USA, Florida Everglades              | *Sigmodon hispidus* |                     |                                   |

(Continued)
Arenaviruses and their natural reservoir hosts — cont’d.

| Virus | Place of isolation | Primary hosta, Hr / host reservoir, Hr | Secondary hosta, Hp | Hr, main biotope |
|-------|--------------------|---------------------------------------|---------------------|-----------------|
| WWWV  | USA, southwest     | Neotoma albigula                      | Neotomys mexicana, N. cinerea, N. micropus, N. fuscipes |                 |
|       |                    |                                       |                     |                 |
| New World Arenaviruses (South America) |                     |                                       |                     |                 |
| ALLV  | Peru               | Oecomys bicolor                       | Oecomys paricola    |                 |
|       |                    |                                       |                     |                 |
| AMAV  | Brazil, north-eastern Amapa | Oryzomis capito                   | Neacomys guianae, Oryzomis gueldi, Neacomys spinosus | Amazonian tropical forest |
|       |                    |                                       |                     |                 |
| CPXV  | Brazil, north-eastern Amapa | Oryzomis megacephalus               | Oryzomys capito    | Forest          |
|       |                    |                                       |                     |                 |
| FLEV  | Brazil             | Oryzomis capito                       | Oryzomys spp.      | Tropical forest |
|       |                    |                                       |                     |                 |
| JUNV  | Argentina          | Calomys musculus Calomys laucha      | Calomys musculus, Akodon azarae | Extensive agricultural area (corn fields) |
|       |                    |                                       |                     |                 |
| GTOV  | Venezuela          | Zygodontomys brevicaudata             | Sigmodon alstoni, Zygodon longicaudatus |                 |
|       |                    |                                       |                     |                 |
| LATV  | Bolivia, Brazil    | Calomys callosus                      |                     | Low tropical savanna |
|       |                    |                                       |                     |                 |
| MACV  | Bolivia, eastern   | Calomys callosis                      |                     | Low tropical savanna |
|       |                    |                                       |                     |                 |
| OLVV  | Argentina          | Bolomys obscurus                      |                     | Pampa           |
|       |                    |                                       |                     |                 |
| PARV  | Paraguay           | Oryzomys bucinatus                    | Bolomys obscurus    |                 |
|       |                    |                                       |                     | Primary fog forest (eleva- tion 1,500 m) |
| PICV  | Colombia: Cali, Medellin, Popaya | Oryzomys albignula-ris               | Thomasonmys fiscatus, Zygodontomys spp. |                 |
|       |                    |                                       |                     |                 |
| PIRV  | Venezuela          | Sigmodon alstoni                      | Zygodontomys brevicaudata |                 |
|       |                    |                                       |                     |                 |
| SABV  | Brazil, central    | unknown                               | unknown             | Secondary clearing forest |
|       |                    |                                       |                     |                 |
| TCRV  | Trinidad           | Artibeus lituratus palmarum           | Artibeus jamai- censis trinitatus | Tropical forest |

*aPrimary hosts are those most commonly infected in nature by the virus, secondary hosts are those that have been accidentally infected or have been consistently found with reactive antibody to specific arenaviral antigens. The habitat refers to that of the primary host.*
2.1 Co-evolution Process

Specific rodents are the principal hosts of arenaviruses (Childs and Peters 1993; Bowen et al. 1997). Usually one rodent species, less often two closely related species, act as the principal host(s) (virus reservoir) of each arenavirus species, in which natural infection is usually a chronic mild or inapparent infection. The only exception is Tacaribe virus, which has only been associated with a chronic infection of bats. It is now widely recognized that the diversity of arenaviruses is the result of a long-term, shared evolutionary relationship (termed co-evolution or co-speciation) between viruses of the family Arenaviridae and rodents of the family Muridae (Johnson et al. 1965; Gonzalez 1986a; Bowen et al. 1996). The time scale of the co-evolutionary divergence of specific arenaviruses and their rodent hosts is still under discussion. From our observations and analyses, we strongly favor an ancient co-evolutionary process with several transfers, parallel and diffuse evolution. Our hypothesis is that an ancestral arenavirus type was chronically infecting a common rodent ancestor before New World sigmodontine and Old World murids diverged, approximately 35 million years before the present (Mybp). Each lineage (i.e., New World sigmodontine and Old World murid rodents) evolved independently with their own arenaviruses (co-evolution and co-speciation) resulting in a specific association between rodent species and arenavirus type, as we see today. In addition, when rodent and virus phylogenies are compared, major rodent subfamilies (Sigmodontinae and Murinae) correspond with the major arenavirus clades (i.e., New World arenaviruses vs Old World arenaviruses). A similar association is also evident among South American arenavirus strains and among the South American neotropical Sigmodontiae due to the same evolutionary processes. However, discrepancies from the general hypothesis of co-evolution have also been observed, suggesting that spillover from one species or genus to another might occur, and that genomic segments might also be exchanged in some instances (Gonzalez et al. 1986b, 1996a, 1996b; Hugot et al. 2001). Thus the emergence of new virus types and pathogen transmission to humans appears likely to be associated with specific rodent species and their ecology and behavior (Figs. 3, 4).

