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Review Article

Immune Response to Dengue Virus Infection: Mechanisms and Implications

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ABSTRACT

Particularly in tropical and subtropical areas, dengue fever is a fast-expanding worldwide health concern with major hazards from severe forms including dengue hemorrhagic fever and dengue shock syndrome. With an eye toward processes including antibody-dependent enhancement, T-cell dysregulation, and the cytokine storm—all of which are vital in the pathophysiology to severe disease—this article discusses the immune-mediated pathogenesis of dengue. A serious issue during heterotypic serotype secondary dengue infections, antibody-dependent enhancement aggravates immune activation and promotes virus multiplication, therefore contributing to severe results. By causing an overproduction of pro-inflammatory cytokines, dysregulated T-cell responses exacerbate the situation even more and cause shock and vascular leaks. The consequences of these immune systems for the creation of dengue treatments and vaccines also are covered in the paper. The first licensed vaccination, Dengvaxia®, has sparked questions concerning antibody-dependent enhancement in people who are not dengue-naive, therefore stressing the need of safer substitutes. Though they show promise, new vaccination candidates such TAK-003 and TV003/TV005 need more research. Though further study is required, treatment choices like monoclonal antibodies and antivirals have promise for controlling severe dengue. Future studies underline enhancing vaccination safety, knowledge of immunological pathophysiology, and creation of creative treatments to better control and avoid severe dengue. Reducing the worldwide dengue load and improving disease outcomes in impacted populations depend on addressing these obstacles.

Keywords: Antibody-Dependent Enhancement, Cytokine Storm, Dengue Virus, Dengue Vaccine, Immune-Mediated Pathogenesis, Therapeutic Interventions.

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INTRODUCTION

Dengue fever, induced by the mosquito-transmitted dengue virus (DENV), represents a significant global health issue. The World Health Organization (WHO) reports that dengue infects almost 390 million individuals each year, with nearly 96 million cases exhibiting clinical symptoms. The disease has broadened its geographical distribution, presently impacting more than 100 countries in tropical and subtropical areas.[1,2] Severe manifestations of dengue, such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), result in considerable morbidity and mortality, especially in areas with little healthcare access.[3] Recent epidemics have emphasized the increasing public health burden, underscoring the necessity for effective responses.

An essential facet of dengue is its intricate interplay with the human immune system. Primary infections with one of the four serotypes of DENV typically result in mild sickness and immunity to that specific serotype; however, secondary infections with heterotypic serotypes frequently result in severe consequences. The contradictory function of the immune response, capable of both safeguarding and worsening the disease, highlights the necessity of comprehending immune-mediated pathogenesis.[4] Mechanisms including antibody-dependent enhancement (ADE), dysregulated T-cell responses, and cytokine storms are pivotal in the progression of severe dengue. This study examines these pathways and their implications for enhancing vaccine development and therapeutic methods to alleviate the global burden of dengue.

Management of dengue depends on an understanding of the processes underlying these immune responses, particularly with relation to vaccine development and treatment plans.[5] Emphasizing important processes such ADE and T-cell mediated pathogenesis, along with their consequences for clinical management of the disease, this study aims to investigate the theoretical underpinnings of immunological responses to the dengue virus. Examining these immunological mechanisms helps us to better understand the challenges faced in the creation of effective dengue vaccines and treatments.[6,7] **Error! Reference source not found.** shows the WHO's definition of the classification of symptomatic dengue infection.

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OVERVIEW OF THE DENGUE VIRUS AND IMMUNE SYSTEM INTERACTION

Structure and Serotypes of the Dengue Virus

Classed within the Flavivirus genus, the single-stranded RNA virus known as the dengue virus (DENV) includes other mosquito-borne viruses like West Nile and Zika.[8,9] Four separate but closely related serotypes characterize the dengue virus (DENV: DENV-1, DENV-2, DENV-3, DENV-4). Every serotype has unique antigenic properties; whereas protection to the other three serotypes is temporary and partial, primary infection with one serotype offers permanent immunity to that particular serotype. This process significantly influences the severity of secondary infections, as subsequent infections with a different serotype might elevate the chance of developing severe manifestations of the disease, including "DHF" and "DSS".

