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IMMUNOPATHOGENESIS OF DENGUE DISEASE (DENV)

Aman Mishra, Aman Chauhan, Aniket Singh, Hargobind Makkad, Dr. Gunjan Singh
Sharda University, Schoolof Pharmacy, Greater Noida, Uttar Pradesh.

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ABSTRACT

There is a lot of research on the varied evolution of dengue virus (DENV) infection in humans. Dengue shock syndrome (DSS), dengue hemorrhagic fever (DHF), and animal models, and human data since DENV's cellular and tissue tropism are thought to be significant dengue illness factors. Dengue virus research spanning more than 50 years has yielded a substantial dataset demonstrating the relationship between virulence variables and detrimental host responses and the defective hemostasis and increased vascular permeability caused by DHF and DSS strains. DSS's underlying vascular hyperpermeability may be facilitated by targeted differentiation of particular vascular beds. A personalized approach to development research will reveal the basis of individual risk for the development of DHF and DSS and identify genetic and environmental factors for distinct risk factors for the development of serious disease.

Corresponding author
Aman Mishra
Sharda University,
Schoolof Pharmacy
Greater Noida, Uttar Pradesh.

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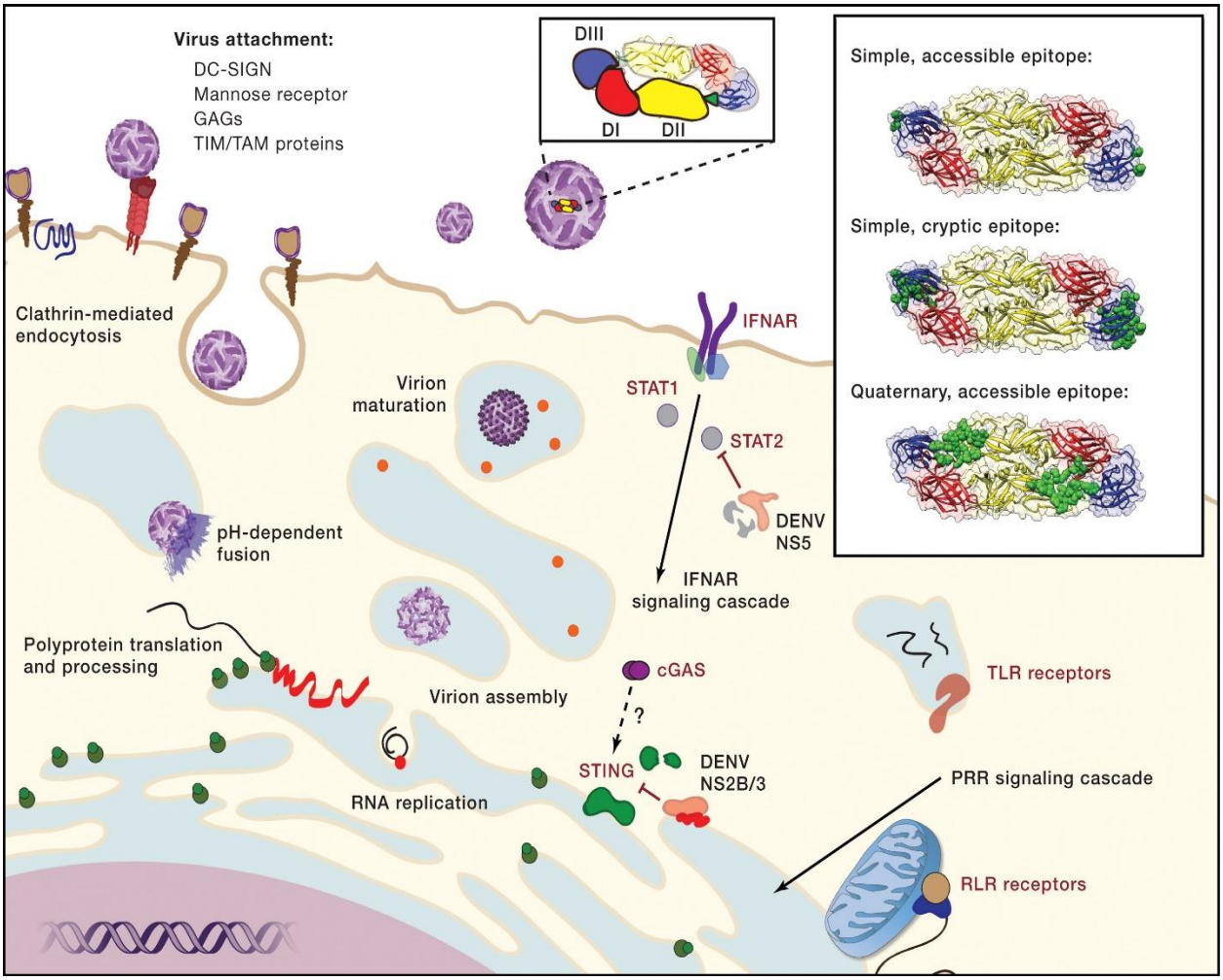
INTRODUCTION