2.2 A Brief Ancient History of Rodents

We use the most common theory on rodent radiation to support part of our hypothesis. From the Eurasian continent, cricetid rodents, ancestors of murid rodents, spread into the Americas, and then, from Asia, murid rodents spread to Europe and Africa. The term “murid” corresponds to the Murinae subfamily of the family Muridae (Wilson and Reeder 2005). The term “sigmodontine”
refers specifically to New World rodents of the subfamily *Sigmodontinae* of the family *Muridae* (previously classified as being in the family *Cricetidae*) and includes the New World rats and mice. As early as the Eocene, 65 Mybp, a rodent ancestor bearing *Muridae* characters, *Simimys*, was recognized within North America. During the Oligocene (37 Mybp), the *Muridae* distribution became holoartic. The New World *Sigmodontinae* colonized the Americas by waves of migration northward and southward. As a result, the sigmodontine fauna of South America derived from North America and today, the South
Fig. 4  Phylogeography of New World arenaviruses. The geographic distribution is shown for three indigenous arenaviruses from North America and 14 indigenous arenavirus types from of South America.
American group can be distinguished from the less diversified sigmodontine rodents of genera such as Neotoma and Peromyscus of North America.

In Asia, murid rodents probably came from North America and were present during the Oligocene (35 Mybp). Arising from an original pool, successive waves of murids spread to Europe during the late Miocene (15 Mybp), but there was only a limited extension into Africa where they became underrepresented.

From Asia, murid rodents spread around the Mediterranean basin to Europe approximately 14 Mybp. During that period, the subfamily Murinae extended from Europe into North Africa and rapidly became the most widely distributed rodents in Africa.

From the Pleistocene era (2 Mybp), murid rodents were present in northern Africa. They then spread southward, although their species radiation was severely influenced by arid climate and geomorphology. During that time, speciation reached its highest point influenced by climate variation and physical isolation because of physical barriers such as the Rift Valley and the division of the African continent by the Sahara. More recently, humans have played an important role in the spread of rodents, particularly commensal species such as Mus. Some rodent genera from the Pleistocene are still present in East Africa, while others from North Africa have disappeared. However, it likely that murid ancestors were very closely related to the present extant genera (Gonzalez 1996a) (Fig. 5).

**Fig. 5** The rodent migration and emergence and spread of arenaviruses and their rodent hosts. Rodent expansion shows the path of virus dispersion. The subfamilies Murinae and Sigmodontinae are indicated by red and blue, respectively, by the approximate time of expansion and speciation. After 34 Mybp (Oligocene), the Eurasian continent became colder and arid with a general shrinking of forest cover; 30 Mybp, rodents probably emerged from Central Eastern Asia and started their Asian radiation journey through Europe. Temperature changes and warmer periods (15 Mybp) would have helped separate the original rodent lineages of Asia and Europe and further their spread in Africa and the Americas. However, back-migrations occurred by way of the Bering Strait and other land bridges such as the Panamanian isthmus in the Americas.
2.3 Rodent Migration Within the Americas and an Astonishing Diversity

Comparative phylogenetic analyses of N and GPC proteins showed that the three North American arenaviruses (Whitewater Arroyo, Tamiami, Bear Canyon) group together; however, depending upon the gene used for analysis, these viruses group within different lineages. They are more closely related to lineage A viruses in N protein-based analyses, whereas they are more closely related to lineage B viruses in GPC protein-based phylograms. This suggests that WWA, TAMV, and BCNV share a common ancestor, which must have been a recombinant of lineages A and B (Fig. 6).

According to the history of rodent migrations within America, rodents migrated across the Panamanian isthmus, from North America to South America, where rodent diversification was able to expand explosively because of the absence of predators and highly favorable ecological conditions. It is postulated that recombination events among arenaviruses most likely occurred in South America and the resulting chimeric viruses were then introduced into North America during the back migration of certain rodent populations.
Fig. 7 Rodent migration and American arenavirus recombinations. Rodent diffusion in the Americas. Blue arrow shows the first migration of murids from North to South America, corresponding to the split between Old World and New World rodents, estimated at 35 Mybp. First migration from North to South America estimated at 15 Mybp. Purple ovals indicate rodent speciation in South America (an explosive radiation of species, 10 Mybp), and arrows indicate the back-migration (across the Panamanian land bridge between 10 and 8.6 Mybp) of extant rodent species into Central and North America harboring recombinant arenaviruses (Fig. 8)

(e.g., Sigmodon spp.) across the Panamanian land bridge. Although dating the period of recombination is difficult because of controversial data for time estimation of rodent migrations, the paleobiogeography of sigmodontines suggests that recombination could have occurred as far as back as 10 Mybp (Engel et al. 1998) (Fig. 7, 8).