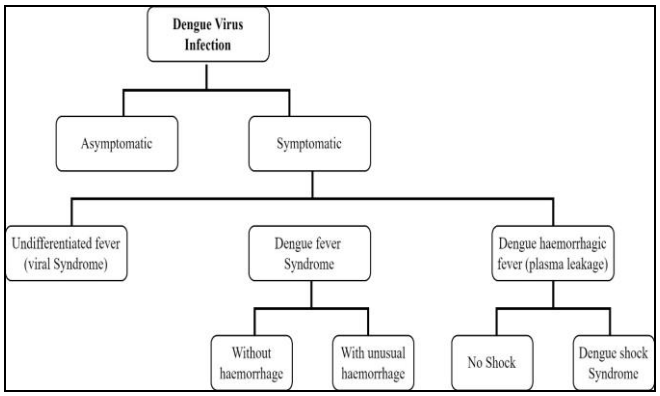

Figure-1: WHO Categorizing Disease Severity into Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS)

PRIMARY IMMUNE RESPONSE TO DENGUE VIRUS

Following infection, the body initiates an immunological response commencing with the innate immune system. DENV primarily infects and replicates within the cells of the mononuclear phagocyte system, such as dendritic cells, monocytes, and macrophages.[1] These cells identify DENV using pattern recognition receptors (PRRs) like Toll-like receptors (TLRs), which sense viral RNA. This initiates the synthesis of type I interferons (IFN-α and IFN-β), essential antiviral cytokines that assist in restricting viral replication during the initial phases of infection.[10-12]

The innate immune system additionally stimulates other immune cells, including natural killer (NK) cells, to eliminate contaminated cells. Furthermore, the infected dendritic cells go to lymph nodes, where they give viral antigens to naive T cells, so triggering the adaptive immune response.[10,13] Notwithstanding the swift activation of innate defenses, DENV has developed strategies to circumvent these responses, including the inhibition of interferon signaling pathways and the manipulation of host immunological responses to augment viral replication.

Adaptive Immune Response to Dengue Virus

The adaptive immunological response to DENV encompasses both B and T lymphocytes.[14] During the initial infection, B cells generate neutralizing antibodies that are unique to the infecting DENV serotype. These antibodies are essential for managing the illness and ensuring long-term immunity against reinfection with the identical serotype. In secondary infections with a distinct serotype, pre-existing, non-neutralizing antibodies from the initial infection may attach to the new serotype, promoting viral entrance into host cells through Fc receptors, a phenomenon termed ADE.[15] ADE results in elevated viral load and an augmented risk of severe illness.

CD4+ and CD8+T cells are crucial to the immunological response. CD4+T cells facilitate antibody synthesis, but CD8+ T cells directly eliminate infected cells.[16,17] In severe dengue instances, memory T cells from a prior infection may become hyperactivated during a secondary infection, resulting in the overproduction of pro-inflammatory cytokines, including TNF-α, IFN-γ, and IL-6. The cytokine storm can lead to increased vascular permeability, plasma leakage, and shock observed in DHF and DSS.[15,17]

MECHANISMS OF IMMUNE-MEDIATED PATHOGENESIS IN DENGUE

DENV infections can lead to a broad range of clinical manifestations, from mild dengue fever (DF) to severe dengue, encompassing "DHF" and "DSS".[18,19] The advancement to severe illness is frequently propelled by immune-mediated processes that intensify the infection instead of mitigating it. Comprehending these mechanisms is essential for formulating successful therapies. Principal immune-mediated pathways encompass "ADE", T-cell responses, and the cytokine storm.[19] **Error! Reference source not found.** is showing the immune mechanism in DENV.

