The Host's Immune Response against Dengue Virus Infection

Book · August 2023

3 authors:

Ghanem Mohammed Mahjaf
Shendi University
66 PUBLICATIONS 3 CITATIONS
SEE PROFILE

Tibyan Abdalmajed Altaher
Shendi University
27 PUBLICATIONS 1 CITATION
SEE PROFILE

Mosab Nouraldein Mohammed Hamad
Elsheikh Abdallah Elbadri University
560 PUBLICATIONS 167 CITATIONS
SEE PROFILE

One of the biggest global public health issues is dengue virus (DENV) infection, particularly in tropical areas of the world where 75% of dengue cases occur. While most DENV infections are moderate or asymptomatic, about 5% of cases go on to develop a severe version of the illness. This is primarily related to several infections with various DENV serotypes that occurred in succession. Numerous immunopathogenic pathways involving virus and host variables influence the severity of dengue. New research suggests that an inadequate immune response, by limiting viral clearance and causing severe inflammation, which ultimately results in dengue hemorrhagic fever and dengue shock syndrome, contributes to the progression and severity of the disease. The natural history of viral infections, notably dengue, is greatly influenced by the host's innate and adaptive immune responses. In this context, it has been noted that RNA interference (RNAi) is becoming more prevalent in viral infection processes and immune defense in recent years.

Dr. Ghanem Mohammed Mahjaf:
Researcher, Excellence Research Center, Elsheikh Abdallah Elbadri University.
Dr. Tibyan Abd Almajed ALtaher:
Researcher, Excellence Research Center, Elsheikh Abdallah Elbadri University.
Mosab Nouraldein Mohammed Hamad:
Assistant Professor, Microbiology Department, Faculty of Medicine, Elsheikh Abdallah Elbadri University.

9 786206 779391

Ghanem Mohammed Mahjaf
Tibyan Abd Almajed Altaher
Mosab Nouraldein Mohammed Hamad

The host's immune response against dengue virus infections

LAP LAMBERT Academic Publishing

Ghanem Mohammed Mahjaf
Tibyan Abd Almajed Altaher
Mosab Nouraldein Mohammed Hamad

The host's immune response against dengue virus infections

Ghanem Mohammed Mahjaf
Tibyan Abd Almajed Altaher
Mosab Nouraldein Mohammed Hamad

The host's immune response against dengue virus infections

LAP LAMBERT Academic Publishing

Imprint

Cover image: www.ingimage.com

Publisher:
LAP LAMBERT Academic Publishing
is a trademark of
Dodo Books Indian Ocean Ltd. and OmniScriptum S.R.L publishing group

120 High Road, East Finchley, London, N2 9ED, United Kingdom
Str. Armeneasca 28/1, office 1, Chisinau MD-2012, Republic of Moldova, Europe
Printed at: see last page
ISBN: 978-620-6-77939-1

The host's immune response against dengue virus infections

Dr. Ghanem Mohammed Mahjaf

Researcher, Excellence Research Center, Elsheikh Abdallah Elbadri University.

Dr. Tibyan Abd Almajed ALtaher

Researcher, Excellence Research Center, Elsheikh Abdallah Elbadri University.

Mosab Nouraldein Mohammed Hamad

Assistant Professor: Microbiology Department, Faculty of Medicine, Elsheikh Abdallah Elbadri University.

List of contents

Subject	Page Number
Dedication	**2**
Acknowledgement	**3**
Abstract	**4**
Introduction	**6**
Structural Details of Dengue Virus	**8**
Host Immune Cell Responses to Dengue Virus Infection	**11**
Involvement of T Cells in the Pathogenesis of DENV Infection	**13**
Antibody-Dependent Enhancement-Mediated Immunopathogenesis	**21**
Cytokine Storm-Mediated Immunopathogenesis	**24**
Immune Escape Mechanism of DENV Contributes to Disease Severity	**28**
Dengue Serotypes Contribute to Disease Severity	**30**
Diagnosis and control of DENV infection	**32**
Conclusion	**38**
References	**40**

Dedication

To my: grandmother's soul Salam.

To my: Father: Mohammed Ghanem Mahjaf.

To my: great mother Mona Mahjaf.

Acknowledgement

To all medical researchers who are working to promote the life of man, through the gate of knowledge.

Abstract:

One of the biggest global public health issues is dengue virus (DENV) infection, particularly in tropical areas of the world where 75% of dengue cases occur. While most DENV infections are moderate or asymptomatic, about 5% of cases go on to develop a severe version of the illness. This is primarily related to several infections with various DENV serotypes that occurred in succession. Numerous immunopathogenic pathways involving virus and host variables influence the severity of dengue. New research suggests that an inadequate immune response, by limiting viral clearance and causing severe inflammation, which ultimately results in dengue hemorrhagic fever and dengue shock syndrome, contributes to the progression and severity of the disease. The natural history of viral infections, notably dengue, is greatly influenced by the host's innate and adaptive immune responses. In this context, it has been noted that RNA interference (RNAi) is becoming more prevalent in viral infection processes and immune defense in recent years. The context microRNAs (miRNAs) go for stands out as their presence during viral infection, both in the replication of the virus and in the defense against these infections, becomes more noticeable. As a result, it is becoming more and more important to understand the role of these small RNAs within viral infection by DENV and what their consequences are in aggravating the consequences of patients affected by this disease. Additionally, DENV specifically targets immune mediators to inhibit antiviral signal transduction and invisibly hides to avoid immune surveillance. The initial line of defense against viral infections is innate immunity, where type I interferons are a key component. Many viruses manage to get past inherent defenses and infect the host. Numerous investigations have demonstrated that in order to circumvent the host's immunological response, viruses like DENV decrease type I IFN production. The

dengue virus has four widely recognized serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. A fifth serotype was recently discovered in 2013. Although DENV serotypes are roughly 65% similar, infection with various serotypes causes a variety of clinical symptoms. In addition to the host cell's cellular machinery being used by the virus, a host cell also produces different antiviral reactions. The creation of interferon-dependent cytokines, the induction of inflammation, and cell death through inducing apoptosis or autophagy are just a few of the ways the host immune system fights virus infection. We go over processes that are essential for the Dengue virus reproduction cycle in mammalian cells, its pathogenicity, and several antiviral defenses put forth by the host cell in this overview. Understanding the Dengue virus replication cycle and the host proteins that the virus uses as a resource might be crucial for creating antiviral targets and is of utmost relevance for maintaining public health.

1. Introduction

Infection with the dengue virus (DENV), which can cause dengue fever (DF), is the most quickly spreading viral disease carried by mosquitoes in the world. The numerous serious side effects of dengue fever, including dengue hemorrhagic fever and dengue shock syndrome, are its deadliest feature. The most common flavi/arboviral infection worldwide, dengue fever is an acute disease that has a large socioeconomic and disease burden on many tropical and subtropical locations. **[1,2].** According to "The Global Burden of Disease," dengue fever is spreading faster than any other infectious disease, with a 400% growth in just 13 years (2000-2013). **[3].** Dengue has a history of being ignored, although statistics show significant recent investments in the creation of a vaccine and cutting-edge vector management strategies **[4].** A significant section of the world's population was recently immunized as a result of the COVID-19 vaccine's rapid and affordable production. This will give an indication that future dengue vaccine development may be possible for other viral infections **[5,6,7].** The goal of this Book is to draw attention to the overall dengue-related trends, the work that went into generating the vaccine, and the clinical outcomes. Vaccination, the most crucial aspect of illness management, is one of the tactics used in the prevention and treatment of dengue fever. The DENV-1, 2, 3, and 4 serotypes are the four main serotypes **[8].** After being bitten by a female Aedes mosquito (*Aedes aegypti* or, less frequently, the cold-adapted *Aedes albopictus*), DENV infection results. Due to cross reactivity, initial infection with any of the DENV serotypes only partially protects against all four serotypes; this cross-reactive immunological memory seems to be transient. If the patient contracts the same serotype of infection again following neutralization of the immunological memory, a protective response may be produced. The risk of mortality is increased and subsequent infection with various serotypes is linked to more severe disease manifestations **[9].** Since all DENV serotypes have the potential to be disease-causing, producing a DENV vaccine that is highly effective against all four serotypes is a difficult task. The World Health Organization has recommended CYD-TDV (Dengvaxia®), which has been licensed in 20 countries, for people aged 9 to 45 who live in endemic areas and have confirmed prior DENV infection, among the DENV vaccine candidates currently undergoing clinical evaluation. However, serious safety concerns have been raised **[10].** In fact, CYD-TDV raises the risk of a severe DENV infection, as determined by hospitalization, in people who had not previously been exposed to DENV before vaccination **[11].** Therefore, a detailed understanding of the immunological correlates of protection against DENV infection is necessary for the creation of effective DENV vaccines. The pathogenesis of DENV infection is assumed to be the complex interaction of the virus, host genes, and host immunological response, with the host immune response playing a key role. In reality, DENV infection only manifests as the severe form of the disease when the infection is being cleared up by the host immune response and does not correspond with the peak viral load **[12].**

Additionally, infection-induced antibody-dependent enhancement (ADE) contributes to the pathophysiology and severity of the illness **[13].** Antibody-dependent enhancement develops after the antibodies from a previous heterotypic infection fail to neutralize a secondary infection with a distinct subtype, even after binding with the viral proteins **[14].** The virus–antibody complex is then phagocytosed by the cells via crystallizable fragment-γ (Fcγ) receptors and results in increased viremia and pathology **[15].**

2. Structural Details of Dengue Virus

The Dengue virus has an icosahedral nucleocapsid and is roughly spherical in shape. It is an encapsulated single-stranded positive-sense RNA virus. The 11 kb long DENV genome can serve as mRNA, and like eukaryotes, it has untranslated regions (UTRs) bordering the open reading frame (ORF) at both the 5′ and 3′ ends **(Figure 1).** The type I 5′ cap serves as an initiation site for translation, while the 3′ end lacks the poly-A tail and instead has a stem loop. Within the 5′UTR, there are stem-loop (SL) structures—SLA and SLB, upstream and downstream regions concerning AUG denoted as the 5′UAR (upstream AUG region) and 5‘DAR (downstream AUG region), C-coding hairpin (cHP), and 5′ cyclization sequences (5′CS). The DAR, cHP, and 5′CS are located in the C protein-encoding region. The 5′UTR comprises sequences of 95–101 nucleotides in the four DENV serotypes, DENV-1 to DENV-4, while the 3′UTRs' length is variable among the serotypes **[16].** A polyprotein, which is the precursor to 10 mature proteins, is encoded by the ORF flanked by UTRs. Three structural and seven non-structural proteins are produced as a result of the co- and post-translational processing of this polyprotein. The structural proteins—Capsid (C), Envelope (E), and pre-Membrane (prM)—are what the name suggests; they are what make up a virus particle and are crucial for the virion's maturation, envelopment, and encapsidation of viral RNA. The numerous enzymatic activities of the non-structural proteins NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 are being investigated for their multiple functions in an infectious cycle **[16,17].** To name a few functions of NS proteins: While NS3 has RNA-triphosphatase (RTP), nucleoside triphosphatase (NTPase), and helices activities, NS5 also has nuclear localization sequences (NLS) and S-adenosyl methionine methyltransferase (MTase) activity, giving both NS3 and NS5 the capacity to play a crucial role in RNA replication. Along with the other NS proteins NS1, NS2A, NS4, and NS4B, NS2B is a viral serine protease that participates in a variety of viral replication, assembly, and release processes **[16,17].**

