Review

# Immunologic Crosstalk and Host-Specific Immune Signature Associated with Dengue

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**ABSTRACT:** In tropical and subtropical regions, dengue fever is a common febrile illness that is mostly spread by Aedes mosquitoes. Urban population migration, inadequate water storage facilities, and high mosquito density are features associated with this disease. The severity of the illness ranges from mild to deadly dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), often with severe cases causing profound shock from extensive plasma leakage, and may result in demise. The symptoms of the illness include headache, myalgia, retro-orbital pain, and hemorrhagic signs. There may also be an intermittent shift in blood vessel integrity and coagulation, but recovery is typically complete and rapid. In this review, we emphasize the immunological aspects of this illness. The intricate interactions



among the virus, host genes, and host immune systems impact the pathophysiology of dengue. Postinfection antibody-dependent enhancement is prominent, which significantly influences the etiology and virulence of the disease. Whereas the severe form only manifests when the host immune system is actively working to eradicate the infection by secreting several inflammatory cytokines, chemokines, and lipid mediators, for example, early dengue virus infection (DVI) resulted in the production of Interleukin 2 (IL-2), IL-6, and later infection, IL-4, IL-5, and IL-10. Higher concentrations of interferons gamma (IFN-gamma), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage migration inhibitory factor (MIF), IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, and IL-13 were found in DHF patients. These are significantly more prevalent in severe infections than in mild ones. Numerous immunopathogenic processes involving both virus and host variables influence the severity of dengue. There is growing evidence that a compromised immune system limits viral clearance and causes severe inflammation, which in turn causes dengue hemorrhagic fever and dengue shock syndrome. Furthermore, the capacity of DENV to infect a broad range of immune cells, such as macrophages, dendritic cells, mast cells, T and B cells, and monocytes, further dysregulates these cells' antiviral activities, leading to the spread of the virus. Even though a number of risk factors linked to the advancement of the disease have been suggested, further research and evaluation of novel technologies are necessary to understand the complicated etiology and develop reliable and effective vaccines to fight against this febrile illness.
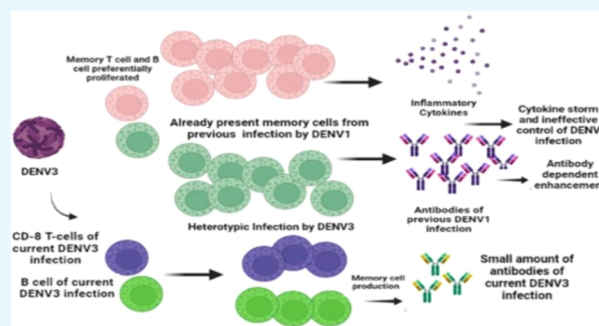
## INTRODUCTION

Over the past three decades, dengue has been a common arthropod-borne life-threatening febrile illness in tropical and subtropical countries.[1] The risk factor for dengue fever (DF) is infestation with Aedes mosquitoes. The hot and humid climate in tropical and subtropical areas promotes mosquito breeding, leading to high mosquito density. The poor water storage facilities, a high population density, and large movement of people toward urban areas help to manifest the dengue virus (DENV) with secondary infection in the host.[1] The degree of illness starts with mild DF to the most deadly dengue hemorrhagic fever (DHF) and sometimes severe DHF may cause profound shock from extensive plasma leakage in dengue shock syndrome (DSS) that may result in demise.[2] This most prominent arbovirus illness is characterized by headache, retro-orbital pain, myalgia, and, on rare occasions, hemorrhagic

manifestations.[3] Whereas, the clinical predisposition of DHF includes increased capillary permeability without morphological damage to the capillary endothelium, altered leukocyte number and functions, increased hematocrit, and thrombocytopenia.[4,5]

Severe dengue is characterized by a brief alteration in blood vessel integrity and coagulation, with recovery often being quick and complete.[6,34] This is likely due to functional changes in the vasculature, primarily caused by local biological

**Table 1. Different TLR Expression and Significance to DENV Infection**

| TLR Subfamily | Types of Cell | Soluble Mediators | Significance | References |
|---|---|---|---|---|
| TLR1 subfamily | Monocytes, neutrophils, bone marrow dendritic cells [BMDC], bone marrow macrophages [BMM], endothelial cells | IL-8, IL-6, TNF-alpha, neutrophil extracellular traps (NETs), Th2 profile cytokines | Antibody-dependent enhancement (ADE), inflammation, coagulopathies, proinflammatory imbalance | 16 and 17 |
| TLR3 subfamily | NK, mast cells, fibroblasts, THIP1, macrophage, dendritic cells, HepG2, U937 | Type 1 IFN, type III IFN, IL-8, IL-6, NO, histamine, CCL2, CCL5 CXCL10 | Antiviral response, antiviral states, cell recruitment, vascular permeability | 16 and 17 |
| TLR4 subfamily | Monocytes, endothelial cells macrophages, platelets | Inducible nitric oxide synthase/nitric oxide (iNOS/NO), IL-6, TNF-alpha, IL-8 | Coagulopathies, bleeding, vascular permeability | 16 and 17 |
| TLR7 subfamily | Monocytes, mast cells, pDC | Type 1 IFN, TNF- alpha, IL-8 | Antiviral response, antiviral states, viral neutralization | 16 and 17 |

mediators like cytokines and other soluble factors, such as in early dengue virus infection (DVI), Interleukin 2 (IL-2) and IL-6 were released, whereas later IL-4, IL-5, and IL-10 were released. In DHF, higher levels of IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, interferons gamma (IFN-gamma), granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage migration inhibitory factor (MIF) were observed.[6,34] In severe dengue cases, class switching of the Type 1 T helper (Th1) to the Type 2 T helper (Th2) is prominent. Cluster of differentiation 8+ (CD8+) T-cells play a crucial role in viral clearance, lysing virus-infected cells by producing IFN-gamma, perforin, and granzyme. T-cell mediated viral clearance plays a crucial role in lysing virus-infected cells by producing IFN-gamma, perforin, and granzyme together helping in the recognition of viral peptides with a length of 9−10 amino acids by the T cell receptor (TCR), which is found on the cell surface of antigen-presenting cells and virus-infected cells together with components of the human leukocyte antigen (HLA) system.[7] CD4+ T cells recognize longer peptides of 12−15 amino acids, performing a wider range of tasks. They are also responsible for producing both B cell and CD8+ T cell memory responses and an effective antibody response. Understanding the functional and developmental aspects of CD4+ and CD8+ T cells is essential for vaccine development, as they are crucial for protective immunity against viral diseases.[7]