Antibody-Dependent Enhancement (ADE)

ADE is a well-researched immunological mechanism linked to severe dengue.[20] ADE transpires when non-neutralizing or sub-neutralizing antibodies from a previous dengue infection enhance viral entrance into target cells, especially monocytes and macrophages.[21] During this procedure, the pre-existing antibodies attach to the surface proteins of an alternate DENV serotype but do not neutralize the virus. The virus-antibody combination is internalized into immune cells through Fc gamma receptors (FcγRs), which increases viral replication and elevates the viral load.[21,22]

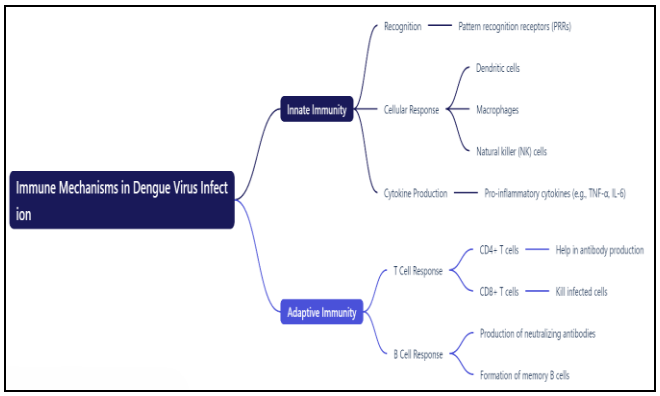

Figure-2: Immune Mechanisms in Dengue Virus Infection, Highlighting the Roles of Antibody-Dependent Enhancement (ADE), T-cell Activation, and Cytokine Storm in Disease Progression

Because the presence of cross-reactive, non-neutralizing antibodies worsens illness severity, ADE is particularly significant in future dengue infections with a different serotype. People with heterotypic secondary infections may be more likely to experience DHF and DSS as a result of this process. Research conducted by Katzelnick, Gresh[21] (references not clear) demonstrated that individuals with intermediate levels of cross-reactive antibodies were more likely to experience severe disease, highlighting the importance of ADE in the development of dengue fever.[17,23]

Apart from allowing viral entrance, ADE also controls the immunological response by increasing the activation of immune cells, hence producing synthesis of pro-inflammatory cytokines and chemokines. This inflammatory response can compromise vascular integrity, leading to plasma leakage—a feature of DHF and DSS.[17] **Error! Reference source not found.** is showing the possible monocyte function in severe dengue pathogenesis. Monocytes, both classical and non-classical, include many activating FcgRs that enable ADE, including FcgRI, FcgRIIA, and FcgRIIA. FcgRI and FcgRIIA downstream signaling reduces several cell antiviral responses, including RIG-I/MDA5-induced type I IFN, TNFa, and IL-12 production. Non-classical (CD14+CD16++) monocytes are more vulnerable to DENV infection by ADE because immune complexes bind to their FcgRIIIA (CD16a) receptors. This increases IL-10, decreases IFNb, and activates iNOS. IL-10 increases SOCS3, which inhibits JAK/STAT signaling and IFN production. DENV NS1 disrupts the endothelium glycocalyx and causes vascular leak by producing inflammatory cytokines via TLR-4. Other DENV structural proteins degrade IFN signaling molecules, impairing RIG-I signaling. DENV non-structural proteins suppress STAT-1 phosphorylation, reducing IFN generation. NS1 antibody-antigen immune complexes trigger NLRP3 via FcgRIIIA (CD16a) receptors. Cellular antiviral defense mechanisms are changed, increasing inflammatory cytokines including IL-10. Both IL-1b and TNFa cause vascular leakage. IL-10 inhibits T cell degranulation, activation, and cytokine production. Non-classical monocytes produce BAFF and APRIL, driving resting B cells to become plasma cells and potentially producing DENV-specific antibodies.

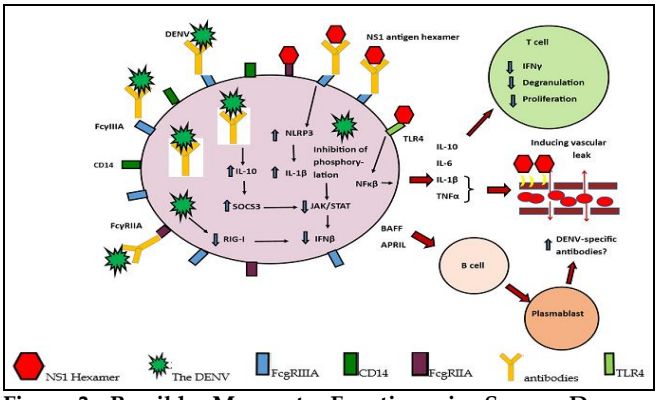

Figure-3: Possible Monocyte Functions in Severe Dengue Pathogenesis, Illustrating Ade-Mediated Viral Entry, Cytokine Production, and the Resulting Vascular Damage

