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AFRICAN ARENAVIRUSES – COEVOLUTION BETWEEN VIRUS AND MURID HOST?

JAMES N. MILLS, MICHAEL D. BOWEN AND STUART T. NICHOL
Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, Department of Health and Human Services, Atlanta, Georgia, USA, 33033.
email: jum0@cdc.gov

Abstract. The Arenaviridae is a family of enveloped, negative-stranded RNA viruses which cause severe hemorrhagic fever in humans in areas of Africa and South America. Each arenavirus is generally associated with a single small-mammal host species in which it establishes a chronic infection involving shedding of virus in secretions and excretions. Infection in humans occurs via inhalation of aerosolized virus or ingestion or direct contact with food or fomites contaminated with infectious animal wastes. Genetic analysis shows that known arenaviruses fall into a New-World and an Old-World complex. New-World arenaviruses are associated with species of the rodent subfamily Sigmodontinae and Old-World viruses with the subfamily Murinae. This pattern suggests that an ancestral arenavirus was associated with an ancestral murid rodent before the two subfamilies diverged > 20 million years ago, and that distinct arenaviruses may have coevolved with murid species since that time. If this hypothesis is true, the phylogeny of the arenaviruses should mirror the phylogeny of their rodent hosts. Although the prediction of coincidence of host and virus phylogenies is supported for another group of viruses with murid hosts (the hantaviruses), a comparison of arenavirus and host phylogenies reveals several important inconsistencies. These irregularities may reflect cross-taxon transfer of viruses as well as the relatively incomplete knowledge of the systematics of African and South American murids. Doubtless, many more arenavirus/host associations remain to be discovered within Africa. Continued studies of the relationships among African murids and collaboration between mammalogists and virologists are important to the development of both disciplines.

Key words: Arenavirus, Arenaviridae, hemorrhagic fever, Lassa fever, coevolution, *Mastomys*.

INTRODUCTION

The Arenaviridae is a family of enveloped, negative-stranded RNA viruses. Arenaviruses are responsible for severe hemorrhagic fever in humans on two continents. The South American arenaviruses that are pathogenic for humans include Junín, Machupo, Guanarito, and Sabiá viruses. Junín and Machupo viruses are the etiologic agents of Argentine and Bolivian hemorrhagic fevers, respectively. Sabiá virus has been responsible for a single, naturally acquired, fatal case of hemorrhagic fever in São Paulo State, Brazil. Lymphocytic choriomeningitis virus (LCMV) is widespread in both the New and Old Worlds. LCMV usually produces a syndrome of fever, myalgia, and leucopenia, although, occasionally, severe encephalitis may ensue. The only African arenavirus known to cause human disease is Lassa virus, the etiologic agent of Lassa fever. There is also a large group of arenaviruses which are not associated with human disease, for a total of

TABLE 1

Arenaviruses associated with rodent hosts of the family Muridae

Virus	*Host*	*Known Distribution of Virus*	*Disease*	*Reference*
A. Subfamily Murinae				
Lymphocytic choriomeningitis	*Mus musculus* L., 1758	Europe, Americas, perhaps worldwide	Lymphoctic choriomeningitis	ARMSTRONG & LILLIE 1934
Lassa	*Mastomys* spp.	West Africa	Lassa fever	FRAME *et al.* 1970
Ippy	*Arvicanthis* spp.?	Central African Republic	None recognized	SWANEPOEL *et al.* 1985
Mopeia	*Mastomys natalensis* (Smith, 1834)	Mozambique, Zimbabwe	None recognized	WULFF *et al.* 1977
Mobala	*Praomys jacksoni* (De Winton, 1897)	Central African Republic	None recognized	GONZALEZ *et al.* 1983
B. Subfamily Sigmodontinae				
Junìn	*Calomys musculinus* (Thomas, 1913)	Central Argentina	Argentine hemorrhagic fever (AHF)	PARODI *et al.* 1958
Machupo	*Calomys callosus* (Rengger, 1830)	Beni Department, Bolivia	Bolivian hemorrhagic fever (BHF)	JOHNSON *et al.* 1965
Guanarito	*Zygodontomys brevicauda* (Allen and Chapman, 1893)	Central llanos, Venezuela	Venezuelan hemorrhagic fever (VHF)	SALAS *et al.* 1991 FULHORST *et al.* in press
Sabiá	Unknown	Near Sao Paulo, Brazil	Not named	COIMBRA *et al.* 1994
Amaparì	*Neacomys guianae* (Thomas, 1905) *Oryzomys capito* (Olfers, 1818)	Amapa Territory, Brazil	None recognized	PINHEIRO *et al.* 1966

