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Review Article

EMERGING THERAPY FOR DENGUE

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ABSTRACT

Dengue fever is acute febrile diseases, it's caused by one of four closely related virus serotypes of the genusare Flavivirus, family Flaviviridae. Each serotype is sufficiently different that there is no cross-protection and epidemics caused by multiple serotypes can occurs. It's transmitted to humans by the mosquito. The incidence of dengue has grown around the world in recent a period of ten years. However, several classes of agents are in under investigation as potential anti-dengue drugs, including direct host modulators, antivirals, and RNAi therapeutics. These anti-dengue drugs in development will be reviewed here.

Keywords: Dengue viruses, Aedes mosquito, Treatment

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INTRODUCTION

Dengue fever is the fastest emerging arboviral infection spore. Dengue has the most important arboviral infection world with more than 30 million. Dengue fever estimated to occur each year. The dengue virus is the cause of dengue fever. Dengue viruses are arthropod its born viruses (arboviruses) in the genus Flavivirus [1]. (*Family flaviviradae*) with the positive polarity. Single–stranded RNA. is utilized Aedes (stegomyia) spp primarily. Albopictus as vector for domatic and peridomasti transmission. And arboreal Aedes vector for enzootic transmission of the flavivirus genus including other important pathogens such as yellow fever. Dengue viruses are the causative agent of a dengue fever. Its genome is about 11000 bases that the codes for three structural proteins (Membrane protein M, capsid protein C,andenvelop protein E) and seven nonstructural proteins itis also including the short non-coding reign on both the 5 and 3 ends. The dengue virus genome is 11644 nucleotides in length, and is composed of three structural protein genes encoding the core protein (C),), envelope protein (E), a membrane-associated protein (M), and seven nonstructural protein (NS) genes. Non-structural proteins is enveloped by glycoprotein, NS1 is of diagnostic and pathological importance. It is a 45 kDa in size and associated with viral haemagglutination and neutralization activity [2, 3].

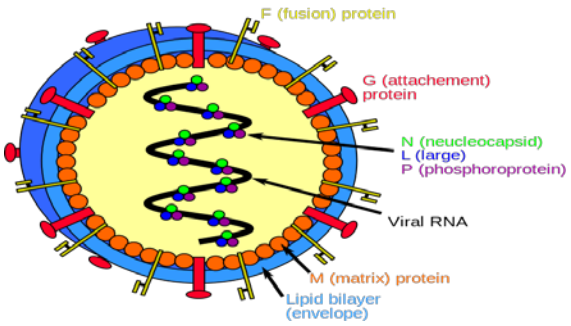

Fig. 1: Dengue virus

History

In the 18th century, dengue has caused repeated epidemics worldwide [2]. H. Graham in 1903 implicated *Aedesaegypti* as the vector for the disease and the virus was isolated in 1944 by Albert Sabin *et al.* Dengue haemorrhagic fever gained nosologic status in 1954 and subsequently its became a endemic in many areas of tropical Asia. India belongs to category B, where dengue is an emerging disease with cyclical epidemics becoming more frequent [1, 2].

Dengue fever [1]

Dengue fever (DF) and its severe forms dengue hemorrhagic fevers (DHF) and dengue shock syndromes (DSS) have become major international public health concerns. Dengue is the most prevalent arthropod-borne viral illness in humans, with the half of the world population at risk for infection and up to 50 million cases of dengue estimated each year. Dengue fever is also known as break bone fever is a mosquito borne tropical disease it's caused by the dengue viruses. The dengue has transmitted by the several species of mosquito the genus is Aedes, The virus has five different types, and usually it gives long-life immunity to that type but only short-term immunity to the other subsequent infection with a different types increase the risk of several complication.

Causes

It is caused by a virus (Dengue Virus), which has got four different types (Type I, II, III, IV). Common name of the disease is 'break-bone fever'"(Haddi Tod Bukhar)" because of severe body and joint pains produced [1].

Spread

The Dengue virus is present in the blood of the patient. Suffering from Dengue fever. Whenever an aedesmosquitoes bites a patient of dengue fever, it sucks blood and, the dengue virusis enters into its body. The virus undergoes further development of in the body of the mosquito for a few days. When the virus containing mosquito bites a normal human being (Healthy person), the virus is injected into the Healthy person body and he/she becomes infected and can develop the symptoms of dengue fever [1].