T-Cell Responses and Immunopathology

T-cells are essential in controlling viral illnesses including dengue by spotting and killing contaminated cells. Particularly in secondary infections, T-cell responses in dengue may become dysregulated and cause immunopathologys.[24] Specific to the first infecting serotype, memory T cells may hyperactivate upon coming upon a different DENV serotype during a sequel infection. The mechanism known as "original antigenic sin" results in a poor

immune response whereby memory T cells predominantly react to the first serotype rather than the currently infecting serotype.[25]

Tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and interleukin-6 (IL-6) hyper-activated memory T cells produce in significant levels creating a "cytokine storm." Important traits of DHF and DSS are endothelial cell damage, increased vascular permeability, and plasma leakage, which follow from overproduction of cytokines.[25,26] Dejnirattisai, Wongwiwat,[27] Mongkolsapaya, Dejnirattisai,[28] found that T cells from those with severe dengue produced higher levels of pro-inflammatory cytokines, therefore underscoring the importance of T-cell-mediated immunopathology in severe disease.

Error! Reference source not found. is elaborating the dengue virus ADE. In patients with non-neutralizing antibodies, ADE can worsen dengue infection during secondary heterologous infection. Two components make up ADE: Extrinsic ADE enhances virus entry in susceptible cells by triggering endocytosis (actin- or clathrin-mediated) by interacting the Fc of the antibody–virus complex with the Fc receptor in the cell membrane. This facilitates the initial steps of viral replication. (B) Intrinsic ADE targets TLR signaling, type I interferon, and Th2 immune activation to boost viral generation.

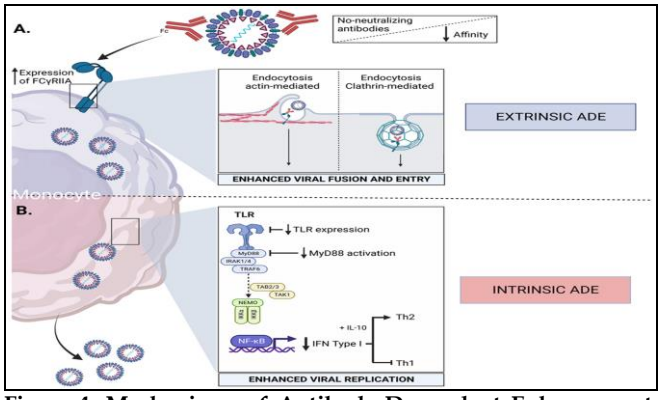

Figure-4: Mechanisms of Antibody-Dependent Enhancement (Ade) in Dengue Virus Infection, Detailing Extrinsic and Intrinsic Pathways that Increase Viral Replication and Modulate Immune Signaling

The Cytokine Storm and Vascular Permeability

A hallmark of severe dengue is heightened vascular permeability, resulting in plasma leakage, shock, and organ failure. The "cytokine storm" induced by hyperactivated immune cells is pivotal in this process. Pro-inflammatory cytokines, including TNF-α, IFN-γ, and IL-6, elicit alterations in endothelial cells, compromising the integrity of the vascular barrier. This causes plasma to leak into adjacent tissues, resulting in hypovolemia, shock, and, in certain instances, mortality.[21] The cytokine storm further enhances the recruitment and activation of more immune cells, including macrophages and neutrophils, which secrete further inflammatory mediators, worsening tissue damage.[9] The immune response in severe dengue is paradoxical: it seeks to eliminate the virus, yet the resultant inflammation and immunological hyperactivation cause extensive damage and vascular impairment. Research indicates that increased cytokine levels are associated with illness severity, as individuals with DHF/DSS exhibit markedly higher concentrations of TNF-α, IFN-γ, and IL-6 than those with mild dengue.[9,29] Alongside proinflammatory cytokines, additional elements, including matrix metalloproteinases (MMPs) and vasoactive agents such as nitric oxide, also have a role in vascular permeability. MMPs dismantle elements of the extracellular matrix, thereby compromising the vascular barrier. Nitric oxide, generated by activated immune cells, promotes vasodilation and enhances vascular permeability.[30,31] **Error! Reference source not found.** depicting the Severe dengue cytokine storm. Due to complicated virus-host interactions, subsequent heterologous infections induce a vigorous immunological response, causing immune cells to produce cytokines, chemokines, and other soluble substances. These mediators increase plasma leakage by increasing vascular permeability.