## HOST VIRUS INTERFACE

DENV binds to host cells through cell surface receptors and moves further inside the cell via endosome by the process of receptor-mediated endocytosis.[8] Two favorable conditions are required to access the viral genome from the endosome to the cytosol of the cell. One is that the acidic environment of the cell helps to develop a negative charge on the endosomal membrane leading to the release of nucleocapsid, followed by the viral ribonucleic acid (RNA) release.[9]

All flavivirus proteins are synthesized as a single polyprotein that is cleaved into 10 functional viral proteins by viral and cellular proteinases in the rough endoplasmic reticulum.[10] This proteolytic processing produces 10 mature viral proteins called structural proteins capsid(C), pre/membrane structural protein (prM), and envelope protein (E) that make up the first quarter of the polyprotein, followed by seven non-structural proteins (NS1−5). The viral polyprotein was first introduced into the endoplasmic reticulum membrane and then transported to the lumen for proteolytic processing induced by both viral and cellular proteinases.[10] The viral RNA is replicated by nonstructural proteins. To replicate a virus, positive mRNA must first be transcribed to negative sense

RNA, which then acts as a template for the creation of additional positive sense RNA strands. The translation can then proceed using the positive-sense RNA.[10,11]

The nucleocapsids are encapsulated in an endoplasmic reticulum (ER) membrane along with glycoproteins, to create immature virus particles, where the freshly generated viral RNA is surrounded by capsid (C) protein and virus assembly takes place.[10]

Then the immature virus particles travel in vesicles to the acidic trans-Golgi network (TGN) where they undergo glycosylation and furin-mediated cleavage of the membrane structural protein (prM). Thus, the mature viruses leave the cell by exocytosis.[10]

## PATTERN RECOGNITION RECEPTORS

Pattern recognition receptors (PRRs) are essential for triggering innate immune responses by pathogen-associated molecular patterns (PAMPs) and/or damage-associated molecular patterns (DAMPs) such as lipopolysaccharide through Toll-like Receptor 4 (TLR4). PRRs are expressed on the cell surface, endosomes, and cytoplasm of all innate leukocytes[12] and in nonimmune cells, including fibroblasts and epithelial cells. It initiates signaling cascades by releasing interferons (IFNs), chemokines, and inflammatory cytokines.[13] The five primary PRR superfamilies are toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-like receptors (RLRs), AIM2-like receptors (ALRs), and lectin-C-like receptors (CLRs).[14] The significance of TLRs in DENV infection is highlighted in this review.

## SIGNATURE OF TOLL-LIKE RECEPTOR SIGNALING

TLRs are a class of 13 transmembrane receptors that are critical to both immunity and embryonic development, classified as TLR1 to TLR13. To date, there are 10 different TLRs identified in humans. The TLR superfamily has also been subclassified into five subfamilies according to their positions on the phylogenetic tree: subfamily TLR1, subfamily TLR3, subfamily TLR4, subfamily TLR5, and subfamily TLR7. The toll-interleukin-1 receptor homology domain (TIR) transmits TLR signals, engages in interactions with adaptor proteins, and starts signaling cascades that produce immune mediators and have an antibacterial effect.[15,16]

In reaction to DENV infection, specific cell types differentiate themselves based on the TLR subfamily. In addition to activating monocytes and dendritic cells (DCs), the TLR1 subfamily has also been linked to pro-inflammatory imbalance and coagulopathies.[16] The TLR4 subfamily has been linked to vascular diseases, including bleeding and increased vascular permeability (2022) (Table 1).[16,17] Platelet and endothelial

cell activation may be the primary routes causing these events. Through natural killer cells (NKs), mast cells (MCs), DCs, and plasmacytoid dendritic cells (pDC) cells, the TLR3 and TLR7 subfamily is linked to protective antiviral responses (Table 1).[16,17]

## SIGNATURE OF T CELLS IN THE PATHOGENESIS OF DENV INFECTION

Dengue endemic areas often experience multiple serotypes of the DENV infection, and long-term cross-serotype protective immunity is inadequate after primary infection.[18] CD8 T cells play a crucial role in the destruction of the DENV infection.

Patients with secondary DENV infection experience 10- to 20-fold more severe dengue symptoms, possibly related to the adaptive immune system's priming. The primary DENV serotype increases the probability of severity following secondary infection with various serotypes (2019).[19]

Severe symptoms such as cytokine storm, coagulopathy, and vascular leak are more common when viremia declines rapidly. Naive CD8 T-cells are activated by primary DENV infection and undergo effector cell differentiation, forming effector T cells that either lyse virus-infected cells or produce cytokines to clear the infection.[18] DENV-resistant individuals have different HLA-restricted T-cell epitopes on different viral proteins. CD4 and CD8 T-cells mediate the detection of DENV's structural and nonstructural proteins.[20,21] On the basis of the epitope identified, T-cells can react to a secondary infection brought on by a different DENV serotype.[22]

Acute DENV infection is associated with higher frequencies of DENV-specific T-lymphocytes with activated characteristics, such as the early activation marker CD69 and later other activation markers like CD38, CD71, and human leukocyte antigen-DR isotype (HLA-DR).[23,24] A greater expression of several inhibitory receptors involved in TCR signaling is also seen in HLA-DR+CD38$^+$CD8$^+$ T-cells.[25]

Both primary and secondary infections result in the development of DENV-specific cross-reactive CD8 T-cells, but the severity of the disease is not correlated with the number of these cells. It was discovered that HLA alleles are associated with a stronger multifunctional CD8 T-cell response, which is related to a lower risk of developing severe dengue sickness.[23]

Determining the distinction between mild and severe DENV infections required analysis of the DENV-specific cells. Although CD8 T-cells are capable of cytolysis during a mild DENV infection, their cytokine production capacity is impaired.[25] The majority of CD8 T cells from dengue patients become cytokine unresponsive due to TCR signaling deficiencies, according to stimulation and transcriptomics evaluation.[25] With severe initial and secondary DENV infection, CD8 T-cells show increased IFNs and TNF-cytokine responses, potentially impacting viral control and escalating immunopathology.