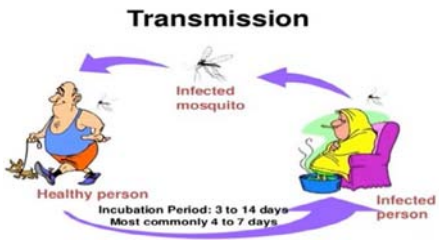

Fig. 2: Life cycle

Life cycle

Until a few hundred years ago dengue virus itwas transmitted in sylvatic cycle's inthe Asia and Africa between mosquitoes of the genus Aedes and non-human primates with rare emergences into the human population [5]. The global spread of dengue virus, has followed its emergence from sylvatic cycles and the primary life cycle now exclusively involves transmission between humans and Aedesmosquitoes[6]. Vertical transmission from mosquito to mosquito has also been observed in some vector species [9].

Symptoms

- Severe Headache, Pains in muscles and joints.
- Pain behind the eyeballs especially on pressing the eyes or on moving the eyeballs.
- Sudden onset of high fever with feeling of chills ("Thandi Lagna").
- Loss of appetite, feeling of nausea.
- Change in taste sensations in mouth.
- Mild pain in throat.
- Rash on the skin

Methods of bioanalysis for anti-dengue activity [4, 5]

Pre-clinical

Dengue it is a positive stranded RNA virus with an 11kb genome, encoding a polyprotein precursor cleaved to generate at least 10 proteins, including three structural proteins (core, membrane associated protein, and envelope protein), and seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4b, NS5). DENV is transmitted by silent, urban mosquito vectors. Including *A. albopictus* and *Aedesaegypti*,*A. polynesiensis*and *A. scutellaris*, to man. Other modes of transmission include via blood products, vertical transmission and organ transplant.

In man, the initial cellular target of dengue is thought to be dendritic cells, followed by lymphatic spread and then distribution to macrophages and monocytes. The full host of cells infected *in vivo* remain a subject of investigation, but may also include hepatocytes, myocytes, and other cell types [8].

Clinical

Clinical methods for evaluation of anti-dengue effects are development. A major hurdle facing DENV clinical trials is the need for establishment of accurate diagnostic testing for case identification. The current diagnostics for DENV available in the US and other high resource countries (IgM and IgG ELISA, PCR) are limited by a requirement for skilled workers, specialized and refrigeration, equipment [9].

Current point-of-care (POC) diagnostic tests for DENV. Based on lateral flow detection of secreted IgMand DENV NS1 protein in plasma/serum/blood or saliva IgA [8, 9].

Treatment

Agents in development for anti-dengue activity

Direct acting antivirals

Nucleoside analogues

Balapiravir (RG1626) is a prodrug of a nucleoside analog, R1479, which it must be triphosphorylated for conversion into active form. Balapiravir was initially developed for the treatment of HCV, but clinical trials were stopped due to toxicity during extended treatment courses (2-3 months) in combination with pegylated interferon and ribavirin. Because R1479 displayed *in vitro* anti dengue activity, and because of the shorter projected treatment duration for acute dengue infection (limiting toxicity), anti-dengue effects of balapiravir were explored in a phase II clinical trial [11].

RNA dependent RNA polymerase (NS5) inhibitors

N-sulfonylanthranilic acid derivatives were identified as DENV RdRp inhibitors through screening of one million compound. The identified hit was found to bind DENV NS5 at the site of entrance to the RNA tunnel. While this specific compound is not under further development, the concept of inhibiting polymerase through the tunnel as well as other allosteric pockets is being pursued [10].

BP13944

A screen of 60,000 chemical compounds in a DENV serotype 2 luciferase harboring replicon (BHK-21 cells). Itis recently identified BP13944, a quaternary ammonium salt, as an NS3 protease inhibitor [12].

Protease (NS2b-NS3) inhibitors

Recombinant retrocyclin 1. Rothan *et al.* produced recombinant NS2B-NS3 protease in E. coli and identified recombinant retrocyclin 1, a cationic cyclic peptide theta defensing analogue with anti-HIV activity. A potent DENVprotease inhibitor [8].

α-ketoamides

Electrophilic trap for the serine component of the DENV NS2b-NS3 serine protease, and have identified α-ketoamides as DENV protease inhibitors [8].

Quinoline containing compounds

Using virtual screening for DENV protease inhibitors followed by scaffold hopping, to expand chemical diversity, then a DENV luciferase reporter replicon assay, Deng et al. have described 17 new compounds with NS2b-NS3 protease inhibitor activity, which can now serve as potential lead structures for further discovery efforts [8].

NS4b inhibitor

Van Cleef *et al.* recently screened the NIH Clinical Collection of drug-like small molecule for anti-DENV activity in HeLa cells harboring a sub genomic DENV2-replicon reporter and identified the δ opioid receptor antagonist SDM25N as potent DENV inhibitor [8].

Translation inhibitors

A high throughput screen for reduction or elimination of DENV CPE and identified benzomorphan compounds that inhibit DENV through suppression of RNA translation and also inhibit DENV viremia in mice, though higher doses were limited by toxicity.