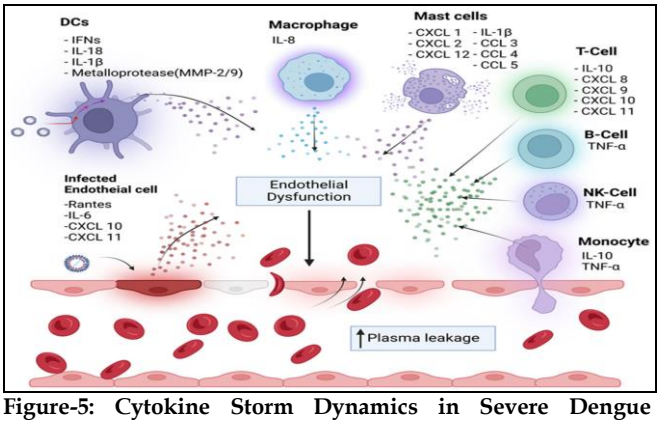

Figure-5: Cytokine Storm Dynamics in Severe Dengue Infection, Showing the Overproduction of Pro-Inflammatory Cytokines and their Role in Vascular Permeability and Plasma Leakage

CONSEQUENCES FOR DENGUE VACCINES AND TREATMENTS

The intricacy of immune responses to DENV infections poses considerable obstacles for the advancement of vaccines and treatment strategies. The immune system's dual roles as both protective and pathogenic, particularly the potential for ADE and cytokine storm, require meticulous consideration in the development of vaccines and therapies. Recent progress in vaccine research and antiviral medicines demonstrates attempts to address these issues; yet, certain obstacles persist.

Vaccines for Dengue

The creation of a safe and efficacious dengue vaccine has been a global health priority, particularly due to the rising frequency of dengue epidemics. The existence of four unique DENV serotypes hinders vaccine development. An effective vaccination must elicit protection to all four serotypes without heightening the risk of severe illness in later infections. The inaugural licensed dengue vaccine, Dengvaxia® (CYD-TDV), created by Sanofi Pasteur, obtained clearance in multiple countries in 2015. Dengvaxia® is a live-attenuated, tetravalent vaccination formulated to confer immunity against all four serotypes of DENV. Nevertheless, post-licensure investigations demonstrated that the vaccine's efficacy fluctuates based on the recipient's previous exposure to DENV. The vaccine is more efficacious in persons with a prior dengue infection but poses a heightened risk of severe disease (due to ADE) in dengue-naive recipients. This discovery led the World Health Organization (WHO) to advise the vaccine exclusively for persons with verified previous dengue exposure. This limitation highlights the difficulty presented by ADE in dengue vaccine efforts. In response to these challenges, novel dengue vaccines are currently under development. Takeda's TAK-003 vaccine, a live-attenuated tetravalent formulation, has demonstrated encouraging outcomes in clinical trials. In contrast to Dengvaxia®, TAK-003 has shown efficacy in both dengue-naive and previously infected populations, with reduced safety concerns associated with ADE. The vaccine candidate TV003/TV005, produced by the U.S. National Institutes of Health, is presently undergoing late-stage clinical trials and has demonstrated substantial protection against all four serotypes, accompanied by a positive safety profile. The new vaccines seek to achieve a balance between eliciting extensive immunity and preventing immune-enhanced pathology; nonetheless, long-term monitoring is essential to assess their efficacy and safety in diverse populations. **Error! Reference source not found.** is showing the classification of implication for vaccine development.