2.4 Mechanisms of Virus Evolution

There are three possible mechanisms driving the evolution of arenaviruses: (1) accumulation of point mutations; (2) intersegmental reassortment; and (3) intrasegmental recombination.

2.4.1 Accumulation of Mutations

In the Arenaviridae family, the accumulation of mutations appears to be the mechanism most often responsible for virus diversity observed between isolates within a given viral species. By analogy to other RNA viruses, it is believed that mutations are caused by the absence of proofreading activity of the viral RNA-dependent RNA polymerase during virus replication. With respect to the
rate at which rate mutations are produced and accumulated in arenaviruses, experimental data generated in vitro with a partial region of the polymerase of LCMV suggest mutation frequencies ranging from 1.2 to $3.5 \times 10^{-4}$ substitutions per nucleotide per genome replication (Grande-Perez et al. 2005). These mutations lead to the generation of virions exhibiting various fitness patterns, and only the best-adapted virions are presumably selected and maintained. The factors driving the selection are multiple and complex and change over time. The occurrence of mutations together with natural selection account for the creation of the genetic diversity observed within a virus species.

2.4.2 Intersegmental Recombination (Reassortment)

Reassortants of arenaviruses have been generated experimentally (Lukashevich et al. 1992; Rivière and Oldstone 1986), with the genome of the reassortant virus containing one genomic segment from each parent. This mechanism has not been described in nature so far for arenaviruses. Experimental generation of a reassortant arenaviruses consisting of the L RNA segment of Mopeia virus and the S RNA segment of Lassa virus has demonstrated that an exchange of genetic material is possible despite a genetic diversity of 28% at the amino acid level (Lukashevich et al. 1992). It is worth noting that these reassortant viruses...
were produced by co-cultivation on Vero cell monolayers, without the use of sophisticated equipment or complicated molecular techniques. During the current atmosphere of heightened bioterrorism surveillance, this data would suggest that the generation of chimeric viruses is not so complicated and may be attempted with very basic equipment.

Recently, fatal cases of acute hemorrhagic fever in Kenya and Somalia have been attributed to a reassortant bunyavirus—the family Bunyaviridae contain tri-segmented genomes—comprising genomic segments from Bunyamwera virus and from a novel bunyavirus; both were previously unknown as etiologic agents of hemorrhagic fever (Gerrard et al. 2004; Bowen et al. 2001). Bunya-virus reassortment under laboratory conditions had previously documented that exchange of M segments of LaCrosse (LACV) and Snowshoe Hare (SSH) viruses created chimeric viruses; those containing the M segment of LACV, irrespective of S and L segments of SSHV, showed an enhanced capability to disseminate and be transmitted by Aedes triseriatus mosquitoes (Beaty et al. 1982; Beaty et al. 1981). These field and laboratory findings highlight the ability of viral reassortment in creating a chimeric new virus that exhibits increased pathogenicity for humans (as compared to the two parental strains) or specific, novel biologic properties (not displayed by the parental strains).

To identify virus reassortment, complete sequence characterization of viral genomes is a necessary prerequisite. Until recently, the lack of genetic data for the L segment of arenaviruses in all but a handful of virus species hampered the quest for identifying natural reassortment. Recently, however, large genomic programs dedicated to arenaviruses have provided significant sequence data sets containing the complete genomes of almost all arenaviruses. Subsequent sequence analyses and phylogenetic studies, however, were unable to detect any evidence of the natural occurrence of reassortment among arenavirus species, despite an exhaustive search using full-length genomes. Thus, although demonstrated experimentally, it is believed that reassortment may not play a major role in evolution of the Arenaviridae.

