ARTICLE @ VIROLOGY

MXRA8 as a Gateway for Chikungunya Virus: From Pathogenesis, Cross-species Transmission to Novel Therapeutics

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ABSTRACT

Chikungunya virus (CHIKV), transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes, is a growing global health concern. Human infection often manifests with high fever, rash, and debilitating pain and swelling in multiple joints. A pivotal discovery in the field was the identification of matrix remodeling-associated protein 8 (MXRA8) as a key host receptor that facilitates CHIKV cellular entry. MXRA8 is highly expressed in muscle, joint, and tendon tissues, which aligns with the viral primary target organs. MXRA8 knockout significantly inhibits viral infection, while soluble MXRA8-Fc fusion proteins or blocking antibodies can effectively prevent infection and alleviate diseases. CHIKV achieves cross-species transmission by leveraging the highly conserved nature of MXRA8 across different species. Although no specific antiviral drugs for CHIKV are currently approved, therapeutic strategies targeting MXRA8, such as decoy receptors and neutralizing antibodies, show considerable promise. When combined with mosquito control and vaccine development, these MXRA8-based approaches offer a hopeful outlook for controlling the spread of CHIKV.

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Abbreviations: CHIKV, Chikungunya Virus; MXRA8, Matrix Remodeling-associated Protein 8; Cryo-EM, Cryo-electron Micro-scopy; WEEV, Western Equine Encephalitis Virus; MAYV, Mayaro Virus; RRV, Ross River Virus.

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Introduction:the Global Burden of Chikungunya Virus

Chikungunya fever is an acute viral illness caused by the Chikungunya virus (CHIKV), which is spread by the bite of infected Aedes mosquitoes. The northward expansion of these mosquito vectors due to climate change is increasing the global risk of CHIKV transmission[1]. The viral infectivity and transmissibility are further heightened by genetic mutations. For instance, sequencing of CHIKV strains from travelers in Zhejiang Province of China (2019) revealed two specific mutations (E1-K211E and E2-V264A) associated with enhanced adaptability[1,2]. The clinical presentation typically includes high fever (>39° C), rash, and significant polyarthralgia with joint swelling, which can lead to synovial proliferation and substantially impact quality of life [1,2].

While most cases in China are currently imported and self-limiting, the potential for local outbreaks remains. A subset of patients develops chronic infections accompanied by long-term joint pain. The absence of approved specific drugs or vaccines in China underscores the urgent need for effective countermeasures. A deeper understanding of CHIKV and its interaction with the host factors, such as the entry receptor MXRA8, is therefore critical for developing strategies to control its spread.

CHIKV Virology, Epidemiology, and Clinical Spectrum

History and Genetic Lineages

CHIKV was first isolated in 1952 from febrile patients in the Makonde Plateau of Tanzania. As a member of the *Togaviridae* family and *Alphavirus* genus, its name, derived from the Makonde word meaning "to become contorted," aptly describes the stooped posture resulting from severe joint pain [1,3].

The virus is classified into three main genetic lineages: East/Central/South African (ECSA), West African (WA), and Asian. A major turning point in its epidemiology was an E1-A226V mutation in the ECSA lineage, which significantly increased its ability to infect *Aedes albopictus* mosquitoes. This adaptation triggered large-scale outbreaks across the Indian Ocean, Europe, and the Americas[4]. According to the WHO, CHIKV has now been reported in 119 countries, with hundreds of thousands of cases annually, primarily in tropical and subtropical regions [5-7].

Clinical Presentation and Disease Phases

Following a mosquito bite, CHIKV initially replicates in skin fibroblasts and myoblasts before disseminating via the bloodstream to target tissues like the joints, muscles, and lymphatic system, causing viremia. The host immune response is a major driver of pathology. Infection triggers a cytokine storm, leading to the release of inflammatory mediators that contribute to

acute symptoms. Viral replication directly causes cell and tissue damage, further exacerbating inflammation. The persistence of viral RNA is linked to chronic symptoms.