The dengue virus (DENV), which is spread to humans by Aedes mosquitoes, primarily Aedes aegypti, is a member of the genus Flavivirus and family Flaviviridae. Four serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) can be identified using data from neutralisation assays. With an estimated 50 million infections annually and over 2.5 billion persons at risk of infection, DENV infection is a major source of disease in tropical and subtropical regions (75). Any of the DENV serotypes can cause infection, and most cases have no symptoms at all (87). The worst forms of the disease, which are marked by coagulopathy, increased vascular fragility, and permeability, can range from a mild flu-like syndrome known as dengue fever [DF] to a wide range of clinical symptoms (dengue hemorrhagic fever [DHF]). Hypovolemic shock (dengue shock syndrome [DSS]) could result from the latter. Children (≤15 years) infected with DENV have a higher chance of acquiring severe disease in Asia than do adults (30, 80, 109, 172). On the other hand, the majority of cases in the Americas are in adults and result in moderate disease (84, 186, 188). However, there has also been a noticeable increase in cases that advance towards DHF/DSS in adults there (75, 79, 87, 126, 186). Adults, teens, and older children with DF experience a debilitating illness. In addition to a strong headache, retro-orbital pain, myalgia, arthralgia, gastrointestinal distress, and typically rash, it is characterised by a sudden onset of fever. Simple hemorrhagic manifestations include gingival bleeding, petechiae, and epistaxis. A leukopenia is a typical observation, however thrombocytopenia can sporadically be seen in DF patients, particularly in those who exhibit hemorrhagic symptoms (76, 109). DHF is categorised by the World Health Organisation (WHO) into four grades (I to IV). While DHF grades III and IV are more severe and include shock, grades I and II are comparatively moderate cases without shock. Together with hemorrhagic manifestations (positive tourniquet test or spontaneous bleeding), thrombocytopenia, and signs of enhanced vascular permeability (increased hemoconcentration or fluid effusion in the chest or abdomen cavities), DHF is characterised by all the symptoms of DF. At or soon after defervescence, which is characterised by a fast, weak pulse (≤20 mm Hg) or hypotension with chilly, clammy skin in the early stages, is the life-threatening DSS stage. shock phase (grade III). Patients may enter a stage of profound shock, where their pulse and blood pressure become undetectable (grade IV), leading to mortality 12 to 36 hours after the beginning of shock, if they do not receive quick and effective treatment (262a). It's critical to remember that the WHO case definition was first intended to be a clinical diagnostic tool based on the findings of multiple clinical tests. Because it might not be reliable enough to categorise illness severity appropriately nd might not be in good agreement with clinical practise, the WHO classification system presents challenges for routine clinical practise (213). As a result, an update to the WHO classification scheme is anticipated shortly, and it is presently under review. The phase ofProlonged shock can cause disseminated intravascular coagulation (DIC) or hasten its onset (228). Better studies using prospective cohorts are required to show the frequency of DIC in DHF/DSS patients and its association with clinical outcome, as the available data are inconclusive regarding the occurrence of DIC in severe dengue (30, 152, 262). In DHF and DSS, massive blood loss is uncommon and usually limited to the gastrointestinal tract. Anoxia, cell death, and gastrointestinal bleeding are typically the result of prolonged shock, which causes blood to be diverted away from the digestive tract. On the other hand, the milder types of bleeding observed early in infection, like petechiae, are caused by various mechanisms associated with viral infection in conjunction with the cytokine release that is vasculogenic. Comprehending the process that leads to the onset of shock is essential for creating innovative approaches that enhance patient care. It is important to note that patients with DHF and DSS do not have generalised edoema; instead, radiography or sonography can be used to identify a selective plasma leakage that typically occurs in the pleural and abdominal cavities (12, 230, 246, 252, 256). Studies using ultrasound imaging have shown that plasma leakage happens prior to the onset of defervescence or noticeable alterations in hemoconcentration (12, 230, 252). Every aspect of DENV infection, including its clinical, immunological, pathological, and epidemiological characteristics, must be taken into account in an effort to fully understand the pathogenesis of dengue. This review's objective is to summarise DHF/DSS's current view points pathogenesis and to pinpoint the knowledge gaps that pose significant future challenges.