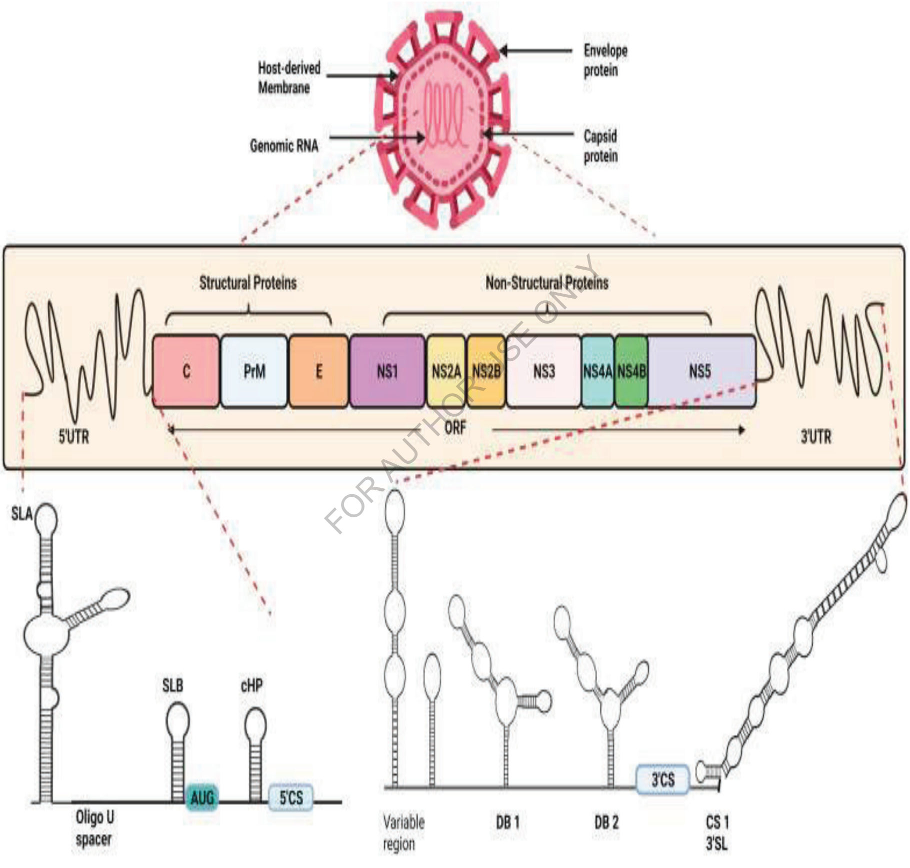

Figure 1: Structural organization of Dengue virus genome: The viral genome consists of 5′UTR, an ORF, and 3′UTR. The ORF encoding polyprotein serves as a template for the translation of 3 structural proteins (C (Capsid), PrM (Pre-Membrane), and E (Envelope)) and 7 Non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5). The representation of 5′UTR depicts Stem-loop structures (SLA and SLB) flanked by oligo U, wherein SLB is followed by initiator AUG and the hairpin structure (cHP) in the C encoding region. The following complementary sequence at 5′UTR is essential for genome circularization, which in turn is important for genome replication. The 3′UTR consists of variable sequences, followed by dumbbell structures DB1 and DB2. The approaching conserved sequence CS1 and stem loop (SL) at 3′UTR play a pivotal role in genome conformational changes facilitating replication.

3. Host Immune Cell Responses to Dengue Virus Infection

Both the innate and the adaptive immune systems of the host network cooperatively rebel against the DENV attack (**Figure 2**). The Langerhans cells (LCs), DCs, and the dermal cells at the site of the mosquito bite are the first encounterers of DENV **[19].** The distribution of DCs in the tissue is such that they do not miss an encounter with the virus **[20].** They along with the macrophages are recruited to the site of the DENV entry via signals from the chemoattractants. The migration of the antigen-presenting cells independently contributes to inflammation as well as the host adaptive responses **[21].** Signals from DCs, such as TNF-α, recruit NK cells, which are crucial in restricting DENV replication and pathogenesis during the early stages of infection by IFN production **[22].** Neutrophils are also recruited to the primary site of infection by the tissue-resident macrophages through the secretion of IL-8, TNF-α, and IFN-β. Antiviral factors such as TNF-α and defensins are generated by neutrophils **[18].** Moreover, the degree of complement activation by the DENV-NS1 protein is greater in DHF patients than in mild/intermediate Dengue Fever (DF) **[23].** The effector functions of these immune cells are the result of certain innate immune pathways and their interactions with each other. The dsRNA intermediates of DENV are recognized by TLR-3, which through the activation of TRIFF lead to the phosphorylation and activation of the interferon regulatory factors IRF-3 and IRF-7 **[24].** The TLR pathogen recognition pathway leads to the production of class I IFNs that restrict DENV replication by successively activating the JAK/STAT pathway **[25].** Other receptors participating in the IFN-mediated combat against DENV are RIG-1 and MDA5 **[26].** By the time, the innate immune system attempts to restrict the virus; the adaptive immune system prepares for an advanced attack for virus clearance. The B cells bind to the DENV antigens to elicit a primary IgM response, followed by an elaborate DENV-serotype-specific-IgG response. The secondary infection is marked by a reduced IgM but an enhanced IgG response **[27].** The antibodies basically target the NS1, E, and prM proteins of the DENV **[28].** The involvement of B cells also indirectly points to the involvement of T cells in the DENV infection response. While CD4+ T cells mainly target the capsid along with the NS2A/B, 3, 5 and E proteins, the CD8+ T cells target the capsid along with the NS3, 4A/B, 5 proteins **[29].** These responses prompt the CD8+ T cytotoxic cells to secrete perforins and granzymes and the CD4+ T cells to involve in Th1 (secreting IFN-γ and TNF-α) effector functions. Moreover, the other T cell subsets such as the Treg cells act to regulate inflammation via TGF-β and IL-10, and the Follicular T cells function to aid the B cells into generating highly specific antibodies with sufficient affinity **[18,30].** Although the entire immune system works together to put up a prodigious fight against DENV, some of these responses may in turn cause host damage, through an event known as the “cytokine storm”.

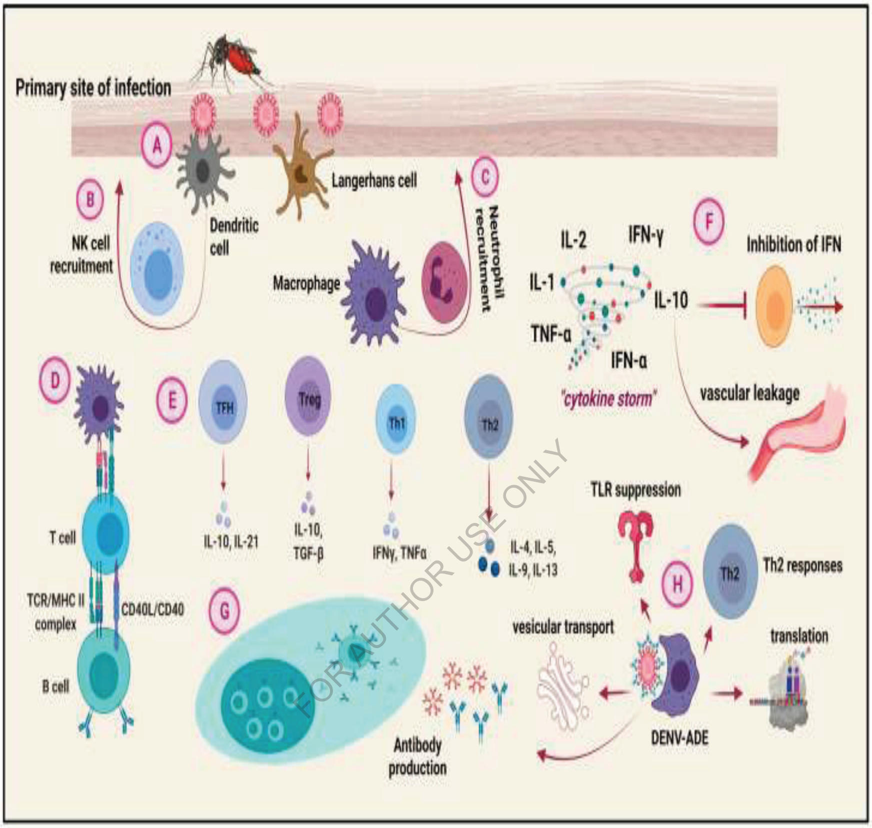

Figure 2: Immune cells involved in the host responses to the Dengue virus: After the mosquito bite injects the Dengue virus into the skin, A. The Langerhans cells and the Dendritic cells (DCs), the primary cells that encounter the Dengue virus, come into play. B. The DCs recruit the NK cells to the site, whereas, C. The macrophages recruit the neutrophils. D. Macrophages infected with DENV present the processed antigen to the T cell, which in turn interacts with the B cell to

aid in B cell development. E. Different types of T cells are activated to elicit various cell-mediated immune responses against the virus. F. A gush of cytokines are secreted in an event called the “cytokine storm”, out of which the overproduction of IL-10 leads to the inhibition of IFN responses as well as vascular leakage. G. The humoral immunity, represented by the B-cell-mediated antibody production from the plasma cells, as a natural immune response to any pathogen, induces ADE in the DENV infection. H. The ADE of the DENV entry into the macrophage via phagocytosis leads to an altered transcriptome of the cell, ultimately leading to TLR suppression, enhanced Th2 responses, along with the dysregulation of vesicular transport and the host translation process.