The disease progression typically follows distinct phases: a. Acute phase (1-2 weeks): sudden onset of high fever, rash, and headache; b. Subacute Phase (weeks to months): persistent arthritis, affecting up to 70% of patients, often in the hands and knees; c. Chronic Phase (months to years): 10% – 30% of patients experience chronic arthritis and morning stiffness resembling rheumatoid arthritis; d. Severe Cases: rare complications include neonatal encephalitis (with high mortality) and myocarditis [8-9].

The Breakthrough: MXRA8 as the Principal Entry Receptor for CHIKV

Identification and Functional Validation

A major breakthrough in 2018 was the identification of matrix remodeling-associated protein 8 (MXRA8) as a principal receptor for CHIKV[10]. The expression pattern of MXRA8-abundant in muscle, joint, and tendon tissues-directly corresponds to the sites of CHIKV pathology, underscoring its critical role. This was functionally confirmed in in vitro models, where MXRA8 knockout drastically reduced infectivity. Similarly, MXRA8-knockout mice showed decreased viral replication and markedly less inflammatory swelling.

Researchers have since developed potent countermeasures, including soluble MXRA8 -Fc decoy proteins and blocking antibodies. These agents significantly inhibit CHIKV infection in various cell models (EC_{50} ≈20 ng/mL) and, in mouse studies, reduce viral load by over 1,000-fold while alleviating arthritis symptoms.

This discovery not only explains the tissue tropism of CHIKV but also opens the door to innovative therapeutic strategies.

Structural Insights into the CHIKV--MXRA8 Interface

Structural studies using X-ray crystallography and cryo-electron micro -scopy (Cryo-EM) have illuminated the CHIKV-MXRA8 interaction[11-12]. The extracellular domain of MXRA8 forms a unique dimeric structure through two immunoglobulin-like domains connected by a flexible hinge in a "head-to-head" configuration.

Cryo-EM analysis revealed that MXRA8 binds within a cleft between the E2 and E1 glycoprotein heterodimers on the viral surface. This work provided the first atomic-level view of an alphavirus-receptor complex, offering a vital foundation for designing vaccines and broad-spectrum neutralizing antibodies (Figure. 1).

MXRA8 as the Molecular Key to Cross-Species Transmission

Conservation & Species-Specific Barriers

The ability of CHIKV to infect humans, monkeys, and mice is facilitated by the high conservation of MXRA8 across these species,

acting as a "universal key" [13]. Interestingly, cattle are resistant because their MXRA8 variant contains a unique 15-amino-acid insertion ("moo" sequence) in the D1 domain that sterically hinders viral binding (Figure 2) [13]. Deleting this sequence restores susceptibility, while inserting it into mouse MXRA8 confers resistance.

Transgenic mice carrying the "moo" sequence showed milder symptoms and lower viral loads upon challenge. Evolution--ary analysis suggests this protective insertion appeared in bovine ancestors over 5 million years ago. This research not only explains a natural barrier to infection but also validates the concept of engineering host resistance.

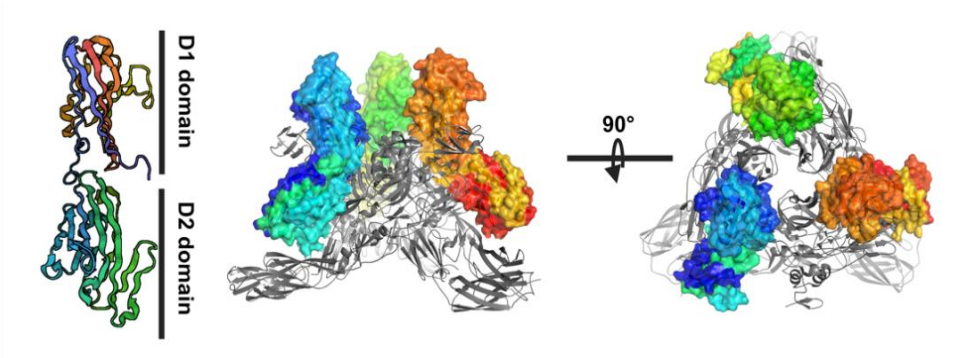

Figure1: Schematic diagram of the molecular structure of MXRA8 binding to CHIKV [11-12].