2.4.3 Intrasegmental Recombination

Intragenic recombination is one of the well-documented mechanisms of evolution of positive-strand, double-stranded and negative-strand RNA viruses (Lai 1992; Hahn et al. 1998; Wörobey et al. 1999; Desselberg et al. 1986; Suzuki et al. 1998; Bergman et al. 1992; Orlich et al. 1994; Sibold et al. 1999). Intrasegmental recombination was recently demonstrated for the three North American arenaviruses (WWAV, TAMV, and BCNV) (Charrel et al. 2001, 2002, Archer and Rico-Hesse 2002), indicating common derivation from a recombinational
event between ancestors in both lineage A and lineage B viruses. Analysis of complete genome sequences for all recognized members of the genus Arenavirus suggest that there are no other examples of intrasegmental recombination. Since these three viruses possess a common ancestor as demonstrated by phylogeny, recombination most likely occurred in this ancestor. It is important to note that recombinant arenaviruses are able to infect humans (Kosoy et al. 1996). Whether they cause disease in infected individuals is still not clearly established; however, three cases of fatal human infections associated with Whitewater Arroyo virus have been reported in California (CDC 2000).

2.4.4
Evolutive Significance of Interspecies Recombination

The evidence for recombination deduced from the genetic analysis of the genomic S RNA raises major questions concerning the nature of situations that may be conducive to intragenic recombination:

2.4.4.1
Co-infection of the Same Rodent by Two Different Arenaviruses Belonging to Distinct Phylogenetic Lineages

In nature, since arenaviruses can establish chronic infections among their rodent hosts, the more likely scenario for interspecific genome recombination would involve superinfection of a rodent already chronically infected with one arenavirus by a second distinct arenavirus. This hypothesis requires the co-existence of distinct arenaviruses in the same geographic area and this situation is present within several regions of a number of countries. For example, the principal hosts of OLLV, JUNV, and LCMV are rodents of the species Necromys benefactus (formerly Bolomys obscurus; Wilson and Reeder 2005), Calomys musculinus and Mus musculus, respectively. These three species and three other common rodent species exist sympatrically in rural regions of Argentina (Mills et al. 1996). Studies of the dynamics of OLLV infection among rodents indicate that dual infections by JUNV and OLLV viruses may occur at low frequency among three species of rodents (N. benefactus, Akodon azarae, and M. musculus) based on comparative IFA titers obtained against specific arenaviral antigens.

Additionally, there is evidence that the principal host for a specific arenavirus can be naturally infected with a different arenavirus associated with a sympatric rodent species. For example, Sigmodon alstoni, the principal host of PIRV (lineage A) can naturally be infected with GTOV (lineage B) (Fulhorst et al. 1999b). Moreover, experimental data have shown that immunization of rodents
with a virus belonging to a given lineage is poorly protective against infection by viruses belonging to different lineages (Weissenbacher et al. 1975). Consequently, although mixed infections of rodents with distinct arenaviruses have not been reported in the literature, field and experimental data suggest that infections by arenaviruses of different lineages are plausible.

2.4.4.2 Co-infection of One Cell by Two Viruses

Experiments performed in cell cultures have clearly established that co-infection of a single cell by two distinct arenaviruses is possible (Bishop et al. 1980; Rivière et al. 1985; Rivière and Oldstone 1986; Whitton et al. 1988; Lukashevitch 1992). This co-infection could potentially allow the generation of recombinant RNA molecules by template switching of the RNA polymerase. According to this mechanism, the RNA polymerase would jump from one template to another during RNA processing, generating a chimeric RNA molecule including sequences inherited from the two parental strains.

Thus, in summary, our current knowledge concerning the ecology of rodents infected by arenaviruses and the natural circulation of these viruses in the New World, together with experimental data, would suggest that recombination between arenaviruses belonging to different lineages could potentially occur in nature. Furthermore, the recombinant nature of the genome of the 3 arenavirus indigenous to North America (WWAV, TAMV, BCNV) suggests that their ancestor may have been endowed with a selective advantage, facilitating the maintenance and transmission of the recombinant over time. This finding reinforces the fact that future phylogenetic analyses of arenaviruses should be based on complete genomic sequences to allow the identification of recombination and/or reassortment events and therefore a better understanding of the processes of co-speciation and the occurrence of crossing-over or reciprocal recombination.

3 From Enzootic to Epidemic: Arenavirus Ecology and Human Health

Persistent infection of the rodent host appears to be a crucial phenomenon in the long-term persistence of the arenaviruses in nature. Infection in the rodent host is associated with a chronic or sporadic viremia and/or viruria and sometimes a life-long shedding of the virus into the environment. The course of the infection is determined by factors such as the age, genetic make-up, immunological resistance, and history of prior infection within the rodent host, but also by the infecting virus strain. Neonatally infected rodents
usually become chronic carriers of virus and excrete the virus for a long time (throughout life) in their urine. Virus transmission within rodent populations can occur through three mechanisms: (1) vertical (dam to progeny) transmission, (2) horizontal transmission through direct or indirect contacts, and (3) a balanced combination of both mechanisms. Female rodents infected as neonates with certain arenaviruses (JUNV, MACV) may show reduced fertility or suffer decreased litter sizes (Childs and Peters 1993; Webb et al. 1975); additionally, neonates born to infected dams may experience stunted growth. Accordingly, the persistence of these arenaviruses within a rodent population requires some degree of horizontal transmission. In contrast, other arenaviruses that do not cause infertility, such as certain strains of LCMV (Childs and Peters 1993), can be maintained in a rodent population exclusively by vertical transmission.