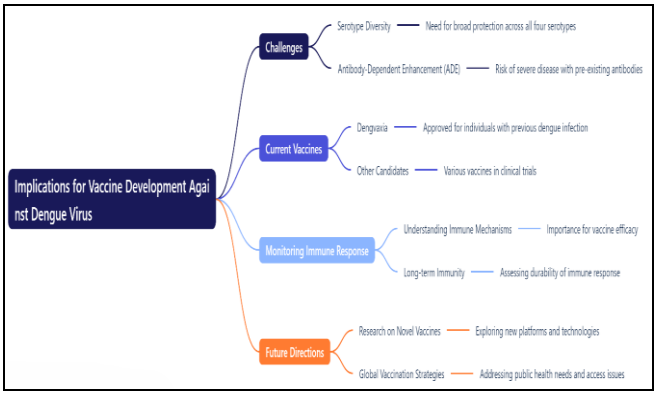

Figure-6: Implications for Dengue Vaccine Development, Summarizing Challenges in Eliciting Immunity Against all Four Denv Serotypes Without Enhancing Disease Severity

The subsequent table presents a summary of significant vaccination candidates and treatment approaches, their mechanisms, and the current status of development and trials, thereby augmenting comprehension of the topics addressed.

THERAPEUTIC INTERVENTIONS

Table : DENV Vaccination Candidates and Treatment Approaches

Category	Intervention	Mechanism of Action	Current Trial Status
Vaccines	Dengvaxia® (CYD-TDV)	Tetravalent live-attenuated DENV vaccination for all four serotypes. Effective for seropositive people but risky for dengue-naive people.	Due to safety concerns in dengue-naive populations, WHO advises use only for those with confirmed past dengue infection.
	TAK-003	Live-attenuated dengue vaccine with promising efficacy in dengue-naive and seropositive persons for further protection and reduced ADE risks.	Current Phase III clinical trials show efficacy across serotypes and good safety.
	TV003/TV005	Balanced DENV serotype immunogenicity live-attenuated vaccine candidate. Designed to avoid serotype bias and ADEs.	Phase III clinical trials show promising efficacy and safety.
	mRNA-Based Vaccines	New platform using mRNA to generate immune responses against DENV proteins without live virus danger.	Preclinical feasibility and immunogenicity investigations.
Therapeutics	Monoclonal Antibodies (mAb C10)	Targets non-cross-reactive epitopes to neutralize DENV serotypes without ADE.	Preclinical trials may avoid serious disease; clinical trials essential for safety and scalability.
	Favipiravir	Broad-spectrum antiviral that reduces DENV replication by inhibiting viral RNA polymerase.	Early therapeutic trials yielded inconsistent efficacy findings requiring dosage and administration modification in people.
	Sofosbuvir	The hepatitis C virus antiviral targets RNA polymerase to suppress DENV replication.	Few clinical studies; more needed to prove efficacy and dengue-specific usage.
	Corticosteroids	Anti-inflammatory drugs to reduce cytokine storms and immunological activation during severe dengue.	Generally ineffective and perhaps hazardous in dengue patients; not recommended for routine use.
	IL-6/TNF-α Blockers	Target key cytokines implicated in inflammation and vascular permeability to decrease cytokine storm and severe consequences.	Experimental stage; limited dengue cytokine-specific blocker trials; promise for future therapies.

Therapeutic alternatives for dengue are constrained, with existing interventions predominantly emphasizing supportive care. As our comprehension of immune-mediated pathogenesis expands, targeted treatments that adjust the immune response or directly impede viral replication are emerging as potential methods. One method entails utilizing monoclonal antibodies (mAbs) to neutralize the virus. The monoclonal antibody DENV-2 specific mAb C10 has demonstrated potential in preclinical trials to avert ADE by neutralizing DENV without exacerbating infection. Such medicines may reduce the risk of serious disease in persons with pre-existing immunity to an alternative serotype. Antiviral medications are now being explored as possible therapies for dengue. Animal studies and preliminary human clinical trials have shown that the broad-spectrum antiviral drug favipiravir can decrease DENV replication. We are also evaluating the efficacy of alternative antiviral options, such as balapiravir and sofosbuvir, in treating dengue. These candidates have shown variable outcomes. To further address cytokine storms and vascular leaks, therapies that control the immune response are also being investigated. The anti-inflammatory drug corticosteroids have not worked in dengue cases and may even make things worse. Possible strategies to prevent the substantial immune-mediated damage seen in DHF and DSS include therapies that target specific cytokines, like IL-6 blockers and TNF-α inhibitors. **Error! Reference source not found.** elaborating the Previous dengue virus (DENV) exposure drives the T cell response in illness progression. During primary infection, naïve T cells develop into effector T cells, resulting in infection clearance through lysis or cytokine release (e.g., IFN- and TNF-). In a secondary heterologous infection, cross-reactive serotype T cells activate early and produce abundant proinflammatory cytokines and chemokines, creating an excessive inflammatory environment that can cause endothelial dysfunction and vascular permeability. In a third or fourth heterologous infection, cross-reactive serotype T cells'