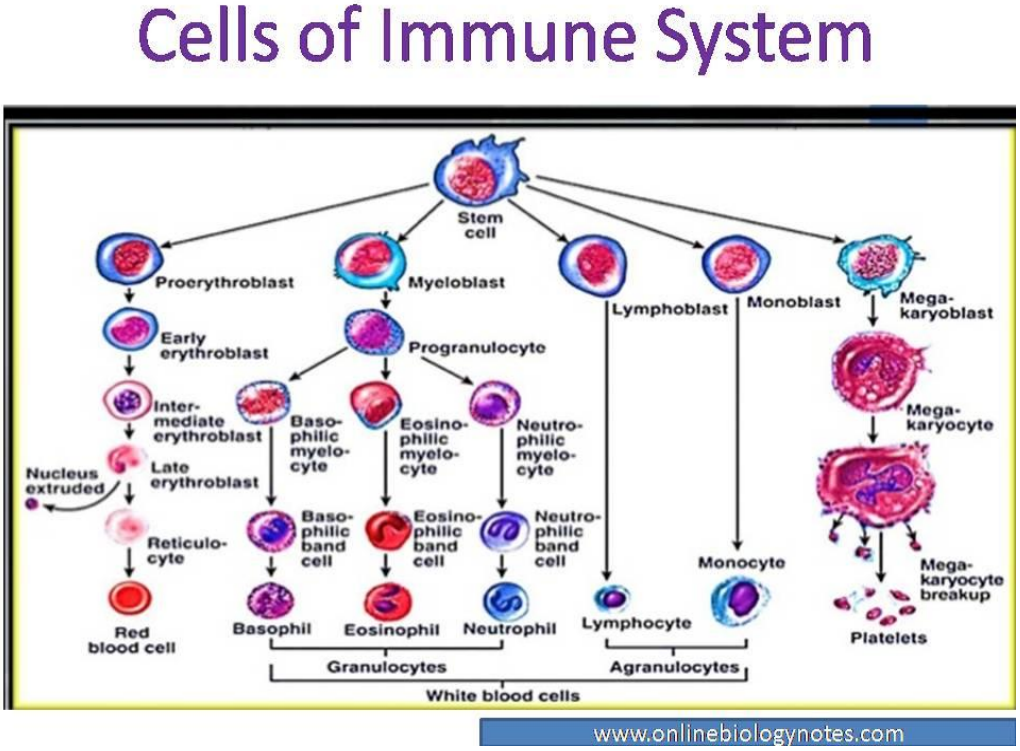
THE HISTORY OF DENV INFECTIONS: CURRENT SUMMARY

DENV Carnival.

The outcome of DENV infections may be significantly influenced by the virus's cell and tissue tropism. The lack of a suitable animal disease model significantly impedes our comprehension of the function of DENV tropism. The immune system, the liver, and the endothelial cell (EC) linings of blood vessels are the three organ systems that appear to be significant players in the pathophysiology of DHF/DSS, according to in vitro data and autopsy studies. The relevance of these events for the overall pathogenesis, the tropism of DENV for cells of the respective systems, and the corresponding pathological effects of DENV infection of these systems of DENV infection will be described.