Methyl transferase (NS5) inhibitors

Using a fragment-based drugdiscovery approach, recently screened 500 drug-likefragments by thermal-sift assay for binding to the DENV NS3 helicase or NS5 methyltransferase, and identified 7 validated MTase binders, each containing 5-6 membered aromatic rings.

Capsid inhibitor

A high throughput small molecule screen with readout of DENV induced CPE was performed on over 200,000compounds and identified ST-148 as a unique inhibitor of the DENVcapsid protein with both *in vitro* and *in vivo* effects (AG129 mice).

Peptide inhibitors of various DENV proteins

Several groupshave recently proposed the use of peptide inhibitors to block DENV infection. For example, Lok *et al.* have identified the mimetic peptide DN59, which corresponds to a region of the dengue virus envelope protein, as an inhibitor of all four serotypes of dengue virus.

Host modulators

This property in attempts to inhibit viral replication through deprivation of these required host factors, or dependency factors. This strategy, targeting host factors to impede dengue viral infection [13].

Ribavirin

Ribavirin is a broad acting inhibitor of DNA and RNA viruses. It is a synthetic guanosine analog which inhibits inosine monophosphate dehydrogenase with resulting GTP pool depletion but has multiple additional proposed mechanisms of action, including antiviral genes. Ribavirin use has been limited by toxicity of bothoral formulations and aerosolized, decreasing its clinical efficacy [14].

Mycophenolic acid

The immunosuppressive agent mycophenolicacid, and a nonnucleoside inhibitor of IMP dehydrogenase, has also been shown to inhibit dengue in cell culture, reproduced in four hepatoma cell lines, by the preventing synthesis and accumulation of viral RNA.

Agents that target host mediated post translational modifications

A Glycosidase inhibitors

α glycosidase inhibitors include in the naturally occurring iminosugar castanospermine and deoxynojirimycin, isolated from Bacillus. Castanospermine was found to inhibit infection with all four DENV serotypes *in vitro*, and also to prevent dengue mortality in an DENV mouse model [8].

Lovastatin

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A(HMG-CoA) reductase, used for the lipid lowering and mortality reduction into the cardiovascular disease, and have an excellent safety profile. Statins have been found to exhibit anti-DENV properties in both cellculture and mouse models. A clinical trial examining the safety and antiviral properties of lovastatin in adult patients is now ongoing in Vietnam [8, 9].

Vitamin D

Treatment of both monocytic (U937) and hepatic cells with 1α, 25-dihydroxy-vitamin D3 was associated with decreased levels of DENV infection.

Host kinase inhibitors

Using an immunofluorescence imagebased assay suitable for identification of a small molecule inhibitors of dengue virus infection and replication.

Heparin and heparan sulfate

It is interesting to note that highly sulfated heparan sulfate is involved in the initial interactions between the DENV E glycoproteis and the host cell, heparin and heparan sulfate like molecules have been found to have anti-DENV properties.

Viral sensor (RIG-I and TLR3) agonists

The innate immune system includes the detection of viral RNA by the helicase domain of RIG-I. A synthetic 5' triphosphate (5'ppp) RNA was designed to stimulate this host innate immune response as an antiviral therapeutic, and was found to have anti DENV effects when transfected into A549 cells as well as primary human monocytes prior to DENV infection.

Interferon

The type 1 IFNs it's, including the IFNα, are among the broadest acting antiviral IFNα is a current component of a anti-HCV therapy and has also been used for hepatitis B, severe acute respiratory syndrome, and Severe viral infection is the result of subversion of the host immune response, rendering that response ineffective. A major common pathway of viral it is a immune escape is suppression of the IFNα pathway. While IFN mechanisms vary from virusto virus, activation of IFN effectors downstream of viral subversion. May identify the common drug targets for restoration of an effective hostantiviralresponse. Although it will be possible to reduce reliance on IFNα in HCV treatment regimens, understanding the mechanism of this broad-acting antiviral will inform design of agents active against many viruses, such as DENV, that antagonize IFNα and for which no current treatment are available [15].

IEG activation will circumvent viral subversion of IFN signaling [16]

In general, IFNα can successfully inhibit the DENV if given preinfection, but not post-infection, and due to DENV mediated suppression of early members of the IFN signaling pathway, though some antiviral effect was observed in post-infection administration of PEGrIFN-alpha-2a, which significantly lowered daily viremia levels and improved virus clearance, in rhesus monkey. Defining where viruses block, or the host IFN response can inform design of antivirals that acsdownstream of that block. In preliminary studies, we have to identified 120 host antiviral candidates in a whole genome siRNA screen for HCV IEGs.