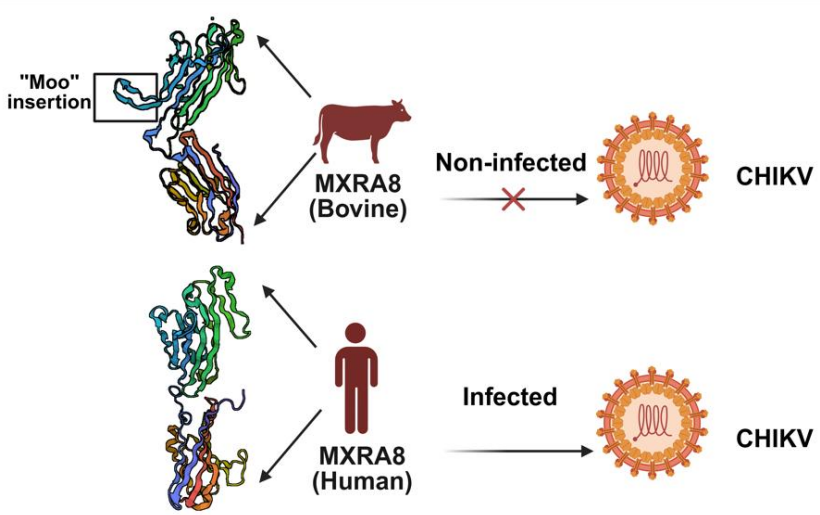

Figure 2: Insertion of the "moo" sequences in MXRA8 of bovines and the cross-species infection barrier [13]

Differential Receptor Usage: Mammalian vs. Avian MXRA8

The specificity of MXRA8 usage extends to virus types. Mammalian MXRA8 is a receptor for arthritogenic alphaviruses like CHIKV, but not for encephalitic viruses such as Western equine encephalitis virus (WEEV). Conversely, avian MXRA8 is used by WEEV but not by CHIKV[14]. Structurally, mammalian MXRA8 binds CHIKV using both its D1 and D2 domains, while avian MXRA8 binds WEEV in a "flipped" orientation primarily via its D1 domain.

Leveraging this insight, a chimeric "duck D1-mouse D2" decoy receptor was designed, which successfully neutralized both virus types *in vitro* and *in vivo*, protecting mice from lethal encephalitis and arthritis. This work paves the way for developing broad-spectrum antivirals (Figure 3).

Translating Discovery into Therapy: MXRA8-Targeted Interventions

The northward shift of mosquito vectors due to climate warming continues to elevate the global risk of CHIKV spread. The emergence of adaptive mutations, such as E1-K211E and E2-V264A found in China, which increase fitness in *Aedes aegypti*, highlights the viral evolving threat [15,16]. While most Chinese cases are imported and mild, effective mosquito control remains the first line of defense to prevent local transmission. The vaccine landscape has seen progress with approvals for a live-attenuated vaccine and a VLP vaccine, though safety concerns have tempered the rollout of the former. Critically, no specific antiviral drugs are available.

Targeting the MXRA8 receptor presents a promising solution. Since MXRA8 is also used by other arthritogenic alphaviruses (e.g., MAYV, RRV), strategies like high-affinity decoy proteins and blocking antibodies offer a potential path to broad-spectrum therapy. Integrating these novel interventions with vector control and vaccination campaigns represents a comprehensive strategy to mitigate the burden of CHIKV worldwide.

Competing interests

The authors declare all financial and non-financial competing interests.