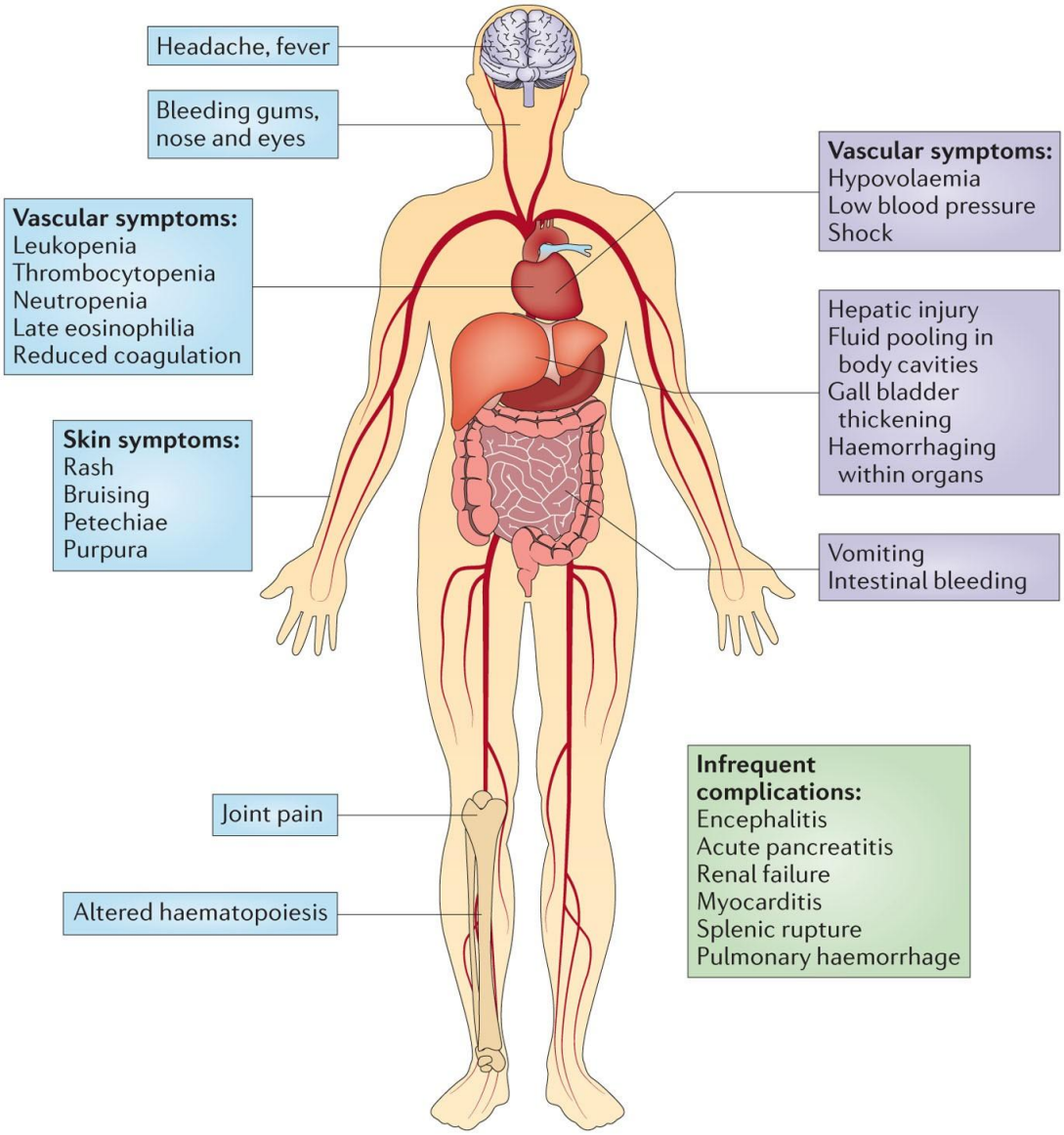
Immune System of Cells



DENV is most likely injected into the bloodstream when mosquitoes feed on humans. This injection causes spillover in the epidermis and dermis, infecting keratinocytes (136) and immature Langerhans cells (epidermal dendritic cells [DC]) (136, 263). After migrating from the infection site to lymph nodes, infected cells recruit monocytes and macrophages, which turn into targets for infection. As a result, viral replication and infection are enhanced via the lymphatic system. Numerous mononuclear lineage cells are infected as a result of this primary viremia, including splenic and liver macrophages (18, 54d, 96, 101, 117), myeloid DC (20, 91, 92, 123, 133), and blood-derived monocytes (59). Additionally, it has been demonstrated that DENV is selective for blood-circulating mononuclear cells and for cells that reside in the bone marrow, lymph nodes, and spleen of AG129-infected mice (124). In experimentally infected nonhuman primates, leukocytes have also been demonstrated to be DENV-infected (156). It should be noted that high concentrations of DENV-specific immunoglobulin G (IgG) will complex newly produced virus that adheres to and is taken up by mononuclear cells during secondary infections with heterologous DENV. After infection, the majority of mononuclear cells die by apoptosis (61, 182), whereas abortively infected or bystander DC are stimulated to produce the majority of mediators involved in the host's hemostatic (48, 60, 97, 120, 236) and inflammatory (22, 47, 91, 133, 145) responses. In this context, variables that impact the number of target cells infected and, in turn, the viremia levels may as well as how the inflammatory response impacts the hemostatic system, ascertain the ratios of various pro- and anti-inflammatory cytokines, chemokines, and other mediators (35, 59). It has also been demonstrated that bone marrow stromal cells are vulnerable to DENV infection (124, 171, 202).