Activated T-cells are less vulnerable to DENV infection than nonactivated T-cells, and both CD69+ and CD69 T cells had their susceptibility to infection assessed. DENV infection did not cause CD4+ and CD8+ T cells to undergo apoptosis, a crucial step necessary for viral clearance, suggesting a potential viral escape mechanism contributing to the severity of the disease.[26] Various parenchymal and nonparenchymal cells, including monocytes, DCs, endothelial cells, and hepatocytes, were shown to undergo apoptosis as a result of DENV infection in other studies.[27−29] Hepatocytes and endothelial

cells in severe dengue cases cause hepatic damage and hemorrhagic symptoms, while monocytes and DCs aid the immune system's response, with apoptosis in pulmonary and intestinal tissue potentially linked to vascular plasma leakage (2022).[30,31]

## CYTOKINE STORM-IN IMMUNOPATHOGENESIS DURING DENV

DENV infection produces pro-inflammatory, immunoregulatory, and antiviral cytokines in the host system. Immune system activation during dengue infection may correspond to illness severity. Cytokine profiles shift as the infection progresses, leading to the production of adhesion molecules such as CD62 antigen-like family member E (CD62E), CD106, and P-selectin (CD62P), which are in turn stimulated by inflammatory cytokines.[31]

In primary DENV infection (2022), the expression of cell surface receptors in endothelial cells and responsiveness to vascular endothelial growth factor-A (VEGF-A) alters as independent of viral-specific markers.[31] The TLR4 subfamily has been linked to vascular problems, including increased permeability and bleeding. Platelet and endothelial cell activation may be the primary causes.[16] VEGF's biological effects are mediated by three receptors: VEGFR-1, VEGFR-2, and VEGFR-3. Inflammatory cytokines IL-1$\beta$ and TNF-$\alpha$ are commonly elevated in dengue cases, which can increase VEGF production through the NF-$\kappa$B pathway. VEGF may also contribute to inflammation by modulating the expression of P and E selectins and integrin-binding adhesion molecules. VEGF may also be involved in the pathogenesis of viral diseases, with some viruses promoting VEGF expression through different mechanisms. Soluble VEGF receptors, such as VEGFR2, play a role in the vascular endothelial cell biology.

Soluble VEGF receptors have also been examined in numerous research. Vascular endothelial cell biology is affected by VEGFR2, which is involved in every aspect of both normal and pathological conditions. VEGFR1 can be down-regulated by sVEGFR1, which binds VEGF and inhibits its binding to VEGFR2. By interacting with endothelial cells and releasing more free VEGF, which can also be produced by particular T cells triggered by DENV, DENV has been demonstrated to directly downregulate the synthesis of sVEGFR2. Thus, as numerous investigations have shown, elevated VEGF levels and surface VEGFR2 expression lead to enhanced vascular permeability and clinical plasma leakage in severe dengue.[32] On the other hand, following secondary infection, there is a widespread increase in the expression of these cell surface receptors and their sensitivity to VEGF-A through the viral-specific markers. DENV-infected DCs produce interferon type I to promote inflammation and release matrix metallopeptidase 2 (MMP-2) and matrix metallopeptidase 9 (MMP-9), increasing endothelial monolayer permeability.[33,34] Whereas DENV proteins, such as nonstructural protein 4B (NS4B) and NS5 induce macrophages and endothelial cells to produce IL-8, furthermore, this endothelial cell also releases IL-6, chemokine interferon-$\gamma$ inducible protein 10 (CXCL10), CXCL11, and "regulated upon activation, normal T cell expressed, and secreted" (RANTES), increasing vascular permeability and inflammation.[33,34]

Endothelial permeability and endothelial cell injury activate macrophages to release TNF. Severe dengue cases are exacerbated by a cascade of immune responses, including the secretion of TNF by immune cells, including monocytes,

**Table 2. Up-regulation and Down-regulation of Different Chemical Mediators During DENV Infection**

| Chemical mediators (up-regulation) | Chemical mediators (down-regulation) | Significance |
|---|---|---|
| Dendritic cells: IFNs-18, IL-1 beta, metalloprotease (MMP-2, MMP-9) [16, 31, 33, and 34] | CD106, CD154, IL-4, IL-6, IL-10, and IL-33 [16, 31, 33, and 34] | Proinflammatory imbalance, ADE, coagulopathies, antiviral response, antiviral states, cell recruitment and vascular permeability [16, 31, 33, and 34] |
| Macrophage: IL-8 | | |
| Mast cells: CXCL-1, IL-1 beta, CXCL-2, CCL-3, CXCL-12, CCL-4, CCL-5 [16, 31, 33, and 34] | | |
| T-Cell: IL-10, CXCL-8, CXCL-9, CXCL-10, CXCL-11 [16, 31, 33, and 34] | | |
| B-Cell: TNF-alpha (pro inflammatory cytokine) [16, 31, 33, and 34] | | |
| NK-Cell: TNF-alpha (pro inflammatory cytokine) [16, 31, 33, and 34] | | |
| Infected Endothelial cell: IL-6 (pro inflammatory cytokine), CXCL-10, CXCL-11, [16, 31, 33, and 34] | | |
| Monocyte: IL-10, TNF-alpha (pro inflammatory cytokine) TNF, IFNs, IL-1, IL-2, IL-6, IL-8, IL-10, IL-12p70, IL-17A, macrophage migration, inhibitory factor, CD54, CD62E, CD62L, and GM-CSF [16, 31, 33, and 34] | | |

macrophages, NK, invariant natural killer cells (iNKT), and DENV-specific CD4 and CD8 T cells. This leads to inflammation and increased vascular permeability, promoting cell death and affecting the coagulation system.[35,36] Different experiments in mice proved that lacking the interferon receptor gene or exposure to high doses of DENV strains, correlated with high TNF and disease severity in DHF,[37] but anti-TNF treatment eliminated hemorrhage in these models. However, patients with severe dengue have TNF levels higher than those of those with milder illnesses. Blocking TNF may be a viable strategy for treating severe dengue infection, but further research is needed to determine its safety and effectiveness. The link between TNF and dengue emergence is well-established.[38,39] TNF, IFNs, IL-1, IL-2, IL-6, IL-8, IL-10, IL-12p70, IL-17A, macrophage migration inhibitory factor, CD54, CD62E, CD62L, and GM-CSF were found to be elevated during dengue infection, while CD106, CD154, IL-4, and IL-33 were down-regulated, shown in Table 2.