4. Involvement of T Cells in the Pathogenesis of DENV Infection

People in dengue-endemic locations typically develop symptomatic infection more than once because the DENV infection is caused by several serotypes and long-term cross-serotype protective immunity is inadequate after primary infection **[32].** Even though CD8 T cells are essential for scavenging dangerous viruses, they have also been linked to the pathophysiology of DENV infection. Patients with secondary DENV infection have 10- to 20-fold more severe dengue symptoms, which may indicate that priming of the adaptive immune system to one DENV serotype increases the probability of severity after secondary infection with various serotypes **[31].** Additionally, when viremia is rapidly dropping, severe symptoms such vascular leak, coagulopathy, and cytokine storm are frequently present. Naive CD8 T cells are stimulated by primary DENV infection to develop into effector T cells, which will either directly lyse the virus-infected cells or produce cytokines to remove the infection **[32].** In those who are immune to DENV infection, different HLA-restricted T-cell epitopes on various proteins are present. By means of CD4 and CD8 T cells, respectively, DENV's structural and nonstructural proteins are recognized **[33,34].** Based on the epitope identified, T cells can react to a subsequent infection brought on by a different DENV serotype **[35].** Individuals who have previously been exposed to the same serotype typically produce a strong immune response, whereas subsequent infection typically results in the development of a cross-reactive serotype T-cell response. Acute DENV infection was associated with higher frequencies of DENV-specific T lymphocytes, and these cells had activated characteristics **[36].** DENV-specific T cells initially expressed the early activation marker CD69 after infection, and later showed other activation markers such CD38, CD71, and HLA-DR **[37].** Investigation of HLA-DR$^+$CD38$^+$CD8$^+$ T cells obtained from DENV-infected patients indicated the upregulated expression of those genes that are involved in T cell activation, proliferation, migration, and cytotoxicity. In addition, HLA-DR$^+$CD38$^+$CD8$^+$ T cells display a higher expression of multiple inhibitory receptors that are involved in T cell receptor (TCR) signaling. Analysis of HLA-DR$^+$CD38$^+$ and HLA-DR$^-$CD38$^+$ effector CD8 T cells in dengue-infected patients from India and Thailand displayed the expansion of both the subsets in these patients, while the effector qualities were more prominent in HLA-DR$^+$CD38$^+$ CD8 T cells and were mostly directed against NS3 **[38].** However, only a small fraction of effector CD8 T cells were producing IFN-γ upon stimulation with virus peptide pools, due to the downregulation of TCR signaling molecules. During primary DENV infection, homotypic T cells are generated against the infecting DENV serotype that correlates with lifelong protection against that serotype. However, secondary DENV infection with different serotypes leads to the development of nonprotective, cross-reactive T cells, resulting in ineffective viral control during secondary heterologous infection, and supports severe dengue disease by induction and excessive inflammatory cytokine production **[36].** In fact, cytokine storms are seen during peak symptoms, whereby high levels of proinflammatory cytokines, such as tumor necrosis factor (TNF), soluble TNF receptor 1 (sTNFR1), sTNFR2, and interferon-γ (IFN-γ), and chemokines such as CXCL8, CXCL9, CXCL10, CXCL11, and CCL5, along with anti-inflammatory cytokine interleukin-10 (IL-10), were observed **[39,40].** This enhanced cytokine response could trigger vascular permeability, which is resolved after patient recovery. Moreover, the presence of soluble markers of T cell activation, including sIL-2R, sTNFR, and sCD8, indicate systemic T cell activation. Indeed, the soluble factors were higher in patients with severe disease compared to those who had a mild form of the disease, which further confirms immune-mediated pathogenesis in DENV infection **[41].** Development of DENV-specific cross-reactive CD8 T cells occurs following both primary and secondary infection. However, these cells do not correlate with the disease severity. Further, it was revealed that a higher polyfunctional CD8 T cell response is associated with HLA alleles, which are related to the reduced risk of severe dengue disease **[36].** This is in accordance with the study showing higher frequencies of cytokine-producing DENV-specific CD8 T cells in children who develop subclinical secondary infection than those with symptomatic secondary infection **[42].** DENV-specific IFN-γ-producing CD8 T cells are mainly effector memory cells (T_{EM}) or effector memory cells re-expressing CD45RA (T_{EMRA}) **[43].** Transcriptomic profile of T_{EM} and T_{EMRA} cells revealed that these cells exhibit specialized gene expression profiles related to activation, co-stimulation, and effector function **[44].** Analysis of DENV-specific T cells revealed differences between mild and severe DENV infection that may be associated with disease severity. During mild DENV infection, CD8 T cells possess cytolytic function, but cytokine-producing abilities are compromised. Conversely, with severe primary and secondary DENV infection, CD8 T cells exhibit higher IFN-γ and TNF-α cytokine responses, but cytolytic activity is impaired, potentially affecting viral control and augmenting immunopathology. DENV-specific CD8 T cells express inhibitory receptor-programmed death-1 (PD-1). However, that does not represent immune exhaustion; rather, these cells exhibit higher proliferation and function, which suggest PD-1 as a marker of activation and functional antigen-specific CD8 T cells in case of DENV infection **[44].** Similarly, expansion of the CD4 T cell population occurs during DENV infection, and the magnitude of the CD4 T cell response correlates with disease severity (**Figure 3**).

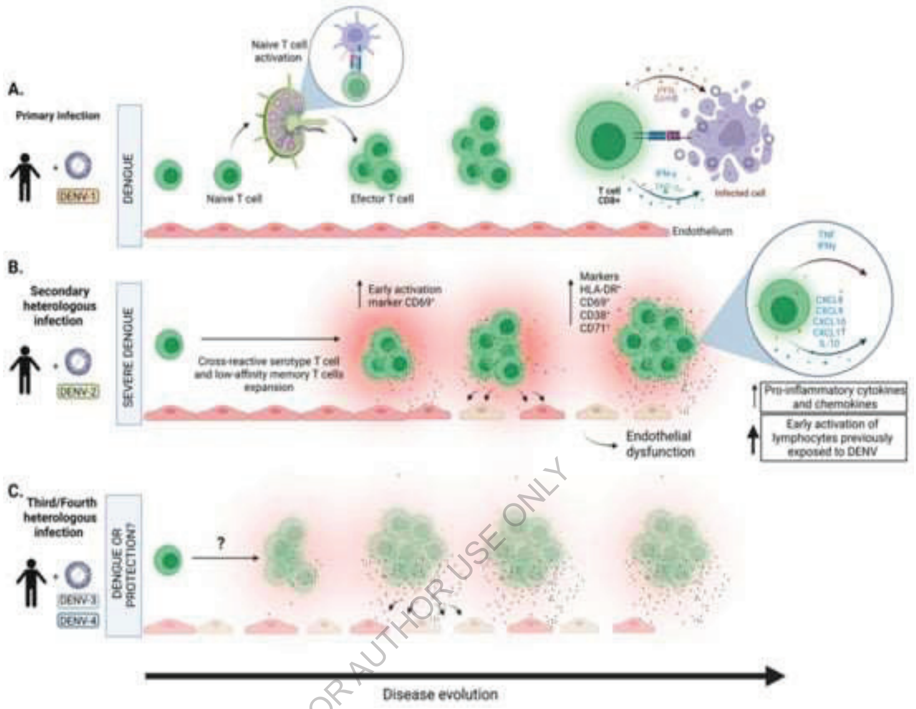

Figure 3. T cell response during DENV infection. History of exposure to dengue virus (DENV) is one of the factors that drive the T cell response in the evolution of the disease. (A) During primary infection, naïve T cells differentiate into effector T cells, leading to clearance of infection by direct lysis or by releasing antiviral cytokines, such as IFN-γ and TNF-α. (B) During a secondary heterologous infection, a robust immune response is developed by the early activation of cross-reactive serotype T cells, which produce abundant proinflammatory cytokines and chemokines, leading to excessive inflammatory environment, causing endothelial dysfunction that could trigger vascular permeability. (C) During a third or fourth heterologous infection, the activation of

cross-reactive serotype T cells and their role in the severity or protection against infection is largely unknown.

Recently, researchers have looked into how DENV and T cells interact during the course of the illness. Primary naive CD4+ and CD8+ T lymphocytes have been shown to be receptive to DENV infection **[45].** Both cell types additionally promote viral replication and secrete live virus particles. In fact, during the acute phase of infection, DENV can infect CD4+ and CD8+ T cells. All four serotypes can infect CD4+ and CD8+ T cells, and their degrees of infectiousness are comparable. DENV interacts with the heparan sulfate moiety to infect and multiply in CD4+ and CD8+ T cells **[45].** Pre-exposure of DENV to heparin, an inhibitor of host heparin sulfate–virus interactions, limited the virus infectivity in both $CD4^+$ and $CD8^+$ T cells in a dose-dependent manner. Further, treatment of $CD4^+$ and $CD8^+$ T cells with heparinase III, a heparin sulfate-cleaving enzyme, reduced DENV infectivity, confirming that heparan sulfate moieties are engaged in DENV binding to T cells. In vitro exposure of healthy peripheral blood mononuclear cells (PBMCs) to all DENV serotypes demonstrated that $CD8^+$ T cells are more vulnerable to DENV infection than those of $CD4^+$ T cells. A caveat to this is that activated T cells are less susceptible to DENV infection than nonactivated T cells. This was confirmed by the polyclonal stimulation of T cells with anti-CD3/anti-CD28 monoclonal antibodies that induced the expression of CD69 (an early T cell activation marker) on these cells. The susceptibility to infection was determined in both $CD69^+$ and $CD69^-$ T cells, which revealed that $CD69^+$ T cells are less inclined to get infected with DENV in comparison to $CD69^-$ cells **[45].** Moreover, DENV infection does not induce apoptosis of $CD4^+$ and $CD8^+$ T cells, a critical step required for viral clearance, suggesting a potential viral escape mechanism leading to disease severity. Other studies reported that DENV infection triggers apoptosis in various parenchymal as well as nonparenchymal cells, including monocytes, dendritic cells (DCs), endothelial cells, and hepatocytes **[46].** Apoptosis of monocytes and DCs influences immune response to infection, while apoptosis of hepatocytes and endothelial cells contributes to hepatic damage and hemorrhagic manifestations in severe dengue cases. Apoptosis of leukocytes and microvascular endothelial cells in pulmonary and intestinal tissue is observed and might be associated with vascular plasma leakage **[47].**

5. Antibody-Dependent Enhancement-Mediated Immunopathogenesis

DENV-specific antibodies serve a variety of purposes. Through a variety of ways, including limiting viral attachment to cell surface receptors or by preventing viral infusion after binding, these antibodies eliminate the infection. The majority of neutralizing antibodies are directed against practically all of the epitopes and primarily target the envelope (E) protein **[49].** Immunoglobulin receptors are expressed by both monocytes and macrophages. Known as antibody-dependent enhancement (ADE) of infection, DENV's affinity for these receptors gives DENV-specific antibodies a chance to promote viral entrance **[50].** The ADE phenomenon, which is itself a subset of immunopathology, contributes to the disease's severe form. When a person contracts a later infection with a different DENV serotype, pre-existing antibodies made from an earlier DENV infection bind to another DENV-infecting particle **[51].** The antibodies from the previous infection are not efficient in neutralizing the virus in secondary infection. Rather, the antibody–virus complex binds to the Fcγ receptor present on circulating monocytes and causes infection in monocytes, resulting in increased viral replication and higher risk of severe dengue. There are two types of ADE, namely extrinsic and intrinsic **[48,52].** The phenomenon of extrinsic ADE occurs externally to mononuclear phagocytes and involves an increased rate of receptor interaction and internalization of the virus–immune complex. Previously, extrinsic factors were considered responsible for the adverse effects of dengue ADE-associated pathogenesis. Later, the intrinsic ADE revealed that it could modulate innate immune effectors by internalized virus–immune complexes inside the infected cells to support increased viral replication and its release **[52].** Intrinsic ADE contributes to enhanced virus production by inhibiting type 1 interferon, activating the biosynthesis of IL-10 and favoring a Th2-type immune response **[48].** If we compare both extrinsic and intrinsic ADE, the latter has a significant contribution in augmenting dengue replication. During secondary DENV infection, thorough revelation of intrinsic ADE might enhance our understanding of DENV pathogenesis and help in identifying unique therapeutic approaches to overcome the adverse effect of ADE **(Figure 4).**