Organ dysfunction

The immune system, the liver, and the endothelial cell (EC) linings of blood vessels are the three organ systems that appear to be significant players in the pathophysiology of DHF/DSS, according to in vitro data and autopsy studies.In the past 60 years, thousands of cases of confirmed dengue have been identified in Southeast Asia and the Americas; however, only a small percentage of these patients have had autopsies, raising questions about whether or not those cases are typical of the viral Tropism during the early stages of an infection is unknown.

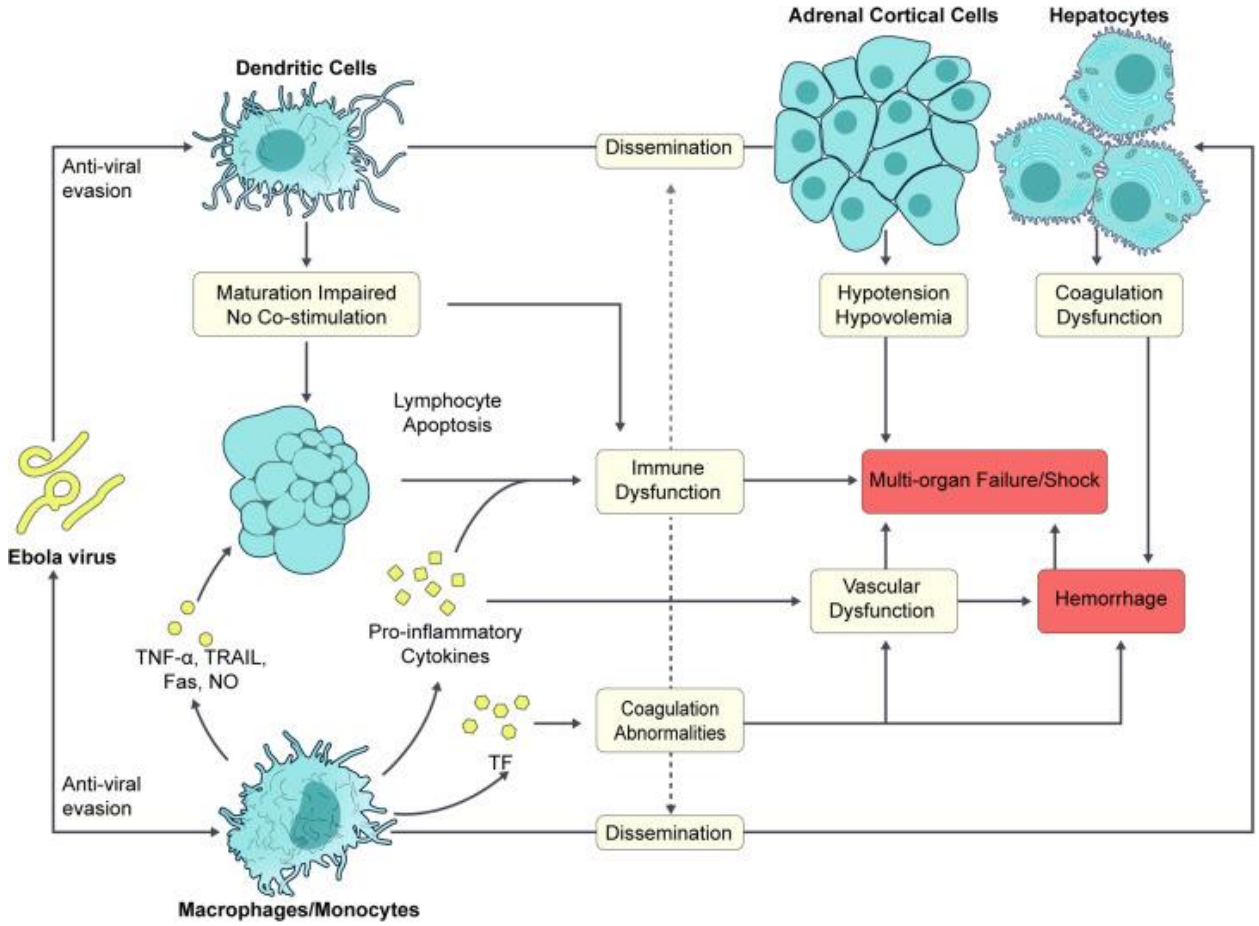


Because fatal cases of DHF/DSS are uncommon and mostly occur in remote areas of the world where appropriate laboratory technology is largely lacking, it is challenging to conduct histopathological research using fresh or frozen patient materials. Further more, most families choose for quick burial or cremation in place of an autopsy in the majority of fatal cases due to cultural and religious customs. A skewed age distribution, varying sample collection times, and the variety of methods used to confirm the presence of virus in affected tissues impede the interpretation of the pathological findings in fatal cases of DHF/DSS in relation to viral tropism reported in the literature. Studies that had employed inferred DENV cell tropism immunohistochemistry, in situ hybridization, or a mix of PCR and virus isolation methods. The presence of DENV in cells was found in the skin (104), liver (13, 14, 53, 54d, 69, 96, 101, 104, 137, 164, 173, 199, 208), spleen (13, 14, 101, 164, 199, 208), lymph node (13, 14, 101, 104, 173, 199, 208), kidney (14, 78, 101), bone marrow (13, 78, 101, 173), lung (13, 78, 101, 137, 164, 173), thymus (106), and brain (164). These findings were based on a review