Flexal	*Oryzomys* spp.?	Pará State, Brazil	None recognized[a]	Pinheiro *et al.* 1977
Latino	*Calomys callosus*	Beni Department, Bolivia	None recognized	Webb *et al.* 1973
Oliveros	*Bolomys obscurus* (Waterhouse, 1837)	Central Argentina	None recognized	Mills *et al.* 1996 Bowen *et al.* 1996
Paraná	*Oryzomys buccinatus*? (Olfers, 1818)	Missiones Province Paraguay	None recognized	Webb *et al.* 1970
Pinchindé	*Oryzomys albigularis* (Tomes, 1860)	Columbia	None recognized	Trapido & Sanmartin 1971
Pirital	*Sigmodon alstoni* (Thomas, 1881)	Central Llanos, Venezuela	None recognized	Fulhorst *et al.* in press
Tacaribe	Unknown[b]	Trinidad	None recognized[a]	Downs *et al.* 1963
Tamiami	*Sigmodon hispidus* (Say and Ord, 1825)	South Florida	None recognized	Calisher *et al.* 1970
Whitewater Arroyo	*Neotoma albigula* (Hartley, 1894)	SW USA	None recognized	Fulhorst *et al.* 1996 Kosoy *et al.* 1996

[a] One documented laboratory infection

[b] Original report lists bats from the genus *Artibeus* as the reservoir; subsequent attempts to isolate virus from *Artibeus* have been unsuccessful

19 currently recognized arenaviruses (Table 1). Fourteen are New World viruses (the Tacaribe Complex), and five are from the Old World Lassa virus (LASV)-LCMV complex.

A hallmark of the arenaviruses is their association with a single host species of the rodent family Muridae (Table 1), in which they establish a chronic, persistent infection that involves the shedding of infectious virus in urine, feces, and saliva. Possible exceptions to this rule are Sabiá virus, whose reservoir is unknown, and Tacaribe virus, which has been isolated only from bats of the genus *Artibeus*. It is questionable, however, that bats are the true reservoir for Tacaribe virus.

Rodent-to-rodent transmission of arenaviruses can occur either vertically (from parent to offspring) or horizontally (from adult to adult). For example, there is strong evidence from field studies that Junín virus is transmitted horizontally, perhaps among adult male animals during aggressive encounters (MILLS *et al.*, 1992). Conversely, Lassa virus and LCMV appear to be transmitted vertically, perhaps transplacentally (MIMS, 1975).

Human infection results from inhalation of viral particles contained in aerosols of infectious rodent excretions and secretions. Infection may also result from direct contact of broken skin or mucous membranes with contaminated objects or, possibly, via the ingestion of food contaminated by infected rodents (PETERS *et al.*, 1996). Person-to-person transmission of arenaviruses is not common, but has been documented, especially with Lassa fever and Bolivian hemorrhagic fever. Person-to-person transmission likely results from direct contact with bodily fluids of patients, from needle-stick injuries, or from reuse of nonsterile needles and syringes.