On the contrary T cells release cytokines that promote inflammation and increase vascular permeability, exacerbating illness. In DHF increased T cell activation and cytokine production have been observed.[40,41] Intravenous infusion of IL-2 or TNF can increase systemic vascular leakage, supporting the idea that T lymphocytes play a vital role in the pathophysiology of DHF.[31]

Data support the cytokine storm theory, indicating a shift in cytokine patterns during dengue infection. The disease progresses to severe cases, with a change in immune response from a Th1-type to a Th2-type response.[42] Severe cases show elevated serum levels of IL-4, IL-6, and IL-10, while IFNs and IL-2 levels are low in severe cases. Early infection levels are high, but during days 4−8, IL-4 and IL-10 levels increase. However, discrepancies exist among studies due to variables.[31]

T and B cell responses are crucial in combating DENV infection but can be pathological during secondary infection due to cross-reactivity (2022).[43,44] The four DENV serotypes share 80% homology, leading to preexisting memory T and B cells rapidly proliferating.[44] As cross-reactive responses may have inadequate avidity and affinity toward the epitopes of the secondary-infecting virus,[45] protective adaptive immunity is more effective against homotypic than heterotypic reinfection.[46] As a result of their increased secretion of pro-inflammatory cytokines and lower cytotoxicity, these cross-reactive T cells can lead to endothelial dysfunction and cytokine storm[47,48] as well as ineffective viral control.[48,49]

During primary infection, such as DENV1, which activates adaptive immune responses (both T and B cells), DENV1-specific T cells are chosen, activated, and clonally increased to combat infection. After neutralization of primary infection, memory DENV1-specific T and B cells are produced and preserved more frequently than other naive cells (Figure 1). A
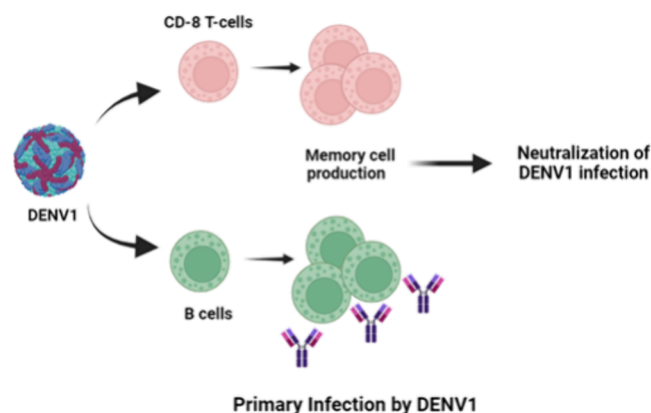


**Figure 1.** Primary infection by DENV-1: During primary infection, such as DENV1, which activates adaptive immune responses (both T and B cells), DENV1-specific T cells are chosen, activated, and clonally increased to combat the infection. After neutralization of the primary infection, memory DENV1-specific T and B cells are produced and preserved more frequently than other naive cells.

secondary infection with the same serotype of DENV (e.g., DENV1) for the second time (homotypic reinfection) (Figure 2), the virus will evoke a memory response that entails in the effective containment of DENV1 by highly specific T and B cell responses. There is a possibility that in a secondary challenge involving a heterotypic infection (a different serotype of DENV, such as DENV3) (Figure 3), the cross-reactive memory T and B cells will be more likely to be activated and multiply than the DENV3-specific T and B cells. Cross-reactive DENV1-specific adaptive immune responses compete with naïve T cells, which are more specific for DENV3. This leads to an increased memory T cell pool with low specificity for DENV3 and poor viral clearance. Antibody-dependent increased replication may also occur after a subsequent, heterologous infection.
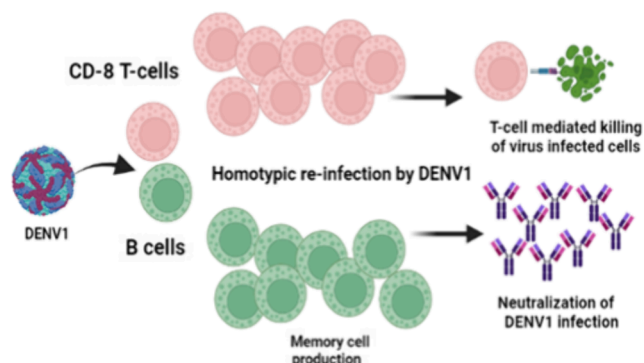
**Figure 2.** Homotypic reinfection: A secondary infection with the same serotype of DENV (e.g., DENV1 same as Figure-1) for the second time (homotypic reinfection), the virus will evoke a memory response that entails in the effective containment of DENV1 by highly specific T and B cell responses.