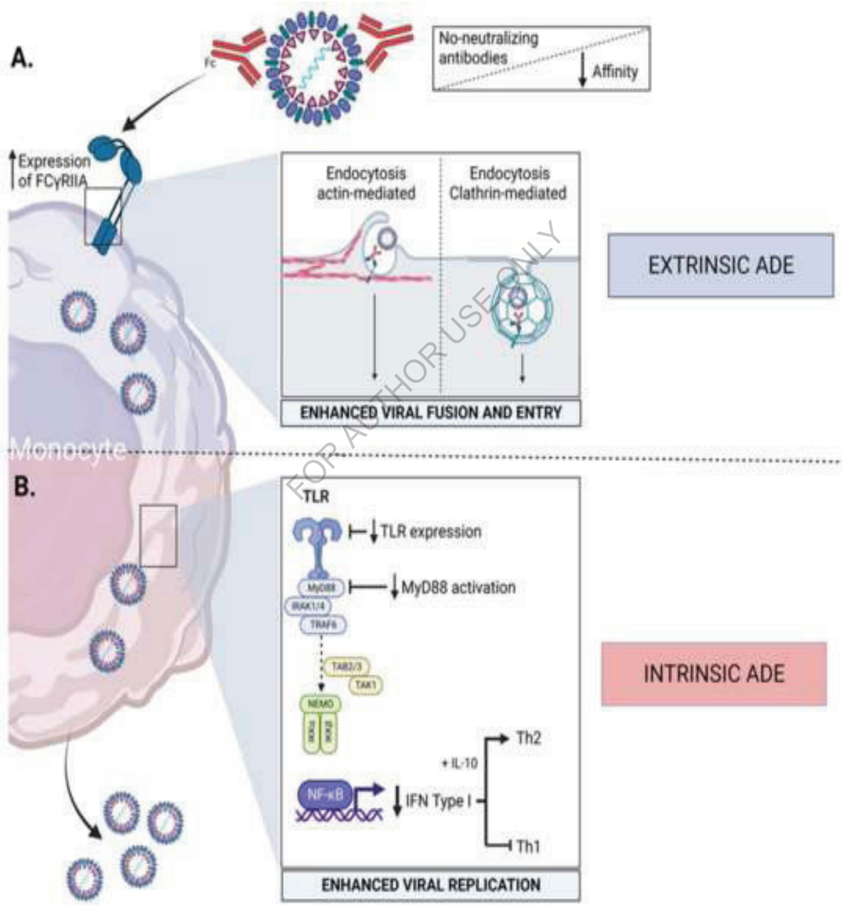

Figure 4. Antibody-dependent enhancement (ADE) in dengue virus infection. ADE is one of the phenomena contributing to the severity of dengue infection during a secondary heterologous infection in a patient with pre-existing non-neutralizing antibodies. The ADE phenomenon has two components: (A) Extrinsic ADE, which contributes to the enhancement of virus entry in the susceptible cells via the interaction of the Fcγ of the antibody–virus complex with the Fcγ receptor in the cell membrane, triggering endocytosis (actin- or clathrin-mediated), facilitating the first steps in viral replication. (B) Intrinsic ADE, which results in increased viral production by targeting different pathways, including downregulation of TLR signaling, inhibition of type I interferon, and a skewed immune activation favoring Th2 response.

Studies have shown that ADE can change molecular signaling to reduce the strength of the host's antiviral defenses. The cell types for ADE in an in vivo context are probably monocytes, macrophages, and DCs because they express Fc receptors on their surface. In fact, a recent study revealed the mechanism to lessen the effects of ADE in the host and evidence that antibody-dependent cellular cytotoxicity (ADCC) antibodies are present in the serum that causes ADE. These ADCC antibodies are effective in triggering natural killer (NK) cells to combat ADE **[53].**

6. Cytokine Storm-Mediated Immunopathogenesis

After DENV interacts with host cells, a number of proinflammatory, immunoregulatory, and antiviral cytokines are produced. DCs are typically known for producing type I interferons, but they are also capable of secreting other chemicals and cytokines that promote inflammation. According to studies, DENV-infected DCs release MMP-2 and MMP-9, which increase the permeability of the endothelium monolayer **[54,55].** Different DENV proteins, including NS4B and NS5, also stimulate the production of IL-8 by macrophages and endothelial cells **[56].** After DENV infection, the release of IL-6, CXCL10, CXCL11, and RANTES from endothelial cells enhances inflammation and vascular permeability, leading to plasma leakage in vivo. Primary infection with DENV alters cell surface receptor expression on human endothelial cells and its responsiveness towards vascular endothelial growth factor-A (VEGF-A); however, these changes were observed in both DENV-infected as well as non-infected cells, suggesting that the endothelial response to DENV is broad and independent of viral-specific cell surface markers. **[57].** Indeed, cytokines produced by T cells have pleiotropic effects and are critical in viral elimination, but they also encourage inflammation and enhance vascular permeability contributing to disease severity. Increased T cell activation and cytokine production has been observed during DHF in both primary and secondary DENV infection **[58,59].** In fact, infusion of IL-2 or TNF can enhance systemic vascular leakage, which provides evidence for the participation of T cells in the pathogenesis of DHF **[60].** In cases of severe dengue, the cascade of immune response mediated by immune effectors leads to disease severity. During DENV infection, most of the immune cells, including monocytes, macrophages, NK, invariant natural killer cells (iNKT), and DENV-specific CD4 and CD8 T cells, secrete huge amounts of TNF-α that contribute to inflammation and enhanced vascular permeability **[60].** In vitro studies have confirmed that endothelial cell exposure to TNF-α not only induces vascular permeability but encourages cell death **[61].** In addition, TNF-α is involved in the coagulation pathway by inducing the expression of platelet tissue factor. In brief, TNF-α is a critical factor in the pathological process of severe dengue. A study reported higher TNF-α levels in patients with severe illness in comparison to those with milder illness, which further proves the association of TNF-α in the development of severe dengue **[62,63].** Considering the crucial role of TNF-α in the pathogenesis of DENV, the blockade of TNF-α can be a potential approach to treat severe dengue infection in humans; however, the safety and efficacy of the TNF-α blocker needs thorough investigation. Interferon receptor gene knock-out mice or mice infected with high doses of either wild-type or mouse-adapted DENV strains revealed that endothelial cell damage was associated with macrophage-secreted TNF-α **[64].** Treatment of these models with anti-TNF-α abrogated hemorrhage. A recent study analyzed a panel of 23 cytokines after a dengue outbreak in Taiwan and found that TNF, IFN-γ, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12p70, IL-17A, macrophage migration inhibitory factor, CD54, CD62E, CD62L, and GM-CSF were elevated while CD106, CD154, IL-4, and IL-33 were downregulated during dengue infection, suggesting the activation of the immune system during dengue, contributing to disease severity, as the dysregulation of certain cytokines has major implications in dengue pathogenesis **[65].** The cytokine profile varies during dengue infection and further disease progression. The study further reported that cytokine levels fluctuate immensely in different groups over the days of fever. In fact, IL-10 emerged as a potential diagnostic marker for dengue fever, and CD121b (an IL-1 receptor) was demonstrated to be a predictive marker for severe dengue. During disease progression, the production of inflammatory cytokines, including TNF-α, IL-6, and IL-10, from the DENV-infected cells, induces the expression of adhesion molecules such as CD62E, CD106, and CD62P that lead to inflammation, endothelial damage, and plasma leakage. Adhesion molecules such as CD54, CD106, CD62E, CD62L, CD62P, and CD154 fluctuated at different days of fever and normalized during the recovery phase, whereas GM-CSF, IL-2, IL-6, and IL-8 remained continuously high, especially during the critical phase of the disease **[65].** Several pieces of evidence suggest the change in cytokine pattern during dengue infection and support the cytokine storm theory in these patients. In addition, a shift from the Th1-type immune response to Th2-type response was observed during disease progression to severe cases of DHF **[66].** Patients with DHF displayed increased serum levels of IL-4, IL-6, and IL-10, mainly in more severe forms. Conversely, IFN-γ and IL-2 were highly elevated during dengue fever and were low in severe DHF. IL-2, IL-6, IFN-γ, and TNF-α were elevated during the early phase of infection, while IL-4 and IL-10 were elevated during days 4–8 of illness. However, the data are contradictory between different studies, which could be associated with several factors, k including the timing of sample collection, sample processing, and importantly, the difference in the study cohort. However, the overall data demonstrate cytokine-mediated pathogenesis in DENV-infected patients **(Figure 5).**

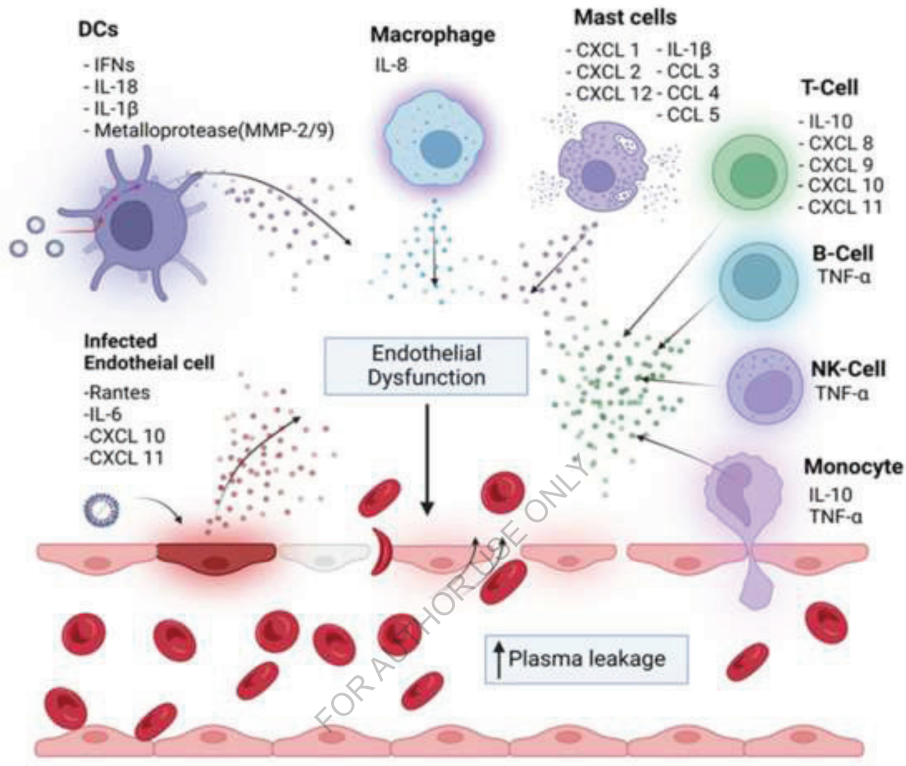

Figure 5. Cytokine storm seen in severe dengue infection. During a secondary heterologous infection, a robust immune response is generated, inducing the production of biological mediators including cytokine, chemokine, and other soluble factors from different immune cells as a consequence of complex interactions between the virus and host factors. These mediators promote vascular permeability resulting in an increase in plasma leakage.

