KARBALA JOURNAL OF MEDICINE

Editorial

Distinct Biological and Epidemiological Features of Old World and New World Arenaviruses

https://doi.org/10.70863/karbalajm.v18i2.4911

Dear Sir,

The *Arenaviridae* family comprises a diverse group of enveloped, bisegmented, negative-sense RNA viruses that establish persistent infections in rodent hosts and occasionally transmit zoonotically to humans [1-2]. Arenavirus infections range from mild febrile illness to severe hemorrhagic fever with high mortality. Based on geographic distribution, genetic relationships, and antigenic properties, arenaviruses are classified into Old World (OW) and New World (NW) groups. Although recent genomic studies have refined taxonomic placement within the *Bunyavirales* order [1, 3–5], the OW/NW distinction remains epidemiologically and clinically relevant.

Arenaviruses possess an ambisense, bisegmented genome consisting of a small (S) segment (~3.5 kb) encoding the nucleoprotein (NP) and glycoprotein precursor (GPC), and a large (L) segment (~7.2 kb) encoding the RNA-dependent RNA polymerase (L) and the matrix zinc-binding protein (Z) [6–8]. The GPC is cleaved by the host site-1 protease (S1P) into GP1 and GP2, forming the surface glycoprotein complex responsible for receptor binding and membrane fusion [9]. Virions are pleomorphic, 60–300 nm in diameter, and display a characteristic “sandy” appearance on electron microscopy due to incorporated host ribosomes, hence the name *arena* (Latin for sand) [1,6,10].

Despite a shared genomic organization, OW and NW arenaviruses differ substantially in phylogeny, receptor usage, host reservoirs, and disease pathogenesis. OW arenaviruses, endemic to Africa and parts of Europe, include the prototype lymphocytic choriomeningitis virus (LCMV) and the highly pathogenic Lassa virus (LASV). LCMV, carried by the house mouse (*Mus musculus*), generally causes mild or asymptomatic infections but can lead to severe disease in immunocompromised or congenitally infected individuals. LASV, endemic in West Africa, is maintained in *Mastomys natalensis* and causes Lassa fever, a significant public health concern characterized by hemorrhagic manifestations, multiorgan failure, and sensorineural hearing loss among survivors. OW arenaviruses typically use α-dystroglycan (α-DG) as their cellular receptor, with post-translational glycosylation modulating viral attachment and tissue tropism.

In contrast, NW arenaviruses are distributed throughout the Americas and divided into three phylogenetic clades (A, B, and C). Several Group B NW viruses, such as Junín virus (JUNV), Machupo virus (MACV), Guanarito virus (GTOV), and Sabiá virus, cause severe hemorrhagic fevers in humans. JUNV, responsible for Argentine hemorrhagic fever, represents a successful model for vaccination with the live-attenuated Candid #1 vaccine. NW arenaviruses exhibit narrow rodent host ranges, and zoonotic transmission usually occurs via aerosolized rodent excreta. Many NW arenaviruses use human transferrin receptor 1 (hTfR1) for entry [11], a determinant of their pathogenicity, as nonpathogenic strains generally fail to bind hTfR1 effectively.

Comparative analyses reveal that OW arenaviruses, particularly LASV, exhibit high genetic diversity across multiple lineages, which complicates vaccine development and cross-protection. Conversely, NW viruses, such as JUNV, exhibit limited diversity within endemic regions, which facilitates vaccine success. Receptor preferences, α-DG for OW and hTfR1 for NW, drive distinct tissue tropisms and immune responses, influencing disease outcomes. From a public health perspective, LASV remains the most consequential arenavirus due to its expanding endemic range and risk of nosocomial transmission. Nonetheless, NW arenaviruses continue to pose an outbreak threat with high case fatality rates.

In conclusion, the *Arenaviridae* family encompasses virologically and geographically distinct pathogens with significant implications for global health. Understanding the biological and

Karbala Journal of Medicine (ISSN: 1990-5483) (E-ISSN: 2958-0889), https://journals.uokerbala.edu.iq/index.php/kj
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epidemiological differences between OW and NW arenaviruses—particularly their receptor usage (α-DG versus hTfR1) [11–13], is essential for developing effective countermeasures, including broad-spectrum vaccines and targeted antiviral therapies.

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