## INVOLVEMENT OF IMMUNE CELLS DURING DENV, CONTRIBUTING TO PATHOGENESIS

DENV can infect various cell types including epithelial and endothelial cells, hepatocytes, muscle cells, DCs, monocytes, macrophages, MCs, and B- and T-cells. The E protein and NS3 DENV antigens are found in various tissues, including the skin, liver, spleen, lymph nodes, kidney, bone marrow, lungs, thymus, and brain.[50−53] The liver and peripheral blood mononuclear cells (PBMCs) are the only organs from which these viral particles have been consistently isolated, suggesting that the immune system and the liver may be the primary targets for DENV replication during infection.[54] DCs, monocytes, macrophages, and B-cells are the main targets for DENV infection in immune cell assemblages. C-type lectins, found on the surface of DCs and macrophages, serve as the main receptors for DENV. Other DC receptors also function as DENV receptors.[55−57]

MCs may be involved in the onset of severe dengue and subsequent vascular leakage, as DENV also infects MCs in the skin, activates cytokines and chemokines, and promotes MCs degranulation.[58,59] Macrophages in lymphoid and nonlymphoid cells serve as the main reservoirs for DENV after it has spread from the skin. DENV infection affects B cell phenotypes, with increased frequencies of CD19⁺ B cells in dengue patients (2021).[60] Hospitalized dengue patients experience B-cell activation and plasma cell formation more frequently than asymptomatic individuals.[61]

## ORIGINAL ANTIGENIC SIN

The concept of "original antigenic sin" was used in 2003 for dengue severity, although the term was introduced in 1960 by Thomas Francis Jr., in the context of influenza disease. In dengue fever this term explained how specific DENV T-cells can increase the severity of secondary infections.[62] According to "initial antigenic sin," memory cells activated by the infecting virus serotype do not outnumber pre-existing cross-reactive memory B- and T-cells, leading to less effective virus eradication due to poor avidity for the infecting serotype's epitopes.[63] These memory cells exhibit a less-than-ideal degranulation process and elevated TNF and IFN production.[62] "The two basic phenomena related to dengue severity are "original antigenic sin" and "antibody-dependent facilitation of infection." Beyond these two occurrences, other factors can also be very important, such as dietary state and human genetics (the various HLA classes of genes). Human genetic variants have been shown in numerous studies to either protect against or predispose an individual to DHF and DSS. Several studies indicated that HLA (HLA-A, HLA-B, and DRB1) alleles are thought to be the primary factor influencing immunity and dengue infection.[64,65] Severe dengue is caused by cytokines, chemokines, and other inflammatory mediators, known as the "cytokine storm," which leads to multiple organ failure, endothelial permeability, and tissue destruction.[66] The
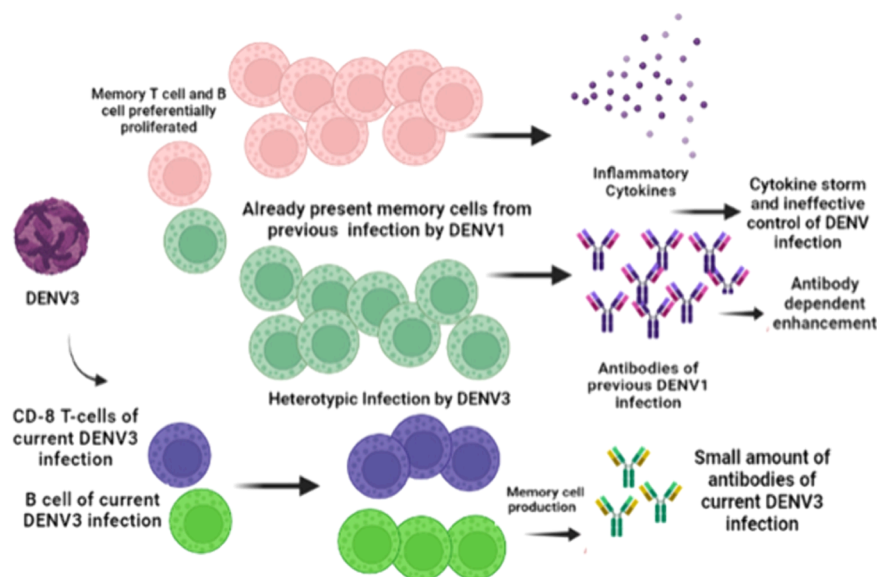


**Figure 3.** Heterotypic infection: After primary infection with DENV 2, a secondary challenge involving a heterotypic infection (a different serotype of DENV, such as DENV3), the cross-reactive memory T and B cells will be more likely to be activated and multiply than the DENV3-specific T and B cells. Cross-reactive DENV1-specific adaptive immune responses compete with naive T cells that are more specific for DENV3. This leads to an increased memory T cell pool with low specificity for DENV3 and poor viral clearance and antibody-dependent increased replication.

host's innate immune response, particularly type I interferon responses, is the first line of defense against dengue infection. DENV can avoid this response, leading to greater viral replication in target cells and increased inflammatory mediator production, leading to endothelial damage and organ dysfunction.[67]

## SIGNIFICANCE OF INTERFERON-STIMULATED GENES DURING DENV

Interferon-stimulated genes (ISGs) have been linked to the replication of DENV, targeting various points in the viral replication cycle.[68] Some ISGs, such as the tripartite motif (TRIM) protein-encoding gene (TRIM69), LGALS3BP, C19ORF66, DDX60, FBXO15, and HELZ2, have been studied for their antiviral potential.[69] In DENV-2 infection, TRIM69 mRNA and protein expression increased in a dose-dependent manner, resulting in antiviral activity and reduced DENV replication. ISGs are a key component of innate immunity and aid in the rapid development of an adaptive immune response to eradicate the pathogen.[69]

Interferons, particularly the type II IFN family, have clear antiviral effects, with the type I and III IFN families being predominantly antiviral IFNs. IFNs are transcriptionally activated by a series of steps involving viral sensors, adaptor proteins, kinases, and transcription factors.[70] IFN-I induces the expression of various genes in infected and noninfected cells, promoting antiviral cytokine production and antiviral immunity.