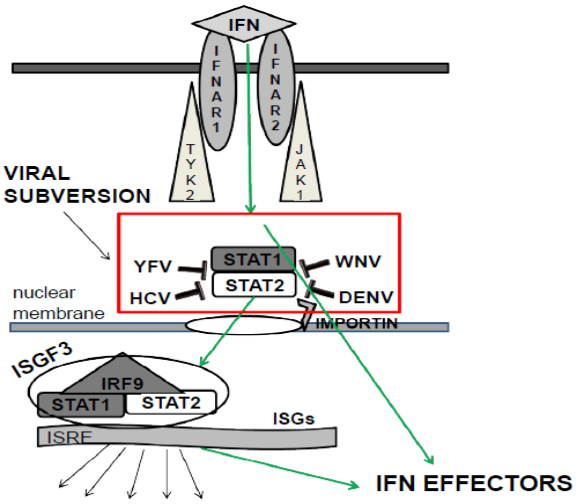

Fig. 3: IEG activation will circumvent viral subversion of IFN signaling

D4 dopamine receptor antagonists [8]

Classes of tricyclic small molecule compound, the dihydro-benzothiepines (DHBTs), in a high through put small molecule screen for the DENV-2 inhibitors, use high content immune-fluorescent assay readout in HEK293T cells. The further determined that SKI-417616, a highly active DHBT, inhibited all 4 DENV serotypes *in vitro* at an early event in the DENV lifecycle, and identified the mechanism of activity as host D4 dopamine receptor inhibition [8].

Pentoxifylline

A small clinical trial of the TNFa inhibitors, pentoxifyllineis showed a potential decrease in mean length of ICU stay and decreased TNFa levels, though viral parameters were not assessed.

Ivermectin

The anti-helminthic drug ivermectinithas been identified as aninhibitor of the nuclear importer import in α/β. Because DENV NS5polymerase activity requires import in α/β, anti-viral properties ofivermectin were explored, and it is revealed that pre-treatment withivermectin inhibited DENV infection of vero cells [8].

Chloroquine [17]

Chloroquine is an inexpensive, well-tolerated lysosomotropic 4-amino-quinoline derivative, which is well known as an anti-malarial drug but also possesses *in vitro* anti-viral activity, including anti-DENV activity, potentially related to its effect of increasing endosomalpH.

Amodiaquine

The quinoline derivative amodiaquine was recently identified in a replicon basedon screen for anti-DENV agents, and it's confirmed to have anti-DENV activity in DENV2 plaque assays and qRT PCR for the both intracellular and extracellular DENV levels [8]

RNAi

RNA interference, is a gene silencing process. Which its degrades the target RNA in a sequence specific fashion. RNAihasto been proposed as a strategy to directly inhibit viral infections, including the DENV. One group showed use of dendritic celltargetingpeptide mediated delivery of siRNA against a conserved sequence in the DENV envelope effectively suppressed DENV replication in macrophages and monocytes. In addition to the RNAi mediated suppression of the

DENV itself, RNAi-mediated suppression of viral dependency factors, or factor is required by the virus for productive infection, has been shown to inhibit DENV. There are currently no RNAi agents registered under clinicaltrials. gov whensearched with dengue [18].

Morpholinos

Taking advantage of RNA–protein interactions required for the DENV replication, antisense peptide-conjugated phosphor-rodiamidate morpholino oligomers (P-PMOs) have been designed to sterically interfere with these interactions.

Other compounds

Other agents that have been suggested to a display anti-dengue activity including genetic in, an aminoglycoside antibiotic, which has been found to have the unique property, among aminoglycosides, of inhibiting DENV and FCI 106, a compound of unknown mechanism identified in a screen for anti-Ebola agents, which has also been found to have anti-DENV activity, in DC-SIGN cells [8].

Medicinal plant derivatives [19]

There is a significant amount of the research dedicated to a hypothesis driven and practice-based identification of a naturally occurring compounds with the anti-dengue properties. It is the important to note that many of the compounds examined inthese studies are selected because they are already in used against denguein traditional settings, underscoring the need to examine their effect ondengue-related outcomes, regardless of whether they will be assessed for drug development.

CONCLUSION

Dengue is emerging as aglobal treat and is pressing public health priority in many countries. The government and the pharmaceutical industries have been taking initiative to develop new strategies to improve the diagnosis and treatment of dengue. The challenge here lies in how effectively the strategies developed are put into use. There also an obligatory need to globalize awareness and precautionary measures among the masses in order to control the incidence. Combined efforts of the health care industries, governing bodies and efforts at individual level would help us to tackle the prevalence of dengue.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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