7. Immune Escape Mechanism of DENV Contributes to Disease Severity

It is a well-known fact that dengue virus takes over the host cellular machinery to complete its life cycle. This leads to the activation of cellular immune signaling, which in turn competes against infection. DENV antagonizes several challenges at each step of its life cycle, starting from the virus entry to the release of mature virions. Moreover, DENV inertly hides to escape immune surveillance and directly targets immune mediators to block antiviral signal transduction. Innate immunity acts as the first line of defense against viral infections, where type I interferons are one of the major players. Many viruses evade innate immunity and develop infection in the host. Numerous studies have shown that viruses including DENV inhibit type I IFN production to evade the host immune response **[67].** Several DENV proteins are involved in the inhibition of type I IFN signaling in the infected cells, leading to the abrogation of IFN genes and thus restricting antiviral function **[68].** Pathogen-associated molecular patterns (PAMPs), including TLRs (TLR3/7/9) present on different APCs, recognize the viral particles and get activated **[69,70].** Cytosolic receptors, including RIG-1/MDA-5, also recognize the viral particles and trigger several pathways, resulting in the production of cytokines and chemokines that control viral infection **[71].** Although DENV is a weak inducer of type I IFN after infection in DCs, it still impairs the type I IFN pathway and decreases the ability of DCs to generate a Th1-type immune response, which enables viral persistence **[72].** DENV can overcome host innate immunity and can infect via two mechanisms: first by evading the collaboration between PAMPs and PRRs, and the other by inhibiting various steps of the innate immune response through the expression of inhibitory molecules, which directly blocks the intracellular pathways required for type I IFN production and signaling **[73].** Moreover, DENV NS4A potentially disturbs the induction of IFN by targeting mitochondrial antiviral signaling protein (MAVS) **[74].** NS4A binds to MAVS and inhibits the binding of MAVS with RIG-1, and thus prevents IFN production. In addition, NS4A associates with the N-terminal CARD-like (CL) domain and C-terminal transmembrane domains of MAVS, as well as the third transmembrane domain of NS4A, which is indispensable for binding to MAVS, suggesting that NS4A is involved in DENV immune evasion through the inhibition of the MAVS-mediated cellular response. Conserved viral RNA conformation is another DENV escape strategy. DENV genomic RNA is capped at the 5′ end, similar to cellular mRNA, which is post-transcriptionally capped at the 5′ end, encompassing one N-7 methylguanosine and one or two 2′-O methylguanosine. Hence, viral RNA deficient in 2′-O-methylation will be recognized as non-self RNA, whereas DENV lacking 2′-O methyltransferase activity enables an early innate immune response in the host cells and replicates with a lower viral load than the wild type, and thus escapes and stays under the radar in host cells **[75].**

8. Dengue Serotypes Contribute to Disease Severity

Although the factors that determine how severe a DENV presentation is might range from asymptomatic to severe, these factors are not well understood. Pathogenesis theories primarily focus on interactions between the virus and its host. Additionally, the host's genetic makeup, some virus strains, and the immune system's reaction to a prior dengue infection predispose to worse results **[76].** It has been reported that DENV serotypes and their structural peculiarities also contribute to pathogenesis **[77].** As viral genetic factors govern its virulence and the magnitude of viral replication determine disease severity, serotypes with higher replication capacity trigger higher antibody production and may be associated with more severe outcomes **[78].** A study of 485 DENV cases in a locality in Brazil highlighted the influence of DENV serotypes on clinical manifestations and outcomes, of which 6.6% presented severe disease, which mostly belonged to the DENV-2 serotype (32.3%) and less in DENV-1 (4.5%) and DENV-4 (6.4%), suggesting that early serotype identification could be beneficial in preventing a growing number of severe outcomes, especially during dengue outbreaks, by predicting the health support required for early diagnosis and interventions **[79].** Other studies also observed similar findings with an increased proportion of severe outcomes, such as DHF and DSS in infections caused by DENV-2 **[80].** DENV-2 appears to be a determinant factor for the emergence of severe dengue in different global regions and epidemics with increased hemorrhagic cases in regions where DENV-2 is the leading serotype; however, the mechanism of virulence is not well defined. One of the possible factors is the stimulatory effect of DENV-2 on nitric oxide production, instigating toxic and inflammatory effects, prompting apoptosis in host cells **[81].** Another contributing factor to the increased pathogenicity in DENV-2 infections is its higher viral replication, leading to high viral load **[82].** Prior reports of DENV in Thai children have reported that secondary DENV-2 is more likely to result in severe disease compared with other serotypes **[83].** Other data from a Nicaraguan cohort further confirmed that 29% of DENV-2 hospitalized cases emerged as DHF/DSS in the 2005/2006 season, while this percentage upsurged to 63% across further seasons **[77].** Overall, these studies indicate that DENV-2 appears to be associated with severe outcomes. However, more recent data involving a Vietnamese large cohort found that having a higher plasma viremia during the febrile phase was associated with adverse outcomes such as vascular leakage, severe dengue, and subsequent hospitalization regardless of infection serotype or host immune status **[84].** Nevertheless, DENV 2 carries the greatest risk of adverse outcomes in this population as well, despite manifesting lower daily viremia compared to other serotypes **[84].**

9. Diagnosis and control of DENV infection

In patients who frequently report with acute start of fever, headache, body pains, and occasionally rash spreading from the trunk and who live in or have recently been to a disease-endemic area in the two weeks prior to symptom onset, DF should be taken into consideration **[85].** The diagnosis can be performed by detecting the virus, viral nucleic acids, antigens, anti-DENV antibodies, or combinations of these techniques **[86].** In the early stages of the disease (seven or less than 7 days after onset of illness), DENV infection can be diagnosed from serum, plasma, circulating blood cells, or from other tissues by detecting viral RNA with nucleic acids amplification tests, NS1 protein using some commercial tests and viral isolation in mammalian or mosquito cell culture to further genotyping and lineage for virus characterization **[85].** DENV is thermally labile; RNA detection and isolation of the virus are highly dependent on well-preserved specimens for accurate diagnosis results **[87].** The samples awaiting shipment to the laboratory should be stored in a refrigerator or freezer. That is, for storage up to 24 h, samples should be stored at 4–8 °C and for long-term storage samples should be frozen in a − 70 °C refrigerator or liquid nitrogen container **[88].**

For patients with suspected DF disease, serum specimens during acute phases (≤ 7 days after onset of illness) would be collected and diagnosed by detecting the viral RNA sequence by reverse transcription–polymerase chain reaction (RT–PCR) or NS1 protein and/or anti-DENV antibodies by enzyme-linked immunosorbent assays (ELISA) or rapid point-of-care tests **[89].** IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) is used for the qualitative detection of DENV IgM antibodies starting 4–5 days after onset of symptoms and is also reliably detectable for approximately 12 weeks. The MAC-ELISA is based on capturing human IgM antibodies on a micro-titer plate using anti-human–IgM antibody followed by the addition of DENV antigens derived from the envelope proteins of the four serotypes. Plaque Reduction Neutralization Tests (PRNTs) that detect specific neutralizing antibodies against DENV and other flavivirus are performed on IgM positive patients to determine the cause of infection or to rule out other *flavivirus*, such as ZIKV, YFV and, in some cases, to determine the infecting DENV serotypes **[86, 85].** Moreover, the recent development of ELISA and dot blot assays targeting the E/M and NS1 antigens has demonstrated that high levels of these antigens in the form of immune complexes are detected in patients with both primary and secondary dengue infections up to 9 days after the onset of illness. The NS1 glycoprotein is produced by all *flavivirus*, secreted by mammalian cells, and generates a very strong humoral response, so that detection of NS1 allows early diagnosis of dengue virus infection, although serotypes are not differentiated **[88].** The nested RT-PCR protocol was developed using universal dengue primers targeting the C/prM region of the genome for the initial reverse transcription and amplification step, followed by a nested PCR amplification for identification of the infecting serotype-specific qualitatively **[90].** Moreover, the combination of the four serotype-specific oligonucleotide primers in a single reaction tube which utilizes one-step multiplex RT-PCR was an interesting alternative to the nested RT-PCR **[91].** The advancement of RT-PCR into real-time (rRT-PCR) by incorporating dyes and probes (SYBR green and TaqMan) in a single step is capable of providing quantitative data **[92].** The presence of the virus by rRT-PCR or NS1 antigen in a single diagnostic sample is considered laboratory-confirmed dengue in patients with compatible clinical and travel histories **[85].** For patient illness of more than 4 days after the onset of fever, DF can be diagnosed by testing serum for IgM antibodies produced against DENV using MAC-ELISA, whereas for patients presenting within the first week after fever, testing for DENV should include detection of rRT-PCR or NS1 and IgM **[85].**

After the acute phase of infection has subsided or after 7 days of fever onset, detection of IgM antibodies is the preferred method of diagnosis using ELISA and hemagglutination inhibition (HI), although NS1 has been reported positive up to 12 days after fever onset **[88, 93].** If the DENV infection occurred in a person who had no previous *flavivirus* infections or had not been vaccinated against *flavivirus,* such as ZIKV, YFV, JEV, and TBE, patients would develop a primary antibody response which slowly increases for a limited time long **[89].** The IgM isotype is the primary emerging antibody and detection rate in serum is increased as follows: by days 3–5 after the disease onset, it is detected in 50% of patients, by day 5 detection increased to 80% of patients and by day 10–99% of patients **[88].** During DENV infection occurs in a place, where other potentially cross-reactive *flavivirus* such as ZIKV, WNV, YFV, and JEV are not a risk, a single serum sample IgM test result strongly suggests a recent DENV infection and should be presumed confirmatory for DF **[93].** The IgM level peaks at about 2 weeks after disease onset and declines to undetectable levels after 2–3 months. Contrarily, IgG started to be detected at low titers in serum, usually at the end of the first week of onset, and slowly increases thereafter and is detected after months and even years **[88].**

During secondary DENV infection or after vaccination or infection with a non-dengue *flavivirus*, the IgG isotype antibody titers rise rapidly; the predominant antibody isotype is detected in secondary infection with high levels in an acute phase and lasts 10 months and sometimes lifelong **[89].** During the convalescent phase, IgM antibodies can be reliably detected but negative for viral RNA or NS1 test **[85].** The IgM levels during early convalescence are significantly lower within secondary than primary infections and may be undetectable depending on the tests used. Hence, IgM detection is a reliable serological diagnostic test target in primary DENV infections **[94].** IgM/IgG antibody ratios and HI tests are used to distinguish between primary and secondary dengue infections **[95].** IgM and IgG anti-DENV antibodies detection are useful to confirm recent or past infection, because where IgM can be formed about 1 week after infection and reaches their peak 2–4 weeks after the onset of disease, the formation time of IgG level is longer than that of IgM but IgG will stay in the body for many years **[86].** The presence of IgM indicates a recent infection; the presence of IgG indicates a previous DENV infection. Similarly, during the clinical course, the IgG/IgM ratio plays an important role in differentiating DENV infection. A ratio of 1.10 or higher is found the optimal cutoff point for differentiating secondary from primary DENV infection **[96].**