All nucleated cells can produce type I IFN upon detection of pathogens. During viral infections, DCs and plasmocytic dendritic cells (pDCs) are specialized cells that release large amounts of type I interferons (IFNs); type III IFNs are produced by macrophages, monocytes, and DCs, although epithelial cells are the primary source.[16] Several literature studies showed that DCs continue to be the predominant source of type I IFNs in the case of DENV.[16]

IFN-I's utility in protecting against viral infections, notably DENV infection, has been proven in several experiments that indicate how this cytokine can restrict viral replication. In vitro therapy with IFN-$\alpha/\beta$ or IFN-$\gamma$ before DENV infection can protect human HepG2 cells from viral multiplication.[71] However, treatment administered after infection does not affect viral replication, suggesting that DENV has evolved an antagonist activity against the IFN-I-mediated immune response in host-infected cells.[71] However, treatment administered after infection does not affect viral replication, suggesting that DENV has evolved an antagonist activity against the IFN-I-mediated immune response in host-infected cells.[71]

## FACTORS AFFECTING DISEASE SEVERITY

**Immune Escape Mechanism of DENV.** The DENV takes over host cells, causing cellular immunological signals to become active and fight off infection. DENV targets immune mediators to inhibit antiviral signal transduction and invisibly hides to avoid immune monitoring. The initial line of defense against viral infections is innate immunity, where type I IFN is a key component. DENV inhibits the synthesis of type I IFN to avoid the host immune system. DENV proteins suppress type I IFN signaling in infected cells, abrogating IFN genes and limiting antiviral activity.[72] DENV damages the type I IFN pathway and reduces DCs' capacity to produce a Th1-type

immune response, promoting viral persistence.[73] Conversely, TLRs and PAMPs identify viral particles and activate them. Whereas, cytosolic receptors like retinoic acid-inducible gene I (RIG-1)/anti-melanoma differentiation-associated gene 5 (MDA-5) release cytokines and chemokines that inhibit viral infection.[74] By evading cooperation between PAMPs and PRRs and blocking innate immune response steps through the expression of inhibitory molecules, DENV can infect the host and bypass innate immunity in two ways.[75] DENV NS4A disrupts type I IFN production and signaling by blocking intracellular pathways and targeting the mitochondrial antiviral-signaling (MAVS) protein, an antiviral signaling protein in the mitochondria.[76] This prevents IFN generation and interacts with the N-terminal caspase activation and recruitment domain (CARD)-like domain and C-terminal transmembrane domains of MAVS, indicating its involvement in DENV immune evasion. Another escape mechanism is conserved viral RNA structure, with viral RNA lacking 2-O-methylation identified as nonself RNA. DENV without 2-O methyltransferase activity promotes an early innate immune response and replicates with a lower viral load, allowing it to sneak past defenses and remain undetected.[77]

**Sero-Prevalence of DENV.** The severity of DENV presentations is influenced by various factors, including interactions between the virus and its host, the host's genetic makeup, certain virus strains, and the immunological response to prior infection.[78,79] DENV serotypes and their structural quirks also play a role in pathogenesis, with higher replication capacities causing increased antibody production and potentially linked to more severe outcomes.[80] A study of 485 DENV cases in a Brazilian community found that 6.6% had severe disease, with the DENV-2 serotype accounting for the majority (32.3%) and less for the DENV-1 (4.5%) and DENV-4 (6.4%) serotypes. Early serotype identification could help prevent a growing number of severe outcomes, especially during dengue outbreaks.[81−83] DENV-2 appears to be a decisive factor in the formation of severe dengue in several worldwide locations and epidemics, with increased hemorrhagic cases in places where DENV-2 is the dominating serotype. Secondary DENV-2 is more likely to cause severe disease than other serotypes. DENV-2, a type of dengue virus, can cause severe disease in children due to its stimulatory action on nitric oxide, leading to apoptosis and increased viral load.[84] Higher viral replication, which results in a high viral load, is another factor that increases pathogenicity in DENV-2 infections (2021).[85] Secondary DENV-2 is more likely to cause severe disease than other serotypes.[86] A Nicaraguan cohort found that 29% of DENV-2 hospitalized cases in 2005−2006 resulted in DHF/DSS, increasing to 63% in subsequent seasons.[87] Recent data from a Vietnamese cohort (2021) found that having higher plasma viremia during the febrile phase was associated with adverse outcomes like vascular leakage, severe dengue, and subsequent hospitalization.[31,88]

**Antibody-Dependent Enhancement.** Patients with subsequent DENV infections and newborns with primary infections are the groups at the highest risk of developing severe dengue. Antibody-dependent enhancement (ADE) is the most frequently mentioned theory for the etiology of severe dengue. The technique through which DENV, complexed with non-neutralizing antibodies, can infiltrate a larger percentage of cells of the mononuclear lineage and therefore increase virus production is known as ADE, albeit the precise mechanisms are still unclear. Humans are normally

shielded from viruses by antibodies in three ways: neutralization (blocking virus interaction with host cell), opsonization (coating the virus and typically directing it toward macrophages and neutrophils for uptake), and antibody-dependent cellular cytotoxicity (ADCC).[16]

In dengue, non-neutralizing heterotypic IgG anti-DENV antibodies produced during a person's initial DENV infection (or subneutralizing levels of antibodies in the case of infants who passively acquired IgG in utero) may form antibody-DENV complexes in the course of a second infection that may facilitate DENV uptake by macrophages. Then, in these macrophages, DENV reproduces, increasing viral load.[16] ADE can promote virus attachment and uptake in secondary infection with a heterologous serotype, which is thought to cause more serious disease. In accordance with the ADE model, DENV can engage with non-neutralizing antibodies and use Fc receptors to enter monocytes and macrophages. However, DENV-2 can directly fuse with the plasma membrane of human peripheral blood monocytes and enter. Different studies reported that endothelial cells, B cells, T cells, and hepatocytes were more prone to infection by DENV in vitro, whereas in vivo monocyte lineage is a crucial target cell for DVI.

## ■ DISCUSSION

Severe dengue fever in Asian countries is predicted to occur around 50 million annually, with the global index of severity rising due to increased infectivity.[89] The disease is more severe in children, increasing mortality if left untreated. There are no scoring systems for dengue, and sequential organ failure assessment (SOFA) is not suitable due to thrombocytopenia and the absence of important factors such as hematocrit and APTT. A study (2020) developed the Dengue Severity Index to assess the severity of illness in patients. The index was applied to 156 patients admitted to a tertiary care hospital in South India from August to September 2019. Results showed that 19 patients had a score of ≥4, suggesting severe dengue illness, with mortality as high as 16%. The Dengue Severity Index can help categorize patients and be more cautious with higher scores, especially during monsoon season.[90]