of the literature describing findings on autopsy samples from a total of 160 fatal cases, most of which were children or young adolescents (4 to 18 years old) who died within 36 hours of developing shock. In these samples, the infectious virus was not always present. Looked into, but generally speaking, the virus could only be isolated from peripheral blood mononuclear cells and the liver. The fact that the majority of organ samples were unable to isolate the virus could mean that the virus present in those tissues was either degraded or complexed with antibodies that inhibit in vitro cell infection. According to the pathophysiology of DHF/DSS, the presence of DENV in multiple organs was generally not linked to microscopic or macroscopic evidence of severe organ pathology (17). Similar organ tropism has been seen in the primate model, where the skin and gastrointestinal tract contained high virus concentrations while the spleen, thymus, and several peripheral lymph nodes contained low virus concentrations (157).

DENV has been isolated from peripheral blood, liver, and spleen. In mice lacking alpha/beta interferon (IFN-α/β), the lymph nodes and central nervous system are affected (13, 267). The tropism of DENV for neuronal cells is one obvious distinction between the human model and the mouse model.

It is interesting to note that a common argument in the literature is that the host response should be a major factor in pathogenesis because, once shock sets in, the virus is no longer detectable in blood (134, 166). While the majority of autopsy data did not specifically compare the levels of nucleic acid or viral antigens in autopsy samples and blood, the scant evidence does indicate that DENV replication might take place in certain organs while viremia is no longer detectable (199).