Humans usually become infected by arenaviruses through direct contact with infected rodents, including bites, through inhalation of infectious rodent excreta and secreta. The domestic and peridomestic behavior of several species of rodent reservoir hosts is a major contributing factor facilitating viral transmission from rodent to human. Transmission of arenaviruses to humans occurs following recreational or agricultural incursions into environments providing critical habitat for rodent hosts. Additionally, professionals handling infected rodents in the field or laboratory are at increased risk of infection (Sewell 1995). Modifications of the environment driven either by human activities, such as modern farming practices, or ecological changes, such as flooding, have been implicated in the emergence of human disease caused by arenaviruses.

Nine arenaviruses are associated with human diseases. LASV, JUNV, MACV, GTOV, and SABV are known to cause a severe hemorrhagic syndrome, in western Africa, Argentina, Bolivia, Venezuela, and Brazil, respectively (Peters et al. 1996). They are highly infectious, virulent pathogens and all are listed on the Category A Pathogen List (as defined by the CDC); such agents can only be handled in Biosafety Level 4 (BSL-4) laboratories. Infection by LCMV can result in acute central nervous system disease and congenital malformations (Barton and Hyndman 2000; Barton et al. 1993). Very little is known about the health consequences of infection with the other arenaviruses: PICV infection has resulted in numerous seroconversions among humans without any notable clinical significance; FLEV has resulted in two symptomatic laboratory infections and should be regarded as dangerous (F. Pinheiro, unpublished data); TCRV virus has caused a single case of a febrile disease with mild CNS symptomatology (J. Casals, unpublished data) (Peters et al. 1996; Karabatsos 1985; Buchmeier et al. 1974). WWAV has recently been associated with three fatal cases of infection in California (CDC 2000).
3.1 Lymphocytic Choriomeningitis Virus

The first arenavirus to be isolated was LCMV, which was discovered in 1933 during the investigation of an epidemic of St. Louis encephalitis in the USA. In regions where LCMV is known to exist, infection in the two closely related reservoir species hosts, *Mus domesticus* and *M. musculus*, is highly focal (Lehmann-Grube 1971). Studies conducted in Baltimore, Boston, and Washington, DC, revealed a spotty distribution of virus-positive mice in houses (Farmer et al. 1942; Childs et al. 1991, 1992). Similarly, in Germany, much higher infection rates prevail among *Mus* in the west-central region than in the southern or northern portions of the country (Ackermann et al. 1964). Human cases of LCMV infection are most common in autumn. This pattern is the result of peak seasonal population densities of rodents and the movement of house mice into homes and barns with the onset of cold weather. In addition, seasonal variation in infection rates of *Mus* sp. may occur. Situations associated with transmission of virus from infected wild mice to humans include substandard housing such as mobile homes or inner city dwellings, the cleaning of rodent-infested barns or outbuildings, and the autumn entry of wild mice into dwellings. Most human LCMV infections occur among young adults, although persons of all ages have been affected. The mode of transmission in most sporadic human infections is not definitely known; however, experimental and epidemiologic observations implicate aerosols, direct contact with rodents, and rodent bites (in that order) as the most likely vehicles (Enria et al. 1999; Farmer et al. 1942; Hinman et al. 1975). Although most sporadic LCM cases are attributed to contact with infected wild mice, outbreaks of disease have been traced to infected laboratory mice and Syrian hamsters (*Mesocricetus auratus*) (Dykewitz et al. 1992). Individual cases or outbreaks of LCM in the United States and Europe have resulted from exposures to infected pet hamsters (Biggar et al. 1975; Ackermann et al. 1972). Recently, a case of LCMV infection in France was traced back to a population of urban *Mus musculus*; virus isolates were obtained from 60% of the mice trapped in the patient’s home (R. Charrel et al).