DENV can be isolated from serum, plasma, and peripheral blood mononuclear cells and obtained from tissue autopsies (e.g., liver, lung, lymph nodes, thymus, or bone marrow), although specimens for isolation should be collected early in the infection process and during the viremia stage (usually before the 5th day) **[97].** Cell culture is a widely used method to isolate DENV as a golden standard for DENV infection diagnosis, using the mosquito cell lines C6/36 (cloned from *Ae. albopictus*) or AP61 (a cell line from *Ae. pseudoscutellaris*) and rarely and mammalian cell cultures, such as Vero, LLCMK2, and BHK21. Consequently, the viral RNA genome sequencing is performed for the genotyping of the serotypes and to characterize the molecular epidemiology of DENV infections **[98, 99].**

Rapid diagnostic tests (RDTs) for detecting NS1 protein antigen, IgM, IgG, and IgA antibodies have been developed by many commercial companies and are widely used due to their ease of use and rapid results. In many DENV endemic settings and areas with limited laboratory diagnostic resources, RDTs provide opportunities for point-of-care diagnosis, as well as secondary infection or convalescent timepoints after recent infections **[100].** The IgM-based RDT format alone is not sensitive enough for acute DF diagnosis. On the other hand, the IgG-based RDT format is not recommended for diagnosing of acute DF, because IgG antibodies persist for lifelong and are more likely to be misdiagnosed as false-positive. The NS1 antigen-based RDTs are important part of modern point-of-care diagnostics, but are sensitive only in the early stages of infection and are not suitable for single use in epidemic settings, where late clinical manifestations may occur **[101].**

Careful medical detection and monitoring of patients with DF can significantly reduce mortality from severe dengue **[102].** Currently, there is no specific treatment for DENV infection. Symptoms of muscle pain, fatigue, and fever can be relieved and reduced by treatment with acetaminophen or pain relievers, such as acetaminophen. Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and aspirin, are not recommended, because these anti-inflammatory drugs have a blood losing effect and blood anticoagulants that can worsen the prognosis of diseases with a risk of hemorrhage. For severe DF, medical care by doctors and nurses familiar with the effects and course of the disease can reduce mortality from more than 20% to less than 1% by maintaining patients' fluid volume, essential for the management of severe DF **[86, 103, 88].** Currently, Dengvaxia® is the only DENV vaccine approved and in use in the United States for children ages 9 to 16 with laboratory-confirmed evidence of previous DENV infection and living in areas, where DF is common **[93].** Control of DF/DHF relies primarily on the use of insect repellents, wearing long sleeves and long trousers, and mosquito repellent inside and outside the home. According to the Global Vector Control Response (GVCR) noted, epidemiological surveillance with case detection and control, and entomological surveillance and control would be pillars to prevent and control DENV infections **[104].**

Conclusion

Over the years, extensive research has been done on the dengue virus to better understand the etiology and cure the related DHF and DSS diseases. We made an effort to compile in this review both the DENV research areas that have already received attention and those that still need it. Finding potential DENV antivirals that are effective against all DENV serotypes requires an understanding of the coordination of cellular responses as well as the modification of the host's resistance. The fact that several medicinal herbs can lessen the effects of the DENV further supports the need for more research in this area. Together, these reviews seek to clarify the numerous facets of the DENV lifecycle and pathogenesis, presenting fresh perspectives on the virus's exacerbation and the host's vulnerability. Although there is a wealth of information regarding DENV, it is only the tip of the iceberg, since numerous functions of viral proteins and the control of viral genome conformation in DENV multiplication are being researched to demonstrate their superiority. The body's immune system serves as its main line of defense against the dengue virus. The innate and adaptive immune systems work together to combat the dengue virus when someone is afflicted. B cells create antibodies that selectively bind to and destroy foreign viral particles, and cytotoxic T cells identify and eradicate dengue virus-infected cells. Individuals who later contract a different strain of the dengue virus may undergo "antibody-dependent enhancement." When the immune response worsens the dengue's clinical signs, the chance of a severe dengue infection increases.

Both host and viral factors, such as nonstructural proteins, subgenomic RNA, genome variation, immune cells and their soluble components, antibody-dependent enhancement, and the presence of cross-reactive T cells, contribute to the pathogenesis of dengue infection. Although there are still some unanswered questions, advances in our knowledge of the immunological processes involved in viral clearance and illness severity may eventually lead to the creation of DENV vaccines that offer strong protection. Further evidence that despite recent advances in our understanding of DENV infection, we are still behind in our understanding of dengue-associated immunopathogenesis and that more research is necessary to fully characterize innate and adaptive immune cells and their relationships to disease severity is provided by the fact that there are currently no specific treatment options available for these patients.

References

1. Bhatt, S.; Gething, P.W.; Brady, O.J.; Messina, J.P.; Farlow, A.W.; Moyes, C.L.; Drake, J.M.; Brownstein, J.S.; Hoen, A.G.; Sankoh, O.; et al. The global distribution and burden of dengue. *Nature* 2013, *496*, 504–507.
2. Afreen, N.; Deeba, F.; Khan, W.H.; Haider, S.H.; Kazim, S.N.; Ishrat, R.; Naqvi, I.H.; Shareef, M.Y.; Broor, S.; Ahmed, A.; et al. Molecular characterization of dengue and chikungunya virus strains circulating in New Delhi, India. *Microbiol. Immunol.* 2014, *58*, 688–696.
3. Fitzmaurice, C.; Allen, C.; Barber, R.M.; Barregard, L.; Bhutta, Z.A.; Brenner, H.; Dicker, D.J.; Chimed-Orchir, O.; Dandona, R.; Dandona, L. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A systematic analysis for the global burden of disease study. *JAMA Oncol.* 2017, *3*, 524–548.
4. Horstick, O.; Tozan, Y.; Wilder-Smith, A. Reviewing dengue: Still a neglected tropical disease? *PLoS Negl. Trop. Dis.* 2015, *9*, e0003632.
5. Khan, W.H.; Ahmad, R.; Khan, N.; Ansari, M.A. SARS-CoV-2 Variants Associated Challenges in the Ongoing Vaccination of COVID-19. In *Prime Archives in Virology*; Raad, H., Ed.; Prime Archives in Virology: Hyderabad, India, 2022; Volume 1, pp. 1–59.
6. Zeyaullah, M.; AlShahrani, A.M.; Muzammil, K.; Ahmad, I.; Alam, S.; Khan, W.H.; Ahmad, R. COVID-19 and SARS-CoV-2 Variants: Current Challenges and Health Concern. *Front. Genet.* 2021, *12*, 693916.
7. Goel, N.; Ahmad, R.; Fatima, H.; Khare, S.K. New threatening of SARS-CoV-2 coinfection and strategies to fight the current pandemic. *Med. Drug Discov.* 2021, *10*, 100089.

8. Yung, C.F.; Lee, K.S.; Thein, T.L.; Tan, L.K.; Gan, V.C.; Wong, J.G.X.; Lye, D.C.; Ng, L.C.; Leo, Y.S. Dengue serotype-specific differences in clinical manifestation, laboratory parameters and risk of severe disease in adults, singapore. *Am. J. Trop. Med. Hyg.* 2015, *92*, 999–1005.
9. Thomas, L.; Najioullah, F.; Besnier, F.; Valentino, R.; Césaire, R.; Rosine, J.; Cabié, A. Clinical presentation of dengue by serotype and year of epidemic in Martinique. *Am. J. Trop. Med. Hyg.* 2014, *91*, 138–145.
10. Wilder-Smith, A. Dengue vaccine development by the year 2020: Challenges and prospects. *Curr. Opin. Virol.* 2020, *43*, 71–78.
11. Paz-Bailey, G.; Adams, L.; Wong, J.M.; Poehling, K.A.; Chen, W.H.; McNally, V.; Atmar, R.L.; Waterman, S.H. Dengue Vaccine: Recommendations of the Advisory Committee on Immunization Practices, United States, 2021. *MMWR Recomm. Rep.* 2021, *70*, 1–16.
12. Singla, M.; Kar, M.; Sethi, T.; Kabra, S.K.; Lodha, R.; Chandele, A.; Medigeshi, G.R. Immune Response to Dengue Virus Infection in Pediatric Patients in New Delhi, India—Association of Viremia, Inflammatory Mediators and Monocytes with Disease Severity. *PLOS Negl. Trop. Dis.* 2016, *10*, e0004497.
13. Narayan, R.; Tripathi, S. Intrinsic ADE: The Dark Side of Antibody Dependent Enhancement During Dengue Infection. *Front. Cell. Infect. Microbiol.* 2020, *10*, 580096.
14. Kulkarni, R. Antibody-Dependent Enhancement of Viral Infections. *Dyn. Immune Act. Viral Dis.* 2019, 9–14.
15. Keeler, S.P.; Fox, J.M. Requirement of Fc-Fc Gamma Receptor Interaction for Antibody-Based Protection against Emerging Virus Infections. *Viruses* 2021, *16*, 1037.

16. Harapan H., Michie A., Sasmono R.T., Imrie A. Dengue: A Minireview. Viruses. 2020;12:829.
17. Murugesan A., Manoharan M. Emerging and Reemerging Viral Pathogens. Elsevier; Amsterdam, The Netherlands: 2020.
18. Sindi, N. Dengue Virus: Infection, Immunological Response, and Vaccine Development. *J. Pharm. Res. Int.* 2021, *33*, 1–19.
19. Rothman, A.L. Immunity to dengue virus: A tale of original antigenic sin and tropical cytokine storms. *Nat. Rev. Immunol.* 2011, *11*, 532–543.
20. Liu, Y.-J. Dendritic Cell Subsets and Lineages, and Their Functions in Innate and Adaptive Immunity. *Cell* 2001, *106*, 259–262.
21. Cerny, D.; Haniffa, M.; Shin, A.; Bigliardi, P.L.; Tan, B.K.; Lee, B.; Poidinger, M.; Tan, E.Y.; Ginhoux, F.; Fink, K. Selective Susceptibility of Human Skin Antigen Presenting Cells to Productive Dengue Virus Infection. *PLoS Pathog.* 2014, *10*, e1004548.
22. Shresta, S.; Kyle, J.L.; Snider, H.M.; Basavapatna, M.; Beatty, P.R.; Harris, E. Interferon-Dependent Immunity Is Essential for Resistance to Primary Dengue Virus Infection in Mice, Whereas T- and B-Cell-Dependent Immunity Are Less Critical. *J. Virol.* 2004, *78*, 2701–2710.
23. Nascimento, E.J.M.; Silva, A.M.; Cordeiro, M.T.; Brito, C.A.; Gil, L.H.V.G.; Braga-Neto, U.; Marques, E.T.A. Alternative Complement Pathway Deregulation Is Correlated with Dengue Severity. *PLoS ONE* 2009, *4*, e6782.
24. Schneider, W.M.; Chevillotte, M.D.; Rice, C.M. Interferon-Stimulated Genes: A Complex Web of Host Defenses. *Annu. Rev. Immunol.* 2014, *32*, 513–545.