THE ARENAVIRIDAE

History

The prototype arenavirus, LCMV, was discovered in 1933 by researchers studying samples from an epidemic of St. Louis encephalitis (ARMSTRONG & LILLIE, 1934). LCMV was not the cause of the epidemic, but was later discovered to be responsible for non-fatal aseptic meningitis in humans as well as a chronic infection in colonies of laboratory mice. This finding led to the discovery of the association of LCMV with its natural host, the cosmopolitan house mouse, *Mus musculus*. Argentine hemorrhagic fever was first recognized in 1953 (ARRIBALZAGA, 1955), and the etiologic agent, Junín virus, was described in 1958 (PARODI *et al.*, 1958). Bolivian hemorrhagic fever was described after an outbreak in northeastern Bolivia in 1959, and the etiologic agent, Machupo virus, was isolated a few years later (JOHNSON *et al.*, 1965). Guanarito virus was isolated after an outbreak of hemorrhagic fever in Venezuela (SALAS *et al.,* 1991). Sabiá virus is known from a single naturally acquired human case, near Sao Paulo, Brazil in 1990 (COIMBRA *et al.*, 1994). Since then, there have been two additional cases due to laboratory infection with Sabiá virus (VASCONCELOS *et al.*, 1993; BARRY *et al.*, 1995).

African arenaviruses

In 1969, Lassa virus was isolated from human patients during an investigation of severe hemorrhagic fever in missionary nurses in Nigeria (FRAME *et al.*, 1970). The host of Lassa virus was unknown until 1972, when it was isolated from *Mastomys* trapped in Sierra Leone (MONATH *et al.*, 1974). Ippy virus was isolated from *Arvicanthis* in the Central African Republic very soon after the discovery of Lassa virus (DIGOUTTE, 1970), but was not shown to be related to Lassa virus until 15 years later (SWANEPOEL *et al.*, 1985). Mopeia virus (formerly known as Mozambique virus), isolated from *Mastomys natalensis* captured in central Mozambique in 1972, was also shown to be related to Lassa virus (WULFF *et al.*, 1977). The most recently discovered member of the complex is Mobala virus, which was isolated from *Praomys* species captured in the Central African Republic (GONZALEZ *et al.*, 1983).

Lassa Fever

Although accurate figures on the incidence of the disease do not exist, Lassa fever is a serious public health problem in West Africa. Thousands of clinical cases occur each year in Sierra Leone, Guinea, Liberia, and Nigeria, with a mortality of about 15% (PETERS *et al.*, 1996). After an incubation period which averages 10 days, Lassa fever has a gradual, insidious onset with fever and malaise, followed by muscle aches and prostration. Gastrointestinal symptoms, including nausea, vomiting, diarrhea, or even constipation, are common, as are sore throat and pharyngitis. Hemorrhagic symptoms are much less common than in the South American hemorrhagic fevers (PETERS *et al.*, 1996). Associated complications include spontaneous abortions and unilateral or bilateral deafness, which may be temporary or permanent (CUMMINS *et al.*, 1990).

Aggressive supportive treatment is important in the management of patients with Lassa fever. Intravenous administration of an antiviral drug, Ribavirin, has been shown to ameliorate symptoms, especially in severe cases (MCCORMICK *et al.*, 1986).

Philogeny of arenaviruses

A phylogenetic analysis of the *Arenaviridae* was recently performed using nucleotide sequences of the nucleocapsid gene (Fig. 1; BOWEN *et al.*, in press). The known arenaviruses fall into two major groups, the New-World Tacaribe complex and the Old-World LASV-LCMV complex. The Tacaribe complex can be further divided into three subgroups, with all of the important human pathogens falling into the same subgroup (Group B, Fig. 1).