Pathogen iVirulence

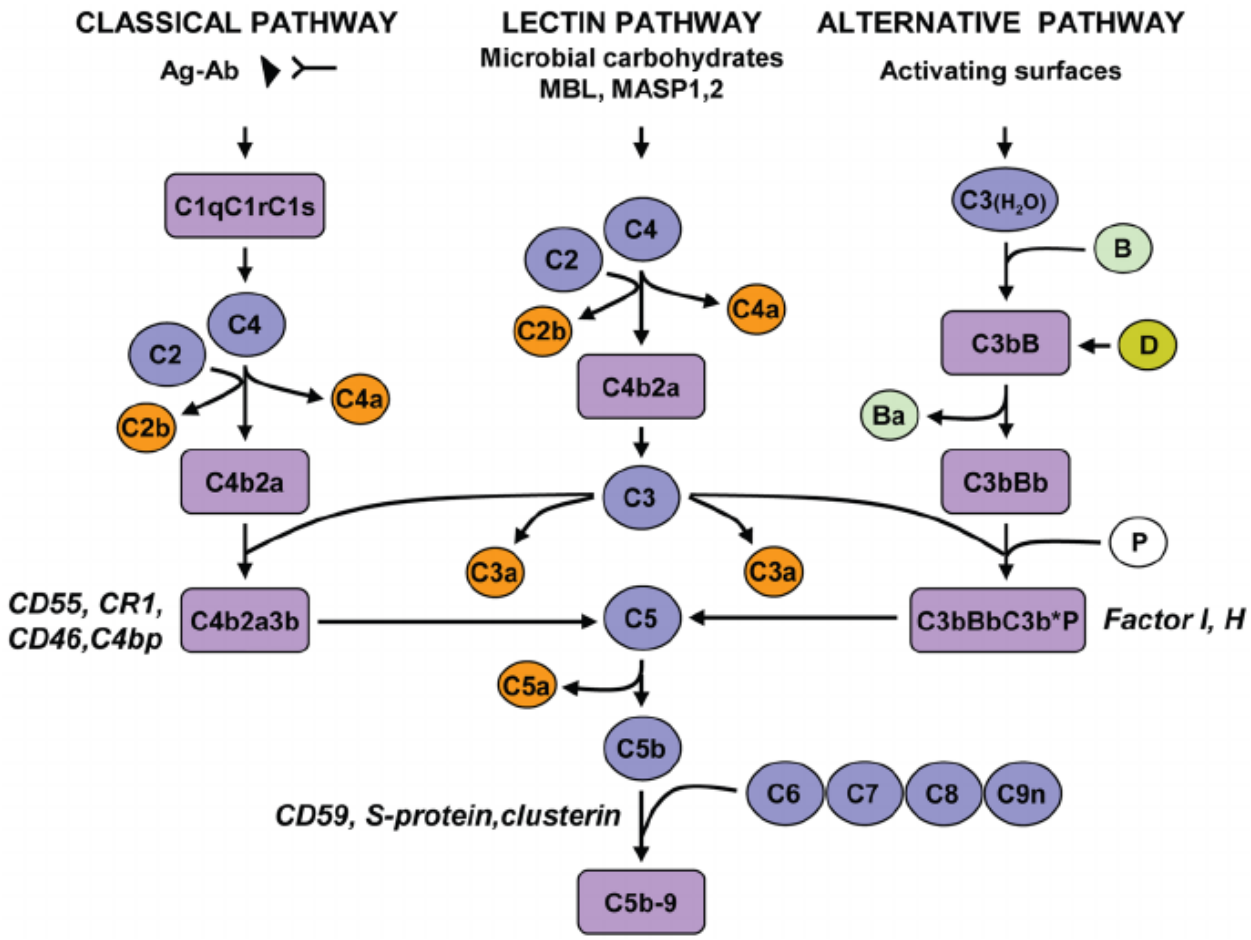


The virus virulence hypothesis states that more severe disease is caused by specific DENV strains. Based on differences in nucleotides, DENV serotypes can be further divided into distinct genotypes. Variations in viral virulence have been linked to genetic variations (51, 131, 206, 248). Surprisingly, the first DHF outbreak in the Americas happened in 1981, around the same time that the less virulent native DENV-2 genotype was already circulating in the area and the possibly more virulent Southeast Asian genotype was introduced (118, 195-197). Additionally, it has been suggested that the circulating DENV's interepidemic evolution may be to blame for the disease's increased severity. It was observed that case-fatality rates and the severity of disease manifestations were higher during the DENV-2 epidemic that struck Cuba in 1981towards the end of the outbreak (118, 119), implying that host passage during the epidemic may have increased the virulence of the circulating DENV-2. Similar circumstances were noted in Townsville, Australia during the DENV epidemic in 1992 (234), and once more in Cuba during the epidemic in 1997 (81). DENV does evolve during an epidemic, according to analyses of their genomes (42, 198); however, further research is required to determine whether interepidemic viral evolution and heightened disease severity are related. The sequence of infection with specific serotypes and the interval between primary and secondary infection may be significant factors in the development of DHF, according to epidemiological observations from Singapore and the Americas. High-incidence DHF epidemics have included. connected to initial DENV-1 infection, then infection with either DENV-2 or DENV-3 (79, 83, 178). These studies also showed that the likelihood of developing a severe illness increased with the length of time between primary and secondary infections. Furthermore, after a secondary infection with heterologous DENV, age has been demonstrated to affect the course of the illness (80). In contrast to the Americas, where infection primarily affects adults and causes milder disease, Asia has a higher risk of severe disease among children than among adults. The structural variations between the two DENV strains

and the variation in disease severity brought about by the Asian and American genotypes are correlated (51, 131). Additionally, research has demonstrated that various regional DENV strains or The capacity of various serotypes to infect distinct cell types or result in serious illness may differ (56, 251). Even with supposedly virulent strains of DENV, the observation that DHF/DSS is observed primarily in a relatively small percentage of secondary infections and to a much lesser extent in primary infections implies that host factors must be important determinants of the development of severe disease.