activation and involvement in infection severity or protection are uncertain.

Current issues have been added to monoclonal antibodies and antivirals discussions. Monoclonal antibodies like mAb C10 can neutralize dengue serotypes without ADE. However, their high manufacturing costs and cold-chain storage requirements limit their use in low-resource, high-burden locations. Broad-spectrum efficacy against all four serotypes is also difficult. In preclinical investigations, favipiravir and sofosbuvir reduced viral replication, but affordability, scalability, and the need to optimize dengue-specific dose regimens limit their clinical usage. Additionally, cytokine modulators such IL-6 and TNF-α inhibitors are being tested to reduce the cytokine storm linked to severe dengue. These methods have promise, but they are expensive, may have off-target effects, and require careful control to avoid weakening protective immune responses. These characteristics show the challenges of turning promising treatment breakthroughs into dengue-endemic population-friendly solutions.

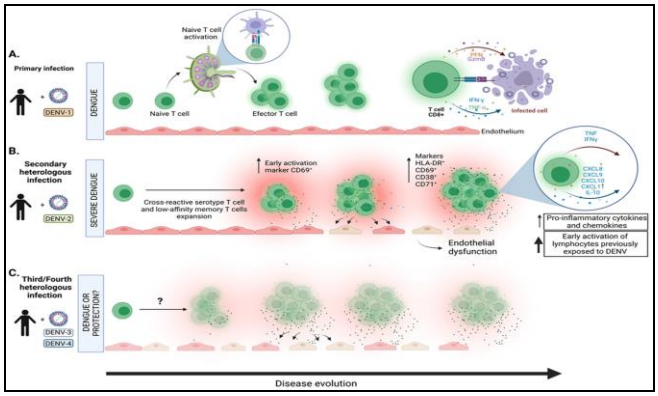

Figure-7: T-Cell Responses During Primary and Secondary Denv Infections, Emphasizing the Role of Memory T Cells in Amplifying Inflammatory Cytokines During Heterotypic Secondary Infections

PROSPECTIVE RESEARCH AVENUES

Even with great advancement in understanding DENV immunopathogenesis and the creation of vaccines and treatments, there are significant information gaps that need for more research. Future studies should focus on clarifying the subtleties of immune responses to DENV, improving vaccine efficacy and safety, and developing creative therapy approaches.

Comprehending Immune Mechanisms in Severe Dengue

Further work is required to identify the exact mechanisms involved in severe dengue, notably the role of ADE and T-cell responses. Although ADE is well established, the particular elements that prompt its onset and its long-term implications in spontaneous infections are well appreciated. Additional study is necessary to investigate the influence of pre-existing immunity to one serotype on the immune response to a subsequent infection with a different serotype. Examining these pathways will allow the development of improved immunizations and therapy therapies that minimize the incidence of ADE. The analysis of T-cell responses in dengue is a promising path for research. The phenomena of "original antigenic sin," in which memory T cells from a former infection are disproportionately activated during a subsequent infection, requires deeper research. An better grasp of T-cell dynamics' role in the cytokine storm and vascular permeability will enable fresh ways for managing immune responses to avert severe disease. Immune evasion by DENV is detailed in **Error! Reference source not found.**.