25. Green, A.M.; Beatty, P.R.; Hadjilaou, A.; Harris, E. Innate Immunity to Dengue Virus Infection and Subversion of Antiviral Responses. *J. Mol. Biol.* 2014, *426*, 1148–1160.
26. Nasirudeen, A.M.A.; Wong, H.H.; Thien, P.; Xu, S.; Lam, K.-P.; Liu, D.X. RIG-I, MDA5 and TLR3 Synergistically Play an Important Role in Restriction of Dengue Virus Infection. *PLoS Neglected Trop. Dis.* 2011, *5*, e926.
27. Mathew, A.; West, K.; Kalayanarooj, S.; Gibbons, R.V.; Srikiatkhachorn, A.; Green, S.; Libraty, D.; Jaiswal, S.; Rothman, A. B-Cell Responses During Primary and Secondary Dengue Virus Infections in Humans. *J. Infect. Dis.* 2011, *204*, 1514–1522.
28. Ubol, S.; Phuklia, W.; Kalayanarooj, S.; Modhiran, N. Mechanisms of Immune Evasion Induced by a Complex of Dengue Virus and Preexisting Enhancing Antibodies. *J. Infect. Dis.* 2010, *201*, 923–935.
29. Tian, Y.; Sette, A.; Weiskopf, D. Cytotoxic CD4 T Cells: Differentiation, Function, and Application to Dengue Virus Infection. *Front. Immunol.* 2016, *7*, 531.
30. Tian, Y.; Grifoni, A.; Sette, A.; Weiskopf, D. Human T Cell Response to Dengue Virus Infection. *Front. Immunol.* 2019, *10*, 2125.
31. Bhatt, P.; Sabeena, S.P.; Varma, M.; Arunkumar, G. Current Understanding of the Pathogenesis of Dengue Virus Infection. *Curr. Microbiol.* 2021, *78*, 17–32.
32. John, A.L.; Rathore, A.P.S. Adaptive immune responses to primary and secondary dengue virus infections. *Nat. Rev. Immunol.* 2019, *19*, 218–230.
33. Weiskopf, D.; Angelo, M.A.; de Azeredo, E.L.; Sidney, J.; Greenbaum, J.A.; Fernando, A.N.; Broadwater, A.; Kolla, R.V.; De Silva, A.D.; de Silva, A.M.; et al. Comprehensive analysis of dengue virus-specific

responses supports an HLA-linked protective role for CD8+ T cells. *Proc. Natl. Acad. Sci. USA* 2013, *110*, E2046-53.

34. Rivino, L.; Kumaran, E.A.; Jovanovic, V.; Nadua, K.; Teo, E.W.; Pang, S.W.; Teo, G.H.; Gan, V.C.; Lye, D.C.; Leo, Y.S.; et al. Differential targeting of viral components by CD4+ versus CD8+ T lymphocytes in dengue virus infection. *J. Virol.* 2013, *87*, 2693–2706.
35. Rivino, L.; Lim, M.Q. CD4(+) and CD8(+) T-cell immunity to Dengue-lessons for the study of Zika virus. *Immunology* 2017, *150*, 146–154.
36. Tian, Y.; Grifoni, A.; Sette, A.; Weiskopf, D. Human T Cell Response to Dengue Virus Infection. *Front. Immunol.* 2019, *10*, 2125.
37. Townsley, E.; Woda, M.; Thomas, S.J.; Kalayanarooj, S.; Gibbons, R.V.; Nisalak, A.; Srikiatkhachorn, A.; Green, S.; Stephens, H.A.; Rothman, A.L.; et al. Distinct activation phenotype of a highly conserved novel HLA-B57-restricted epitope during dengue virus infection. *Immunology* 2014, *141*, 27–38.
38. Chandele, A.; Sewatanon, J.; Gunisetty, S.; Singla, M.; Onlamoon, N.; Akondy, R.S.; Kissick, H.T.; Nayak, K.; Reddy, E.S.; Kalam, H.; et al. Characterization of Human CD8 T Cell Responses in Dengue Virus-Infected Patients from India. *J. Virol.* 2016, *90*, 11259–11278.
39. Srikiatkhachorn, A.; Mathew, A.; Rothman, A.L. Immune-mediated cytokine storm and its role in severe dengue. *Semin. Immunopathol.* 2017, *39*, 563–574.
40. Patro, A.R.K.; Mohanty, S.; Prusty, B.K.; Singh, D.K.; Gaikwad, S.; Saswat, T.; Chattopadhyay, S.; Das, B.K.; Tripathy, R.; Ravindran, B. Cytokine Signature Associated with Disease Severity in Dengue. *Viruses* 2019, *11*, 34.

41. Arias, J.; Valero, N.; Mosquera, J.; Montiel, M.; Reyes, E.; Larreal, Y.; Alvarez-Mon, M. Increased expression of cytokines, soluble cytokine receptors, soluble apoptosis ligand and apoptosis in dengue. *Virology* 2014, *452–453*, 42–51.
42. Hatch, S.; Endy, T.P.; Thomas, S.; Mathew, A.; Potts, J.; Pazoles, P.; Libraty, D.H.; Gibbons, R.; Rothman, A.L. Intracellular cytokine production by dengue virus-specific T cells correlates with subclinical secondary infection. *J. Infect. Dis.* 2011, *203*, 1282–1291.
43. Graham, N.; Eisenhauer, P.; Diehl, S.A.; Pierce, K.K.; Whitehead, S.S.; Durbin, A.P.; Kirkpatrick, B.D.; Sette, A.; Weiskopf, D.; Boyson, J.E.; et al. Rapid Induction and Maintenance of Virus-Specific CD8(+) T(EMRA) and CD4(+) T(EM) Cells Following Protective Vaccination Against Dengue Virus Challenge in Humans. *Front. Immunol.* 2020, *11*, 479.
44. Tian, Y.; Babor, M.; Lane, J.; Seumois, G.; Liang, S.; Goonawardhana, N.D.S.; De Silva, A.D.; Phillips, E.J.; Mallal, S.A.; da Silva Antunes, R.; et al. Dengue-specific CD8+ T cell subsets display specialized transcriptomic and TCR profiles. *J. Clin. Investig.* 2019, *129*, 1727–1741.
45. Silveira, G.F.; Wowk, P.F.; Cataneo, A.H.D.; Dos Santos, P.F.; Delgobo, M.; Stimamiglio, M.A.; Lo Sarzi, M.; Thomazelli, A.; Conchon-Costa, I.; Pavanelli, W.R.; et al. Human T Lymphocytes Are Permissive for Dengue Virus Replication. *J. Virol.* 2018, *92*, e02181-17.
46. Martins Sde, T.; Silveira, G.F.; Alves, L.R.; Duarte dos Santos, C.N.; Bordignon, J. Dendritic cell apoptosis and the pathogenesis of dengue. *Viruses* 2012, *4*, 2736–2753.
47. Srikiatkhachorn, A. Plasma leakage in dengue haemorrhagic fever. *Thromb. Haemost.* 2009, *102*, 1042–1049.

48. Narayan, R.; Tripathi, S. Intrinsic ADE: The Dark Side of Antibody Dependent Enhancement During Dengue Infection. *Front. Cell. Infect. Microbiol.* 2020, *10*, 580096.

49. Wahala, W.M.; Huang, C.; Butrapet, S.; White, L.J.; de Silva, A.M. Recombinant dengue type 2 viruses with altered e protein domain III epitopes are efficiently neutralized by human immune sera. *J. Virol.* 2012, *86*, 4019–4023.

50. Guzman, M.G.; Vazquez, S. The complexity of antibody-dependent enhancement of dengue virus infection. *Viruses* 2010, *2*, 2649–2662.

51. Katzelnick, L.C.; Gresh, L.; Halloran, M.E.; Mercado, J.C.; Kuan, G.; Gordon, A.; Balmaseda, A.; Harris, E. Antibody-dependent enhancement of severe dengue disease in humans. *Science* 2017, *358*, 929–932.

52. Bournazos, S.; Gupta, A.; Ravetch, J.V. The role of IgG Fc receptors in antibody-dependent enhancement. *Nat. Rev. Immunol.* 2020, *20*, 633–643.

53. Sun, P.; Williams, M.; Nagabhushana, N.; Jani, V.; Defang, G.; Morrison, B.J. NK Cells Activated through Antibody-Dependent Cell Cytotoxicity and Armed with Degranulation/IFN-γ Production Suppress Antibody-dependent Enhancement of Dengue Viral Infection. *Sci. Rep.* 2019, *9*, 1109.

54. Pan, P.; Li, G.; Shen, M.; Yu, Z.; Ge, W.; Lao, Z.; Fan, Y.; Chen, K.; Ding, Z.; Wang, W.; et al. DENV NS1 and MMP-9 cooperate to induce vascular leakage by altering endothelial cell adhesion and tight junction. *PLoS Pathog.* 2021, *17*, e1008603.

55. Luplertlop, N.; Missé, D.; Bray, D.; Deleuze, V.; Gonzalez, J.P.; Leardkamolkarn, V.; Yssel, H.; Veas, F. Dengue-virus-infected dendritic cells trigger vascular leakage through metalloproteinase overproduction. *EMBO Rep.* 2006, *7*, 1176–1181.

56. Kelley, J.F.; Kaufusi, P.H.; Volper, E.M.; Nerurkar, V.R. Maturation of dengue virus nonstructural protein 4B in monocytes enhances production of dengue hemorrhagic fever-associated chemokines and cytokines. *Virology* 2011, *418*, 27–39.
57. Azizan, A.; Sweat, J.; Espino, C.; Gemmer, J.; Stark, L.; Kazanis, D. Differential proinflammatory and angiogenesis-specific cytokine production in human pulmonary endothelial cells, HPMEC-ST1.6R infected with dengue-2 and dengue-3 virus. *J. Virol. Methods* 2006, *138*, 211–217.
58. Cruz Hernández, S.I.; Puerta-Guardo, H.N.; Flores Aguilar, H.; González Mateos, S.; López Martinez, I.; Ortiz-Navarrete, V.; Ludert, J.E.; Angel, R.M. Primary dengue virus infections induce differential cytokine production in Mexican patients. *Mem. Do Inst. Oswaldo Cruz* 2016, *111*, 161–167.
59. Sierra, B.; Pérez, A.B.; Alvarez, M.; García, G.; Vogt, K.; Aguirre, E.; Schmolke, K.; Volk, H.D.; Guzmán, M.G. Variation in inflammatory/regulatory cytokines in secondary, tertiary, and quaternary challenges with dengue virus. *Am. J. Trop. Med. Hyg.* 2012, *87*, 538–547.
60. Malavige, G.N.; Ogg, G.S. Pathogenesis of vascular leak in dengue virus infection. *Immunology* 2017, *151*, 261–269.
61. Mallat, Z.; Tedgui, A. Apoptosis in the vasculature: Mechanisms and functional importance. *Br. J. Pharmacol.* 2000, *130*, 947–962.
62. Yadav, M.; Kamath, K.R.; Iyngkaran, N.; Sinniah, M. Dengue haemorrhagic fever and dengue shock syndrome: Are they tumour necrosis factor-mediated disorders? *FEMS Microbiol. Immunol.* 1991, *4*, 45–49.