Although LCMV infection may occur worldwide wherever the house mouse has been introduced, human infection has been conclusively demonstrated only in Europe and the Americas (Lehmann-Grube 1971). LCM cases present most commonly as febrile illnesses with headache and systemic symptoms; leukopenia and thrombocytopenia are usually noted (Peters et al. 1995). After 3–5 days of nonspecific illness, the fever subsides, but it frequently recurs in 2–4 days with several days of even more severe headache. Patients may exhibit meningitis during this second febrile period. In approximately one-third of the cases, cerebrospinal fluid (CSF) exhibits lymphocytic pleocytosis, an elevated protein
content, and hypoglycorrhachia. Sometimes there is more severe damage to the central nervous system (CNS) and transient hydrocephalus has been described. Chorioretinitis and congenital hydrocephalus may occur in fetal infections. The second febrile episode, as well as some of the complications of convalescence, have long been thought to represent immunopathologic phenomena, and antibodies detectable by immunofluorescence appear at about this time (Peters et al. 1995). The prevalence of antibody to LCMV is approximately 5% among adults living in large cities of the United States (Childs et al. 1991). Both CNS and congenital infections caused by LCMV may be more common than appreciated and are undoubtedly underdiagnosed (Enria et al 1999; Barton 1996, 2001).

In 2005, LCMV caused an outbreak of infection among four patients who had received solid organ transplants from an infected donor. Severe illness developed in all four patients, three of whom died (CDC 2005). The donor was probably infected from his pet hamster.

### 3.1.1 South American Arenaviral Hemorrhagic Fever

The clinical picture of the South American arenaviral hemorrhagic fever is almost identical regardless of the virus responsible for the disease. Argentine, Bolivian, and Venezuelan arenaviral hemorrhagic fevers are remarkably similar clinically, and mortality in each is about 15%–30% (Sabattini et al. 1970; Maiztegui et al. 1975; Stinebaugh et al. 1966). The disease caused by all three viruses can include neurological symptoms, hemorrhage, and shock; these clinical findings herald a poor prognosis.

#### 3.1.1.1 Argentine Hemorrhagic Fever: Junin Virus

The rodent host reservoir of JUNV is *Calomys musculinus*, a small field rodent of Argentina (Sabattini and Maiztegui 1970). *Calomys* populations reach their highest densities in cornfields and the surrounding weedy fence lines during the austral fall. In the 1950s, a new disease (Argentinean Hemorrhagic Fever, AHF) emerged in the Buenos Aires province of Argentina, a rich farming region, and was associated with intensive deforestation and intensive agricultural practices that considerably increased the contacts between humans and rodents. Most of the infected persons were male agricultural workers engaged in harvesting corn. Transmission from the rodent is by inhalation of infected aerosols produced from rodent excreta or from rodents caught and shredded in mechanical harvesters (Maiztegui 1975). As a consequence, infection with JUNV is strongly seasonal and peaks during the harvest season in autumn. Since the emergence
of AHF, a progressive geographic expansion of epidemic outbreaks, occurring at variable intervals, has been observed (Maiztegui 1975; Maiztegui et al. 1986). After its first isolation in 1959, human cases were initially recorded within a 16,000-km² area of the rich agricultural pampas north of Buenos Aires province, but AHF progressively expanded to become endemic in a 150,000-km² area in southern Santa Fé, southeastern Córdoba, and northeastern La Pampa provinces (Enria and Feuillade 1998). To date, the human population at risk is estimated to be about 5 million. Several hypotheses were proposed to explain this expansion. Since 1958, cases have been annually recorded, ranging from several hundred to 3,500. An epidemic outbreak of human AHF in southern Santa Fé and northern Buenos Aires provinces was shown to coincide, with a lag of 1–2 months, with the peak density in a rapidly increasing population of *C. musculinus*. The maximum prevalence of JUNV antigen-positive rodents, approximately 25% of adult *C. musculinus*, coincided with peak rodent population density (Mills et al. 1992).

Although human cases present with either neurologic or hemorrhagic manifestations (or a combination of both), molecular studies of JUNV have not associated either syndrome with a particular JUNV genotype (Albarino et al. 1997). Studies of the genetic diversity among JUNV strains circulating in central Argentina demonstrated a high degree of genetic similarity among isolates from the same locale. However, no cluster of related JUNV strains was associated with clinically different forms of AHF (García et al. 2000). Mortality among patients with confirmed AHF was 14%–17% before the routine initiation of immune plasma was implemented (Maiztegui et al. 1979); treatment has reduced the mortality to less than 1%. Introduction of an effective vaccine, using a live-attenuated virus (Candidate#1) (Maiztegui et al. 1998), has decreased the incidence of the AHF to fewer than 100 cases per year (Enria et al. 2002).