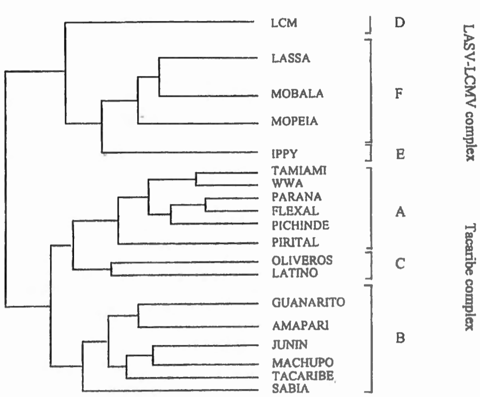

Fig. 1. – Phylogenetic relationships among the Arenaviridae (after BOWEN *et al.*, in press). LCM=lymphocytic choriomeningitis; WWA=Whitewater Arroyo.

The LASV-LCMV complex also can be divided into three subgroups. LCMV and Ippy virus occupy basal lineages; Lassa, Mobala, and Mopeia viruses appear monophyletic and considerable sequence divergence exists within both Lassa and Mopeia viruses. This sequence divergence may indicate that different viral subtypes are associated with different rodent taxa within the poorly understood *Mastomys natalensis* complex (BOWEN *et al.*, in press).

A recent taxonomic reference (MUSSER and CARLETON, 1993) names 8 species of *Mastomys*, but notes that the genus requires careful taxonomic revision. Four morphologically similar species (formerly all considered as *M. natalensis*) have been now separated on the basis of chromosomal traits (DUPLANTIER *et al.,* 1990). These include *M. coucha* (Smith, 1834), characterized by 2N=36 (FN=56); *M. erythroleucus* (Temminck, 1853), 2N=38 (FN=52); *M. hildebrandtii* (Peters, 1878), 2N=32 (FN=44); and *M. natalensis* (Smith, 1834), 2N=32 (FN=54). Mopeia virus is described from *M. natalensis* in Mozambique. Although *M. natalensis* was originally described as the reservoir of Lassa virus, it may be that the species involved in the maintenance of Lassa virus in West Africa are *M. erythroleucus* and *M. hildebrandtii.*

EVIDENCE FOR COEVOLUTION

With the exception of Tacaribe virus, all the arenaviruses with known reservoirs are associated with rodents of the family Muridae (Table 1). The New-World viruses are hosted by rodents of the subfamily Sigmodontinae (New-World rats and mice) and the Old-World viruses by rodents of the subfamily Murinae (Old-World rats and mice). This pattern suggests that an ancestral arenavirus was associated with an ancestral murid and that the distinct arenaviruses have been coevolving with the various species of murids since before the two groups diverged more than 20 million years ago. If this is true, one would expect to see a high degree of similarity between the phylogeny of the rodents and that of the viruses (i.e., viruses associated with closely related rodents should, themselves, be closely related and vice versa).

Clear evidence for coevolutionary relationships is seen when viral phylogeny is compared with host taxonomy for another group of viruses which have murid hosts, the hantaviruses (GLASS *et al.*, in press; HJELLE et al., 1995; NICHOL et al., 1996). One clade of viruses is associated with the arvicolines in both the Old and New Worlds, another with the sigmodontines in the New World, and yet another with the Old-World murines. Even within subfamilies of rodents, closely related genera and species are associated with genetically similar viruses. Finally, a distinct virus (Thottopalayam) is associated with the insectivore, *Suncus murinus*. This close correspondence of phylogenetic patterns indicates that the phylogeny of the viruses might provide clues into the phylogenies of their hosts.

The phylogenetic relationships among the murid rodents are still the subject of much debate. The topology we have depicted (Fig. 2) follows that proposed by STEPPAN (1995) for sigmodontine rodents and CHEVRET (1994) for murine rodents. For simplicity, only rodent tribes and genera which host arenaviruses (and a few important type genera) are depicted. The sigmodontines are generally divided into the North American and South American lineages, and the South American sigmodontines are generally divided into seven or eight "tribes" of purportedly related species (Fig. 2). Among the African genera, *Arvicanthis* is depicted in a separate clade from *Mus*, *Praomys*, and *Mastomys*. *Mastomys* and *Praomys* are poorly differentiated morphologically and are usually treated as closely related genera or subgenera within *Praomys*.