The World Health Organization (2020) estimates 100 million cases and 30,000 deaths worldwide. Early detection and proper medical help can reduce fatality rates to below 1%.[91,92] Dengue's clinical prognosis is related to both viral and host factors, even though the disease's etiology is yet unknown. Together, inflammatory mediators and a variety of immune cells carry out the innate antiviral response against DENV. Tissue macrophages, blood monocytes, and DCs are the main target cells for DENV infection. These cells can identify PAMPs by the use of PRRs. One of the most important steps in starting the innate immune response is identifying the pathogen. TLRs are an essential component of the innate immune response as well as the adaptive immune response and are responsible for the innate recognition of pathogens. Ten unique TLRs are expressed in different types of immune cells in humans. Viral PAMPs activate TLRs, which set off downstream signaling pathways that produce chemical mediators like IFNs, inflammatory cytokines, and other chemicals necessary to stop viral replication.[16]

The pathogenesis of DENV infection is believed to include a complex interplay among the virus, host genes, and host immunological response, with the host immune system playing a critical role. A study discovered that dengue viremia was indistinguishable between patients with severe dengue (SD), dengue with warning signs (DW), and dengue illness (DI), in either primary or secondary infection, but all secondary infection cases in the repeat bleed had significantly higher viremia than primary infections, despite clinical improvement from severe dengue (SD).[93] These observations demonstrate that DENV infects susceptible cells by both ADE-dependent and ADE-independent methods; however, ADE may contribute to prolonged viremia observed in secondary infections, most likely due to delayed viral clearance, as previously reported.[25] The DENV infection does not always correspond with the peak of viral load, because the host immune system is eliminating the viral particle but the severity corresponds with the viremia.[25,93]

The etiology and virulence of the sickness are further influenced by ADE that occurs after infection.[94] ADE occurs when the antibodies produced during a previous heterotypic infection are unable to neutralize a subsequent infection of a particular subtype, even after they have interacted with the viral proteins.[95]

Several inflammatory cytokines, chemokines, and lipid mediators are significantly more prevalent in individuals with severe dengue infection during the fever phase of the illness than in patients with mild infection. Pro-inflammatory cytokines are released when DENV infection occurs in monocytes, MCs, and other immune system cells, particularly when weakly neutralizing antibodies are present. This infection inhibits interferon signaling pathways. The production of immunosuppressive cytokines, such as IL-10 also inhibits cellular antiviral responses. This dysregulated and abnormal immune response leads to a vascular leak and excessive inflammation from high levels of inflammatory cytokines, which in turn causes a reduced removal of the virus and severe dengue (2020).[96] Over the past ten years, there has been a steady increase in the number of dengue cases in India. The complex relationships that exist among the virus, host, and vector are influenced by climate-related factors. A study (2017) mentions the extrinsic incubation time (EIP) and how it varies across India's different climate zones.[97] The EIP was calculated using the daily and monthly average temperatures for the states of Gujarat, Rajasthan, Kerala, Punjab, and Haryana. In general, Kerala (8−15 days at 30.8 and 23.4 °C) had a faster/lower EIP, while Punjab (5.6−96.5 days at 35 and 0 °C) had a slower/higher EIP.[97] According to another significant study (2019), there are differences in the seroprevalence of dengue in each of India's five geographical regions, with three of them having the highest dengue transmission rates. According to the distribution of serotype-specific antibodies, DENV-1 and DENV-2 serotypes were most prevalent in the northern and eastern regions; DENV-3, DENV-2, and DENV-1 serotypes were most prevalent in the western and southern regions; and DENV-3 serotype was most prevalent in the northeastern region. In all regions, younger children had larger infection forces due to their age group's suboptimal immunity.[89] In some studies (2018), much importance is given to epidemiological and entomological surveillance to track seasonal patterns, circulating serotypes, and trends in dengue distribution to guide dengue control activities.[98]

DENV was confirmed by detecting NS1 antigen; immunoglobulin M (IgM) capture ELISA and serotypes were distinguished by type-specific RT-PCR or sequencing (2019). Also, the multiplex Luminex test was used to analyze plasma samples for detecting 41-plex cytokines and chemo-

kines which are biomarkers of dengue infection.[99] The envelope E protein exhibits powerful evolutionary fingerprints with immunological selection. In addition to interserotype drift toward one another, a study discovered evidence of interserotype drift toward each other in general, suggesting selection via cross-reactive ADE. In South India (2023), where half of all E gene mutations in the antigenic sites have been acquired, there was formation of the highly divergent DENV4-Id lineage. Additionally, the DENV4-Id is moving closer to the DENV1 and DENV3 clades, which suggests that cross-reaction antibodies played a part in the evolution of the virus.[100] India's dengue surveillance, reporting, and diagnosis remain inactive, despite changes in all five serotypes.[101] To prevent spread, community-based investigations, vector control measures, and dengue vaccine development are needed.[101] The production of dengue vaccines is challenging due to the presence of five different serotypes. Mexico, Brazil, and the Philippines approved a chimeric live-attenuated vaccine candidate for adults aged 9 to 45. However, limited use calls for further research on a vaccine candidate effective for newborns and uninformed individuals.[102] To develop dengue vaccines (2020) that are both safe and effective, a study analyzes secondary dengue immunological pathways with primary immune responses, looking at how antibodies, CD4+ T cells, and CD8+ T cells affect immunity and memory recall.[103]

Severe plasma leakage monitoring system was developed in 2016 with a record of 49% severe dengue patients having plasma leakage and 51% having warning signs. This protocol introduces intravenous polyelectrolyte solution in hypotension patients.[104]

Severe dengue is caused by DENV-infected cells releasing inflammatory mediators and immune complexes and activating the complement cascade. Memory T lymphocytes recognize DENV and secrete cytokines, leading to tissue inflammation. Clinically significant plasma leakage occurs that leads to endothelial dysfunction theoretically near defervescence and lasts 24−48 h, Figure 4. The endothelial glycocalyx layer is broken down by reactive oxygen species, enzymes, and pro-inflammatory molecules, allowing plasma to leak out of the blood vessel. Patients with dengue often have hypoalbuminemia and proteinuria due to plasma protein leakage. DENV is
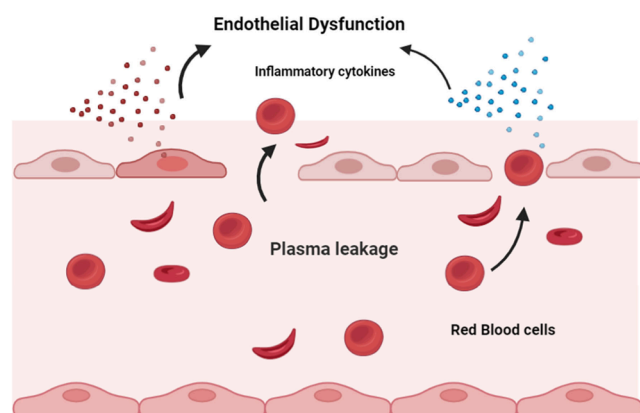