### 3.1.1.2 Bolivian Hemorrhagic Fever: Machupo Virus

The rodent species *Calomys callosus* is the reservoir host of MACV, the agent of Bolivian hemorrhagic fever (BHV) (Johnson et al. 1966). As with JUNV, the dynamics of the rodent population determine the epidemiological features of disease outbreaks among humans (Mercado et al. 1975). In contrast to the rodent host of JUNV, *C. callosus* invades houses during the rainy season, resulting in human cases with identical attack rates among all ages. However, on remote ranches and in fields, adult male patients predominate. A series of outbreaks from 1962 to 1964 in the sparsely populated province of El Beni in northeast Bolivia, involved more than 1,000 patients, 180 of whom died; an increase of rodents invading small towns was coincidentally reported. Transmission was interrupted by a targeted campaign to reduce the rodent population within affected towns.
Bolivian hemorrhagic fever is restricted to the tropical savanna of Beni province and recent investigations have shown that the populations of rodents responsible for the maintenance and transmission of MACV are an independent monophyletic lineage, different from those in other areas of South America (Salazar-Bravo et al. 2002).

The incidence of BHF cases is greatest between April and July (late rainy and early dry season), but the dominant epidemiologic feature is that of small outbreaks in different villages and ranches, with several years of quiescence thereafter. Transmission is thought to occur by aerosols from infected rodents or possibly by contact with food contaminated by infected rodent urine. Most of the recorded infections were acquired by direct contact with *C. laucha* or by aerosol through infected excreta. However, nosocomial transmission of MACV has been clearly demonstrated (Peters et al. 1971; Kilgore et al. 1995). Nosocomial outbreaks have been associated with a single index case who had visited a BHF endemic region. The only recognized hospital-based outbreak resulted in four secondary cases followed by a tertiary case acquired from a necropsy incident; all but one person died. Recently, an epidemic was reported in which seven members of the same family were infected, six of whom died (CDC 1994).

### 3.1.1.3 Venezuelan Hemorrhagic Fever: Guanarito Virus

In 1989, cases of hemorrhagic fever in the central plains of Venezuela were associated with a new *Arenavirus*, designated Guanarito virus after the region where the first outbreak occurred (Salas et al. 1991). The main affected population was settlers moving into cleared forest areas to practice small-scale agriculture. Since its discovery, GTOV has been responsible for at least 200 cases of VHF. For unknown reasons, the number of reported human cases has spontaneously dropped since 1992, although rodent infection can still be readily demonstrated within and beyond the boundaries of the original endemic zone (Weaver et al. 2001). Natural and experimental data initially suggested that two different rodent species were involved in the transmission cycle of GTOV in nature; the cane rat (*Zygodontomys brevicauda*) and the cotton rat (*Sigmodon alstoni*) (Fulhorst et al. 1999a, 1999b; Tesh et al. 1993). Recently, *Z. brevicauda* has been shown to be the primary reservoir host as it develops a persistent infection with lifelong viruria, accompanied by either low or undetectable levels of antibody. In contrast, the cotton rat has characteristics of an intermediate host infected by spillover of GTOV from cane rats, as it produces neutralizing antibodies and excretes virus for only a limited time.

Research undertaken to better understand the geographic distribution and potential variation in GTOV circulating in the VHF-epidemic area of western Venezuela resulted in the genetic sequencing of 29 isolates of GTOV obtained...
from rodents and humans (Weaver et al. 2000). Nine genotypes of GTOV were distinguished, all of which, with the exception of the dominant genotype, were restricted to very small geographic areas. All but one of the strains obtained from humans belonged to the dominant genotype. Closely related strains of the dominant GTOV genotype were obtained from a large area covering approximately 75,000 km² (Tesh et al. 1993, 1999). A single rodent could be infected by a virus population varying less than 0.5% at the nucleotide level (a low-diversity quasispecies). In contrast, the dominant GTOV strain infecting humans was invariant. Human disease was not associated with a unique genotype restricted to a particular rodent host species. However, overall, the available data are insufficient to conclude whether or not certain genotypes are more pathogenic and/or infectious for humans than others. The limited mobility of rodents in isolated metapopulations could account for the coexistence of independent virus lineages without mixing and competitive exclusion.

3.1.1.4
Brazilian Hemorrhagic Fever: Sabia Virus

Sabia virus has caused a single natural human infection that was fatal, and also two none fatal laboratory infections (Coimbra et al. 1994; Barry et al. 1995). No reservoir host has yet been identified.

3.1.1.5
Lassa Fever: Lassa Virus

Lassa fever is named after a small town in Nigeria, where the first epidemic was described in 1969 (Buckley and Casals 1970). LASV is associated with rodents belonging to the genus Mastomys (sometimes referred to as Praomys), which are widely distributed in sub-Saharan Africa. In the regions where LASV is endemic, up to 30% of Mastomys rodents can carry the virus (Keenlyside 1983). Lassa virus is responsible for an estimated 100,000–300,000 infections and approximately 5,000 deaths annually (McCormick et al. 1987). To date, cases have been reported from Nigeria, Liberia, Sierra Leone, Guinea, Burkina Faso, Ivory Coast, Ghana, Senegal, Gambia, and Mali. Among hospitalized patients, mortality is estimated at 15%–20% (Webb et al. 1986). Serologic surveys suggest that subclinical cases also occur (McCormick et al. 1987). Lassa fever occurs through direct or indirect contact with infected rodents. A number of cases acquired by local residents have been associated with the capture and handling of rodents for consumption (Ter Meulen et al. 1996).