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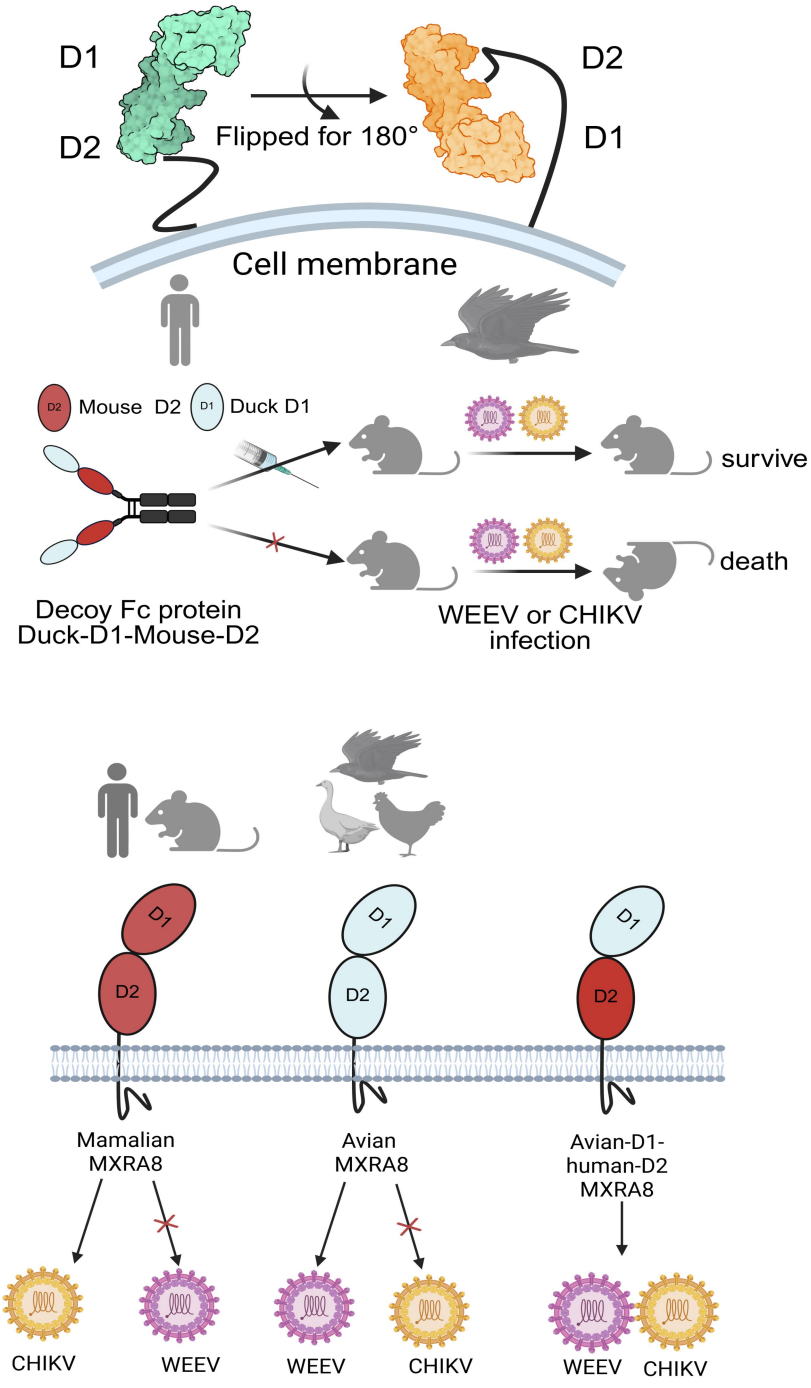

Figure 3: MXRA8 mediates the "inverted binding mode" of infection in mammals and birds[14].

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Editor's Comments

The entry receptor MXRA8 for CHIKV was identified by Dr. Rong Zhang during his postdoctoral fellowship in the laboratory of Michael S. Diamond. Dr. Zhang earned his Ph.D. through a joint program between the Chinese Academy of Agricultural Sciences and the University of Pennsylvania School of Medicine, where he studied mouse coronavirus pathogenesis under the mentorship of Susan R. Weiss. He then completed postdoctoral training at the University of Pennsylvania and Washington University in St. Louis, specializing in arbovirus entry mechanisms in the Diamond Lab.

Dr. Zhang is now a Senior Principal Investigator at the Key Laboratory of Medical Molecular Virology (MOE/NHC/CAMS), Shanghai Institute

of Infectious Disease and Biosecurity, School of Basic Medical Sciences, Fudan University. He has been recognized with several honors, including the U.S. STAT Wunderkinds Award, the National Program for Young Scholars, and the Shanghai Outstanding Academic Research Leader. His laboratory at Fudan University focuses on virus-host interactions, with research aimed at understanding viral entry mechanisms, tissue tropism, and cross-species transmission, as well as developing antiviral strategies against medically important emerging and re-emerging viruses such as coronaviruses and arboviruses.