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An Overview of Therapeutics to Fight against Japanese Encephalitis Virus Infection

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Abstract: Japanese encephalitis is a public health hazard throughout Southeast Asia and the Western Pacific, where many people have been affected and many have died as a result of the virus's spread. The vaccinations that function against different age groups and the quantity of dosage necessary for the formation of antibodies against this virus were the subject of this review. We also concentrated on the creation of antiviral medicines. *Azadirachta indica* is a medicinal plant, and four compounds (Kulactone, Nimbolide, Gedunin, and Ohchinin acetate) from it have been found to have significant binding affinity for the virus's RdRp protein. Oubain and Digoxin, FGIN-1-27, Cilnidipine, Niclosamide, Genistein, Herbimycin A, and PP2 have all been shown to bind to JEV targets with high affinity. However, these proteins are involved in the replication and stability of the replication complex, non-structural and structural proteins are the key targets for the development of therapies against this virus. These medicines may have a critical role in Southeast Asia and the Western Pacific area in reducing JEV FOI. Furthermore, the permeability of the blood-brain barrier following JEV infection is also a problem. Inflammation of the CNS caused by Interleukins and other cytokines is also considered an important target for JEV therapies.

Keywords: Blood brain barrier, CSF, Drugs, Epidemiology, Inhibitors, Japanese encephalitis, RNA, Vaccines.

I. Introduction

Mosquitoes are said to be the deadliest animal on the world. This vector infects millions of individuals every year. Mosquitoes are a vector for a variety of illnesses, including Japanese encephalitis (JE). However, the first instance of Japanese encephalitis was documented in 1871 from the CSF of the patient's brain; the condition is known as Japanese encephalitis [1]. JE is caused by the Japanese encephalitis virus (JEV), Also, carried by the mosquito culex tritaeniorhynchus, which is located around rice fields. Pigs and aves are the major reservoirs for this virus (Fig. 1), while humans and horses are the dead end hosts. According to a research published in 2021, the human as a host encounters the force of infection of this virus, which captures 1.15 billion people in 27 nations throughout Southeast Asia and the Western Pacific, of this population, 28 percent live in the JEV transmission zone [2]. Every year, this virus infects 50,000-70,000 people, killing 10,000-15,000 of them [3]. Thousands of individuals perished despite the availability of immunizations due to inadequate monitoring and cold storage availability, particularly in rural regions. India and China are the most affected countries, but infection rates in China have decreased in recent years as a result of vaccine availability; other countries have also reduced case rates by up to 85%; however, infection rates in India have slowly decreased, but are still lower than in China due to poor monitoring and vaccination programmes in JEV transmission zones [2]. Here, reproduction via +ssRNA, JEV may quickly infect a large number of cells following infection. JEV is a single-strand RNA virus that uses RdRp to initiate transcription (Fig. 2). RdRp is found on the 3' end of the non-structural (NS) 5 proteins. JEV contains seven non structural proteins (Fig. 3) that aid in the stabilization, organization, and assembly of replication complexes (NS1, NS4a, NS4b, and NS2b, respectively), transport of newly replicated RNA from replication complexes to assembly complexes (NS2a), immune response suppression (NS1), protease and Helicase activity (NS3), and MTase and RNA-dependent-RNA-polymerase activity (NS3) (NS5). The structural proteins, on the other hand, are responsible for connecting with RNA for viral packaging (Capsid), engaging with glycosaminoglycans on the host cell to aid in entrance (Envelop), and stabilizing the spike structure by binding with and holding the nearby E protein (PrM) [4].