63. Masood, K.I.; Jamil, B.; Rahim, M.; Islam, M.; Farhan, M.; Hasan, Z. Role of TNF α, IL-6 and CXCL10 in Dengue disease severity. *Iran. J. Microbiol.* 2018, *10*, 202–207.
64. Züst, R.; Toh, Y.X.; Valdés, I.; Cerny, D.; Heinrich, J.; Hermida, L.; Marcos, E.; Guillén, G.; Kalinke, U.; Shi, P.Y.; et al. Type I interferon signals in macrophages and dendritic cells control dengue virus infection: Implications for a new mouse model to test dengue vaccines. *J. Virol.* 2014, *88*, 7276–7285.
65. Puc, I.; Ho, T.C.; Yen, K.L.; Vats, A.; Tsai, J.J.; Chen, P.L.; Chien, Y.W.; Lo, Y.C.; Perng, G.C. Cytokine Signature of Dengue Patients at Different Severity of the Disease. *Int. J. Mol. Sci.* 2021, *22*, 2879.
66. Chaturvedi, U.C.; Shrivastava, R.; Tripathi, R.K.; Nagar, R. Dengue virus-specific suppressor T cells: Current perspectives. *FEMS Immunol. Med. Microbiol.* 2007, *50*, 285–299.
67. Aguirre, S.; Maestre, A.M.; Pagni, S.; Patel, J.R.; Savage, T.; Gutman, D.; Maringer, K.; Bernal-Rubio, D.; Shabman, R.S.; Simon, V.; et al. DENV inhibits type I IFN production in infected cells by cleaving human STING. *PLoS Pathog.* 2012, *8*, e1002934.
68. Castillo Ramirez, J.A.; Urcuqui-Inchima, S. Dengue Virus Control of Type I IFN Responses: A History of Manipulation and Control. *J. Interferon Cytokine Res. Off. J. Int. Soc. Interferon Cytokine Res.* **2015**, *35*, 421–430.
69. Liang, Z.; Wu, S.; Li, Y.; He, L.; Wu, M.; Jiang, L.; Feng, L.; Zhang, P.; Huang, X. Activation of Toll-like receptor 3 impairs the dengue virus serotype 2 replication through induction of IFN-β in cultured hepatoma cells. *PLoS ONE* 2011, *6*, e23346.

70. Uematsu, S.; Akira, S. Toll-like receptors and Type I interferons. *J. Biol. Chem.* 2007, *282*, 15319–15323.

71. Tsai, Y.T.; Chang, S.Y.; Lee, C.N.; Kao, C.L. Human TLR3 recognizes dengue virus and modulates viral replication in vitro. *Cell. Microbiol.* 2009, *11*, 604–615.

72. Rodriguez-Madoz, J.R.; Bernal-Rubio, D.; Kaminski, D.; Boyd, K.; Fernandez-Sesma, A. Dengue virus inhibits the production of type I interferon in primary human dendritic cells. *J. Virol.* 2010, *84*, 4845–4850.

73. Morrison, J.; Aguirre, S.; Fernandez-Sesma, A. Innate immunity evasion by Dengue virus. *Viruses* 2012, *4*, 397–413.

74. He, Z.; Zhu, X.; Wen, W.; Yuan, J.; Hu, Y.; Chen, J.; An, S.; Dong, X.; Lin, C.; Yu, J.; et al. Dengue Virus Subverts Host Innate Immunity by Targeting Adaptor Protein MAVS. *J. Virol.* 2016, *90*, 7219–7230.

75. Chang, D.C.; Hoang, L.T.; Mohamed Naim, A.N.; Dong, H.; Schreiber, M.J.; Hibberd, M.L.; Tan, M.J.A.; Shi, P.Y. Evasion of early innate immune response by 2′-O-methylation of dengue genomic RNA. *Virology* 2016, *499*, 259–266.

76. Waickman, A.T.; Lu, J.Q.; Fang, H.; Waldran, M.J.; Gebo, C.; Currier, J.R.; Ware, L.; Van Wesenbeeck, L.; Verpoorten, N.; Lenz, O.; et al. Evolution of inflammation and immunity in a dengue virus 1 human infection model. Sci. Transl. Med. 2022, 14, eabo5019.

77. OhAinle, M.; Balmaseda, A.; Macalalad, A.R.; Tellez, Y.; Zody, M.C.; Saborío, S.; Nuñez, A.; Lennon, N.J.; Birren, B.W.; Gordon, A.; et al. Dynamics of dengue disease severity determined by the interplay between viral genetics and serotype-specific immunity. Sci. Transl. Med. 2011, 3, 114ra128.

78. Balmaseda, A.; Hammond, S.N.; Pérez, L.; Tellez, Y.; Saborío, S.I.; Mercado, J.C.; Cuadra, R.; Rocha, J.; Pérez, M.A.; Silva, S.; et al. Serotype-specific differences in clinical manifestations of dengue. Am. J. Trop. Med. Hyg. 2006, 74, 449–456.

79. Vicente, C.R.; Herbinger, K.H.; Fröschl, G.; Malta Romano, C.; de Souza Areias Cabidelle, A.; Cerutti Junior, C. Serotype influences on dengue severity: A cross-sectional study on 485 confirmed dengue cases in Vitória, Brazil. BMC Infect. Dis. 2016, 16, 320.

80. Thomas, L.; Verlaeten, O.; Cabié, A.; Kaidomar, S.; Moravie, V.; Martial, J.; Najioullah, F.; Plumelle, Y.; Fonteau, C.; Dussart, P.; et al. Influence of the dengue serotype, previous dengue infection, and plasma viral load on clinical presentation and outcome during a dengue-2 and dengue-4 co-epidemic. Am. J. Trop. Med. Hyg. 2008, 78, 990–998.

81. Chaturvedi, U.C.; Nagar, R. Nitric oxide in dengue and dengue haemorrhagic fever: Necessity or nuisance? FEMS Immunol. Med. Microbiol. 2009, 56, 9–24.

82. Zhang, L.; Zhao, L.; Zhang, Z.; Hong, W.; Wang, J.; Qiu, S.; Yang, H.; Gan, M.; Sun, J.; Zhao, J.; et al. Genetic and pathogenicity diversity of dengue virus type 2 strains circulating in Guangdong, China. Biosaf. Health 2021, 3, 333–342.

83. Vaughn, D.W.; Green, S.; Kalayanarooj, S.; Innis, B.L.; Nimmannitya, S.; Suntayakorn, S.; Endy, T.P.; Raengsakulrach, B.; Rothman, A.L.; Ennis, F.A.; et al. Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. J. Infect. Dis. 2000, 181, 2–9.

84. Vuong, N.L.; Quyen, N.T.H.; Tien, N.T.H.; Tuan, N.M.; Kien, D.T.H.; Lam, P.K.; Tam, D.T.H.; Van Ngoc, T.; Yacoub, S.; Jaenisch, T.; et al. Higher Plasma Viremia in the Febrile Phase Is Associated with Adverse

Dengue Outcomes Irrespective of Infecting Serotype or Host Immune Status: An Analysis of 5642 Vietnamese Cases. Clin. Infect. Dis. 2021, 72, e1074–e1083.

85. CDC. Dengue: Healthcare-providers: diagnosis. [Internet]. Centres for Disease Control and Prevention. 2019 [cited 2022 Jul 15].
86. WHO. Dengue and severe dengue. Fact Sheet [Internet]. World Health Organization. 2022 [cited 2022 Jul 1].
87. de Iani FCM, Caetano ACB, Cocovich JCW, Amâncio FF, Pereira MA, Adelino TÉR, et al. Dengue diagnostics: serious inaccuracies are likely to occur if pre-analytical conditions are not strictly followed. Mem Inst Oswaldo Cruz. 2021;115:e200287.
88. WHO. Dengue guidelines for diagnosis, treatment, prevention and control: new edition [Internet]. World Health Organization. 2009 [cited 2022 Jun 21].
89. WHO. Laboratory testing for Zika virus and dengue virus infections; Interim guidance [Internet]. World Health Organization. 2022.
90. Lanciotti RS, Calisher CH, Gubler DJ, Chang GJ, Vorndam AV. Rapid detection and typing of dengue viruses from clinical samples by using reverse transcriptase-polymerase chain reaction. J Clin Microbiol. 1992;30(3):545–51.
91. Harris E, Roberts TG, Smith L, Selle J, Kramer LD, Valle S, et al. Typing of dengue viruses in clinical specimens and mosquitoes by single-tube multiplex reverse transcriptase PCR. J Clin Microbiol. 1998;36(9):2634–9.
92. Nunes PCG, Lima MRQ, Dos Santos FB. Molecular diagnosis of dengue. Methods Mol Biol Clifton NJ. 2022;2409:157–71.
93. CDC. Dengue; prevention [Internet]. Centres for Disease Control and Prevention. 2021 [cited 2022 Oct 3].

94. Chanama S, Anantapreecha S, A-nuegoonpipat A, Sa-gnasang A, Kurane I, Sawanpanyalert P. Analysis of specific IgM responses in secondary dengue virus infections: levels and positive rates in comparison with primary infections. J Clin Virol off Publ Pan Am Soc Clin Virol. 2004;31(3):185–9.

95. Falconar AKI, de Plata E, Romero-Vivas CME. Altered enzyme-linked immunosorbent assay immunoglobulin M (IgM)/IgG optical density ratios can correctly classify all primary or secondary dengue virus infections 1 day after the onset of symptoms, when all of the viruses can be isolated. Clin Vaccine Immunol CVI. 2006;13(9):1044–51.

96. Changal KH, Raina AH, Raina A, Raina M, Bashir R, Latief M, et al. Differentiating secondary from primary dengue using IgG to IgM ratio in early dengue: an observational hospital based clinico-serological study from North India. BMC Infect Dis. 2016;16(1):715.

97. Begum F, Das S, Mukherjee D, Mal S, Ray U. Insight into the tropism of dengue virus in humans. Viruses. 2019;11(12):E1136.

98. Guzman MG, Fuentes O, Martinez E, Perez AB. Dengue. In: International Encyclopedia of Public Health [Internet]. Elsevier; 2017 [cited 2022 Oct 3]. p. 233–57.

99. Walker T, Jeffries CL, Mansfield KL, Johnson N. Mosquito cell lines: history, isolation, availability and application to assess the threat of arboviral transmission in the United Kingdom. Parasit Vectors [Internet]. 2014;7(1):382.

100. Liberal V, Forrat R, Zhang C, Pan C, Bonaparte M, Yin W, et al. Performance evaluation of a dengue IgG rapid diagnostic test designed to determine dengue serostatus as part of prevaccination screening. Microbiol Spectr [Internet]. 2022;10 (3):e00711-e721.

101. Blacksell SD. Commercial dengue rapid diagnostic tests for point-of-care application: recent evaluations and future needs? J Biomed Biotechnol [Internet]. 2012;2012:1–12.

102. CDC Africa. Dengue Fever [Internet]. Africa Centres for Disease Control and Prevention. 2022 [cited 2021 Oct 3].

103. WHO. Dengue haemorrhagic fever Diagnosis, treatment, prevention and control, 2nd edition [Internet]. 1997 [cited 2022 Jun 21].

104. World Health Organization, UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. Global vector control response 2017–2030 [Internet]. Geneva: World Health Organization; 2017. 51 p.


More Books!
yes
I want morebooks!