**Figure 4.** Plasma leakage and endothelial dysfunction associated with severe dengue: In severe dengue, the endothelial glycocalyx layer is broken down by reactive oxygen species, enzymes, proinflammatory cytokines, and other molecules, allowing plasma to leak out of the blood vessel.

not known to infect endothelial cells, and only minor changes have been detected in microvasculature studies (2019).[105]

Nearly two-thirds of the world's population lives in dengue-endemic regions and is at risk of acquiring the disease. This severity often results from a secondary hemorrhagic dengue infection. The mechanism by which dengue virus promotes vascular pathology and shock has been investigated. Plasma leakage occurs later in infection, after the waning of fever and viremia, likely due to host-immune or mediator-induced response rather than endothelial cell infection and destruction.[105]

Cytokines storm induced by cross reactive T cells stimulated during a second, heterotypic dengue infection mediates vascular leak syndrome. However, treatment trials using corticosteroids to combat cytokine storm have failed. High levels of chymase and tryptase in the blood of patients following dengue infection have been correlated with more severe disease.[105]

Currently, the only treatment for dengue vascular leak syndrome is supportive care. A vaccine for dengue prevention has been licensed, but unprevented cases still require treatment. Recent evidence implicates nonstructural protein 1 (NS1) and mast cells as factors involved in causing endothelial dysfunction. Treatment with nafamostat mesylate for 24 to 48 h reversed endothelial cell junction separation and resolved plasma leakage.[105]

A systematic review (2023) revealed multiple polymorphisms in immune system genes as early markers of dengue progression in Latin Americans.[106]

Understanding the immunological mechanisms triggered by natural dengue virus infection (DENV) is crucial for vaccine design, effectiveness, and deployment strategies. An interesting immunological study (2024) uses an integrative systems vaccinology approach to longitudinally characterize common immunological signals between attenuated dengue virus infection models and their molecular overlap with natural dengue infection (NDI). This comprehensive analysis provides a global picture of the host response to vaccination and identifies potential immunologic signs that can predict vaccine immunogenicity.[107]

A recent development in dengue research involves the evaluation of the immune-transcriptome response of the human host before, during, and after infection with a challenge virus that has been partially attenuated. Clinicaltrials.gov NCT02021968 is the link to it. Inflammatory genes, including type I interferon and viral restriction pathways, are activated during DENV2 viremia and revert to baseline levels following viral clearance. Conversely, postviremia, nonbaseline levels of the myeloid, migratory, humoral, and growth factor immune regulatory factors pathways are detected. Furthermore, it is possible to predict when the attenuated virus-induced immune responses and rash formation will begin based on the baseline gene expression levels before infection (2021). With this method, it is possible to identify primary DENV infection through fresh potential biomarkers and detect attenuated viral infection through a unique immunological profile.[108] Recent studies (2022) have explored the antidengue activity of various plant extracts and agents. Active phytoconstituents such as quercetin, castanospermine, α-mangostin, schisandrin-A, and hirsutin have shown promise in inhibiting all four DENV serotypes. However, novel therapeutics need to be reassessed using high-throughput techniques and in vivo dose optimization.[109] Another study (2021) showed how to identify

potential host miRNAs that target the 3′ UTR of all four Dengue virus (DENV) serotypes, potentially regulating viral gene expression or modulating the host system at different infection steps. Four prediction algorithms were used, and 30 miRNAs were identified, eight of which were of hematopoietic cell origin. The four hemopoietic origin miRNAs target genes involved in the innate immune response, mRNA 3′-end processing, antigen processing, and nuclear-transcribed mRNA catabolic process.[110] A mutation-based study (2024) showed mutations in seven conserved histidine residues of the envelope protein disrupted VLP formation without significant changes. Treatment with an acidotropic amine reversed the defect, suggesting histidines could be involved in maturation and release. Analysis of these mutants could provide insights into envelope protein interactions and aid in drug development. However, novel treatments ought to be investigated with high-throughput approaches.[111]

## CONCLUSION

This perspective represents the immunological, serological, and physiological aspects of dengue. The host immune system is thought to play a crucial part in the intricate interactions among the virus, host genes, and the host immunological response that comprise the pathogenesis of DENV infection. The production of various inflammatory cytokines, chemokines, and lipid mediators by the host immune system is necessary for the severe form to become apparent. For instance, early dengue virus infection (DVI) led to the production of Interleukin 2 (IL-2), IL-6, and later infection IL-4, IL-5, and IL-10. Patients diagnosed with diabetes mellitus had higher levels of interferon gamma (IFN-gamma), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage migration inhibitory factor (MIF), IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, and IL-13. Compared with mild infections, these are noticeably more common in severe infections. Dengue is influenced by multiple immunopathogenic pathways that are dependent on the host, as well as the virus. Moreover, DENV's ability to infect a wide variety of immune cells, including mast cells, T and B cells, macrophages, dendritic cells, and monocytes, further dysregulates the antiviral activities of these cells, facilitating the virus's dissemination. Severe forms of dengue (dengue hemorrhagic fever and dengue shock syndrome) are caused by a weakened immune system that inhibits virus clearance and produces severe inflammation, as evidenced by mounting data. As the disease progresses, several risk variables have been proposed, but further investigation and assessment of cutting-edge technologies are required to comprehend the complex etiology and create trustworthy and potent vaccinations to combat this febrile illness.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c02506.

Abbreviation list (PDF)

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### Notes

The authors declare no competing financial interest.

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