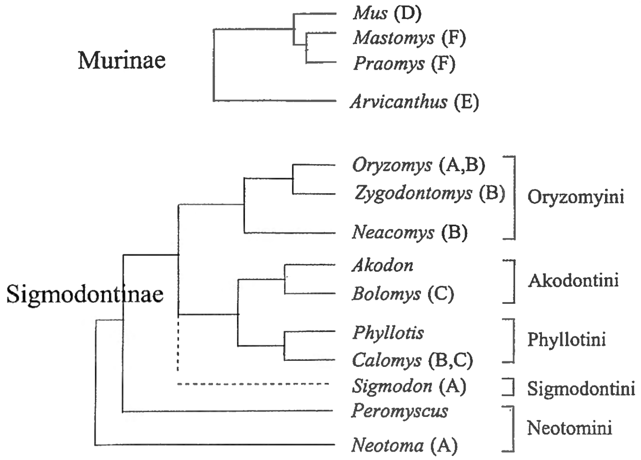

Fig. 2. – Phylogenies of the rodent hosts of arenaviruses (Sigmodontinae after STEPPAN, 1995), Murinae after CHEVRET, 1994). Letters in parentheses refer to viral clades depicted in Fig. 1. The dotted line to *Sigmodon* reflects the unclear position (Sigmodontinae *incertae sedis*, STEPPAN, 1995) of that genus in the three.

An attempt to make similar phylogenetic comparisons among arenaviruses and their hosts is much less successful than with the hantaviruses (Fig. 2). The distant relationship between the viruses of the Tacaribe Complex and the LASV-LCMV complex reflects the distant relationship between the murines and the sigmodontines but, on a finer scale, any coevolutionary relationships are obscure. In the New World, there are viruses of group A among three diverse tribes of rodents, and two genera serve as reservoirs for viruses from two different clades. In Africa, *Mastomys* apparently hosts two different arenaviruses, and Ippy virus is associated with a rodent species only distantly related to the *Mastomys/Praomys* complex. It is quite possible that some of the lack of concordance in phylogenies results from cross-taxon transfer of viruses (spillover of viruses into unrelated hosts may have resulted in the chance establishment of relatively recently derived host-virus relationships). Nevertheless, it is likely that much of the apparent lack of concordance is due to incomplete knowledge of rodent systematics among the South American and African murids, and incomplete knowledge of African arenaviruses.

Given the diversity of arenaviruses in the Americas, it is likely that there are many more arenaviruses in Africa which remain to be discovered. The presence of arenaviruses in both sigmodontine and murine rodents, and the possible specific coevolution between viruses and hosts implies the potential existence of an arenavirus for each murid host species. Past failure to detect human diseases which are related to these viruses is not evidence that they do not exist or that any viruses which remain to be discovered are non-pathogenic for humans. The fact that hantavirus pulmonary syndrome was not discovered in the United States until 1993 (NICHOL *et al.,* 1993; CHILDS *et al.*, 1994) demonstrates that deadly pathogens associated with common and widespread host species can go undetected for many years, even in a country with a relatively advanced disease surveillance system. No systematic search for arenaviruses in murid hosts has been undertaken, yet an opportunistic screening of samples collected for another purpose recently yielded a new arenavirus from the southwestern United States (Whitewater Arroyo virus; KOSOY *et al.*, 1996; FULHORST *et al.*, 1996).

CONCLUSIONS

The complex of African arenaviruses is certain to be much larger than is currently recognized. Unless they are actively sought, these viruses may go unnoticed for many years, even though they may include important human pathogens. Finding and describing these viruses will require collaborative studies between virologists and rodent ecologists. Understanding the phylogenetic and ecologic relationships among the hosts and viruses will require continued studies of the phylogeny and ecology of African murids. Continued and increasing collaboration between mammalogists and virologists will be essential to progress in both fields. The disciplines have much to offer each other.

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