Imported cases of LASV infection among travelers returning from endemic locations have been reported from England, Germany, Japan, the Netherlands, Israel, and the United States.
Nosocomial transmission is a common feature of Lassa fever, and many hospital-based outbreaks have been described (Keenlyside et al. 1983, Fischer-Hoch et al. 1995). However, it is apparent that this aspect of Lassa fever has been overestimated in reports based on infections in hospitals. The additional risk to hospital workers within the endemic zone is not great, as judged by serosurveys, providing that basic hygiene measures are maintained in hospitals dealing with suspected cases (Helmick et al. 1986). Nosocomial cases have been reported only in hospital settings where basic hygiene measures were not enforced. Arenaviruses readily invade the fetus, whether in their natural rodent reservoir, laboratory animals, or humans. Pregnant women infected with LASV often abort and have a high mortality rate; similar observations have been made for Argentinian and Bolivian HF’s (Price et al. 1988).

4 Prevention and Control

Prevention of arenaviral disease consists of interrupting the transmission of virus from rodents to humans, from humans to humans, and from infected specimens to laboratory personnel. Strategies for reducing contact between rodents and humans have been effective in the control of outbreaks of BHF; trapping and removal of C. callosus in towns reduced the incidence of disease to essentially zero. Rodent intervention strategies have proven more difficult for preventing AHF as conditions under which human exposure occurs are primarily rural and associated with the harvesting of corn. The geographic distribution C. musculinus (reservoir host of JUNV) is much wider than C. callosus (reservoir of MACV), and Argentinian agricultural practices continue to place workers at risk of exposure to reservoir hosts.

A collaborative effort undertaken by the US and Argentine governments led to the production of a live attenuated Junin virus vaccine named Candid#1. Its efficacy was proven in a double-blind trial in 15,000 agricultural workers at risk to natural infection in Argentina. Subsequently, more than 100,000 people were immunized with JUNV vaccine in Argentina. A prospective study conducted over two epidemic seasons among 6,500 male agricultural workers in Argentina showed that Candid #1 vaccine efficacy was greater or equal to 84%, and no serious adverse effects were detected (Maiztegui et al 1998).

Recent animal protection studies suggest that the JUNV vaccine could be protective against MACV infections as well. However, attenuated JUNV strains do not protect experimental animals against GTOV challenge. Rhesus monkeys (Cercopithecus aethiops) challenged with purified inactivated LASV developed humoral antibody responses comparable to that among humans who recovered from Lassa fever. However, these monkeys were not protected when
challenged with LASV and died following exposure. A naturally attenuated strain of MOPV from Mozambique protects rhesus monkeys against LASV challenge, but field studies are required to establish the extent and nature of natural human infections with this virus before it can seriously be considered a candidate for human vaccine development. Alternative approaches, including the use of vaccinia virus vectors bearing the LASV GPC or N genes, are being actively investigated and show promising preliminary results.

5 Conclusion

Arenaviruses and their rodent hosts share a common ancient history and the extant diversity of arenaviruses probably evolved through the processes of co-evolution, co-speciation and virus recombination. One can clearly distinguish four major clades of extant arenaviruses which are distributed either in the Old World (including Europe, Africa, and Asia) or the Americas. These observations are congruent with the ancient history of rodents mirroring the ancient paths and spread of Arenavirus ancestors. Such a model of co-evolution between parasite and specific hosts appears to apply to other viral groups such as the hantaviruses (Gonzalez 1996a) and Simian immunodeficiency virus (Kuhman et al. 2001). Two new arenaviruses have been recently discovered in Africa: the Morogoro virus isolated from Mastomys natalensis in Tanzania, and related to Mopeia virus, and the Kodoko virus detected in pigmy mice (Mus Nannomys minutoides) from Guinea. This findings together with the fact that arenavirus have coevolved with their rodent hosts strongly supports that many arenaviruses remain to be discovered not only in Europe, Americas and Africa, but also in Asia and Oceania.

Arenaviruses infect a variety of rodent hosts in which they are often nonpathogenic, whereas several are highly pathogenic for humans, resulting in severe hemorrhagic or neurological syndromes in that accidental host. Since their discovery in the early 1930s, new arenaviruses have been discovered and/or have emerged as human pathogens. As co-evolution and co-speciation occur over a long geological period, recombination appears more likely to occur in the short term and may be potentially most important in giving rise to human pathogenic strains.

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