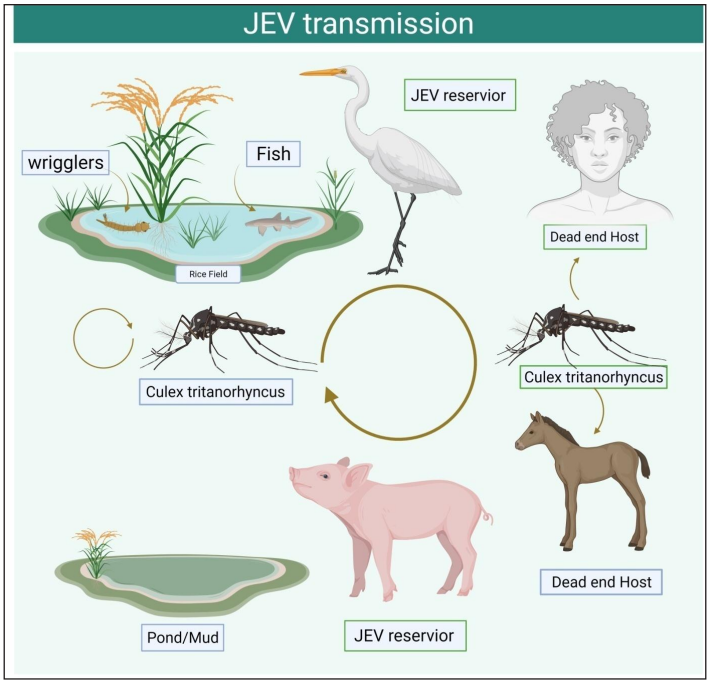

Fig. 1: Near the Paddy Field, JEV Transmission and its Reservoir, Dead End Host

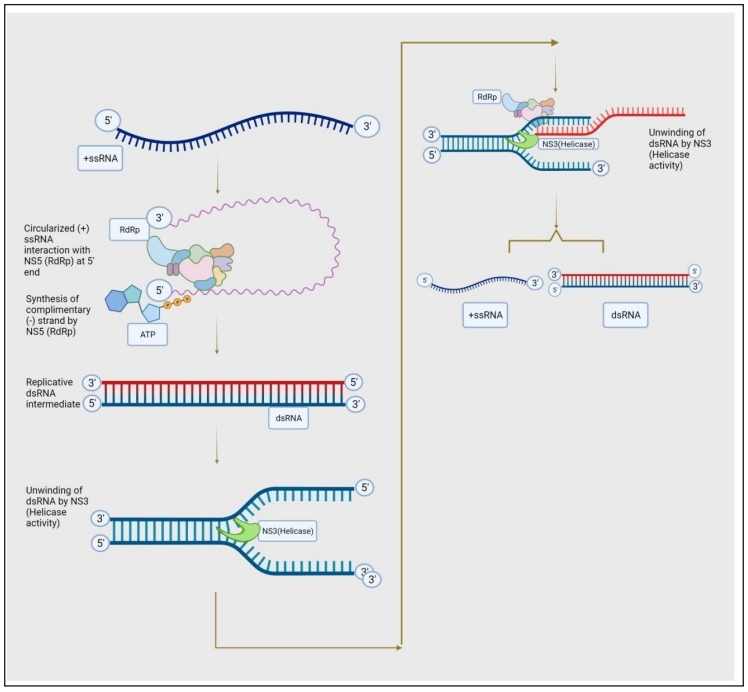

Fig. 2: Unwinding and Complementary Strand Creation in +ssRNA Replication with the Aid of NS5 RdRp and NS3 Helicase Activity (Non-Structural Protein Activity)

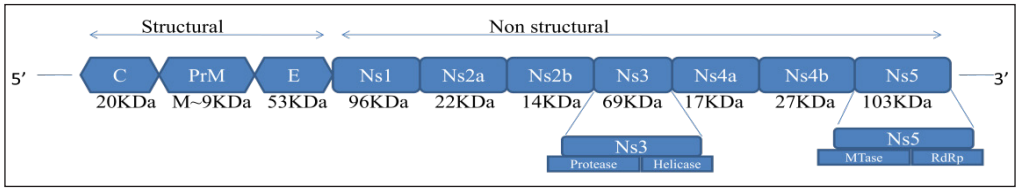

Fig. 3: JEV Genome Includes Structural and Non-Structural Proteins, Molecular Weight, NS3 (Protease and Helicase Activity), and NS5 (MTase and RdRp Activity)

II. JEV and Blood Brain Barrier (BBB)

JEV's ability to pass through BBB with the support of immune cells, including monocyte, macrophages, ostioclast, microglia, dendritic cells, and neutrophiles, 30-50 percent of patients who recover from this illness suffer from lasting neurological disorders. Many viruses, including Dengue Virus, Influenza Virus (H5N1), and Japanese Encephalitis Virus, enter through CLEC5A [5] (JEV). The disruption of tight junction between endothelial cells of the BBB is caused by activation of the C-type lectin domain containing 5A (CLEC5A), which causes cytokine (Tumor Necrosis factor-, Inter leukin-1, Inter leukin -6, Inter leukin -8, and Inter leukin -17A), IL-6, TNF-, and IL-8 activation [3, 5-9].

III. Vaccine for JEV

Walter reed Army Institute developed an inactivated (SA14-14-2 virus strain), purified, whole virus vaccine, cultivated in Vero cells and 0.1% aluminum hydroxide for formulation as an adjuvant [10]. This vaccine does not contain porcine gelatin (stabilizer), thimerosal (preservatives) [10]. In a phase II study (2001-2003) of this vaccine, minimal serious reactions were observed with high rates of seroconversion and show 2 years immune responses after vaccination [11]. Same as phase II study, phase III study at various centers with 867 adult volunteers get two intramuscular doses, shows 98% seroconversion than the licensed vaccine 95% (JE-VAX) [12]. This vaccine injected in shoulder, thigh of young and children respectively. For > 65 year and ≥ 3 year subject, administrated two 0.5 ml doses at a difference of four weeks [13]. Children below the 3 year age administrated two 0.25 ml dose at a difference of four weeks and adults (18-65 years) who encounter JEV frequently, advised to take a second dose up to 11 months after first one and a booster dose after one or two year of second dose, second booster dose after 10 years of first booster dose [13]. If a person suffers from bleeding disorder (low platelet count or hemophilia) then this vaccine can be injected under the skin [13].

IV. Drugs against JEV

Increased vaccine coverage has lowered the number of cases of JE from over 60,000 in 2010 to 45,000 in 2019. Vaccination is thought to have saved around 214,000 cases and 78,000 deaths during the last decade [2]. Despite the availability of vaccines, thousands of cases are reported each year in rural areas due to insufficient monitoring and storage, therefore scientists are working to create treatments against JEV using natural medicinal chemicals; currently, there is no FDA-approved medicine to treat JE. Oubain and Digoxin, FGIN-1-27, Cilnidipine, Niclosamide, Genistein, Herbimycin A, and PP2, Kulactone, Nimbolide, Gedunin, and Ohchinin acetate are some of the antiviral chemicals that have been identified from various databases [4, 14-17].

V. Conclusion

The vaccination is insufficient to combat JEV; a prospective lead chemical to inhibit JEV must be developed urgently. In endemic zones of impacted nations, there is also an urgent need to build excellent monitoring and storage conditions for a robust immunization campaign. We need to build a robust monitoring mechanism to manage the Culex tritaeniorhynchus mosquitoes during the rainy season and in rice fields to decrease the virus's FOI.

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