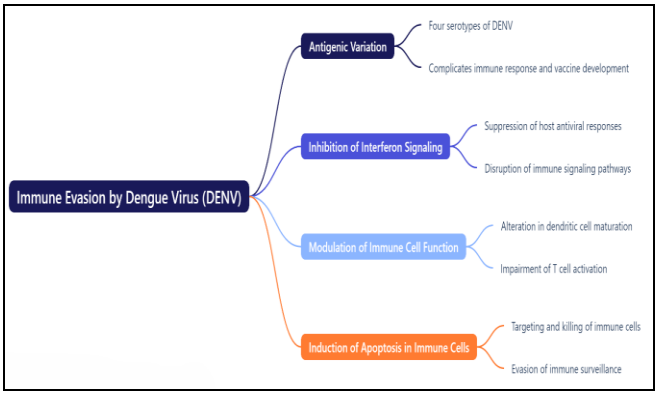

Figure-8: Immune Evasion Strategies By Dengue Virus (Denv), Highlighting Viral Mechanisms that Subvert Host Immune Defenses and Contribute to Severe Disease Outcomes

Although immunological pathways are pivotal in severe dengue outcomes, non-immune variables also substantially influence illness progression. Genetic predispositions, including differences in HLA alleles and polymorphisms in immune-related genes (e.g., TNF-α and IFN-γ), are associated with heightened vulnerability to severe dengue. Comorbidities such as diabetes, hypertension, and obesity are recognized as risk factors that intensify disease severity, presumably due to their effects on vascular integrity and immunological modulation. These considerations underscore the complex nature of severe dengue,

wherein host features interact with immunological processes to affect outcomes.

Improving Vaccine Formulation

The development of second-generation dengue vaccines, particularly TAK-003 and TV003/TV005, has shown promise. Nonetheless, ongoing research is needed to assess their long-term safety and efficacy in diverse demographics and dengue-endemic areas. Enhanced vaccine formulations must address the challenge of providing enough protection against all four DENV serotypes while avoiding immune-mediated disease. Investigations into novel vaccination platforms, such as mRNA-based vaccines, may open up new avenues for inducing widespread and long-lasting immunity without the risk of antibody-dependent enhancement (ADE).

Novel Therapeutics

The investigation of monoclonal antibodies, antivirals, and immune-modulating medicines presents significant promise for future dengue therapy. Subsequent research should concentrate on enhancing the efficacy of these medicines, assessing their safety profiles, and exploring combinations of antivirals and immune modulators to manage both viral replication and immune-mediated harm.

CONCLUSION

Particularly in tropical and subtropical regions, dengue fever still poses a major worldwide public health concern. The pathogenesis of the disease depends critically on the complex interaction between the dengue virus (DENV) and the immune system including mechanisms such antibody-dependent enhancement (ADE), T-cell dysregulation, and the cytokine storm. From mild dengue fever (DF) to severe forms like dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), the immune-mediated mechanisms are fundamental in their development. Although the development of vaccines including dengvaxia® and more recent choices like TAK-003 and TV003/TV005 marks significant advancement, the challenge of providing complete and safe protection against all four DENV serotypes remains unresolved. Safety issues with vaccinations, particularly the possibility of antibody-dependent enhancement (ADE) in people who have never had dengue, highlight the need of constant adjustment and long-term observation of these vaccines.

To address dengue's complex issues, immunologists, virologists, and public health professionals must work together. Policymakers should fund vaccination safety, immunological processes, and innovative treatment approaches research. In endemic regions, improving accessibility and cost of these treatments is crucial for equitable disease management and prevention. To effectively reduce dengue worldwide, several strategies are essential.

With monoclonal antibodies, antivirals, and immune-modulating drugs showing promise in preclinical and clinical studies, therapeutic options are improving. More research is needed to maximize these drugs especially in the treatment of severe dengue patients indicated by immune-enhanced pathogenesis. Future studies should focus on improving vaccine designs to offer more efficient and safer alternatives and on better understanding of immune systems in dengue. By addressing these problems, we can hope to reduce the global dengue load and improve the defense against this possibly fatal disease for sensitive groups.

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Authors Contribution

The following authors have made substantial contributions to the manuscript as under:

DTL & MNS: Conception, study design, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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