It is crucial to understand that virulence has historically been regarded as a microbial characteristic that can only be assessed in vitro, independent of the host, or in animals that are frequently inbred. Nonetheless, a growing amount of data implicates the host immune response in the development of numerous microbial infections (31). Thus, it is important to take into account both host and viral factors when researching DENV virulence.

EnablingtheComplementarySystem

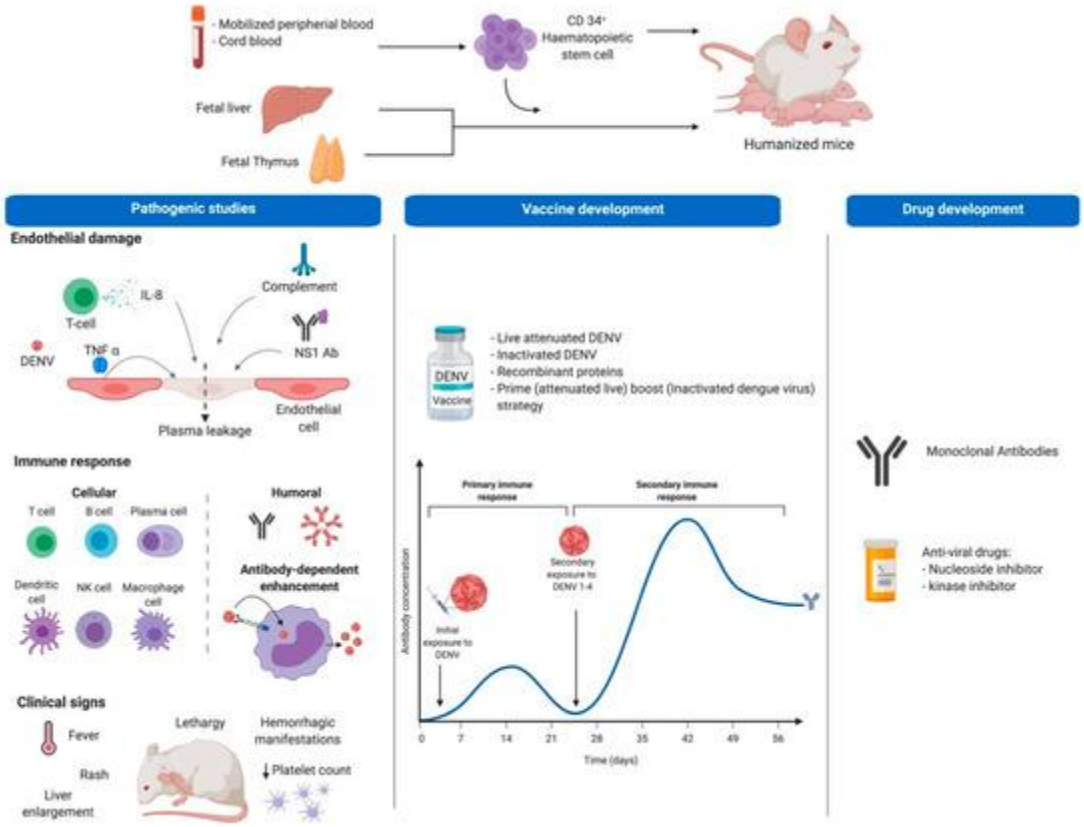


One of the primary humoral elements of innate immunity is the complement system, which works in tandem with the hemostatic system to offer the first line of defence against infections. The host can maximally induce the more slowly developing adaptive immunity thanks to these innate immune mechanisms. Regarding DENV, researchers observed that patients with DSS exhibited accelerated complement component consumption and a marked reduction in complement components around the time of defervescence, when plasma leakage may become noticeable. High levels of the activation products C3a and C5a were also detected in the plasma at this time (50, 174, 214). Complement activation was therefore thought to be crucial to the pathophysiology of dengue. Comparing the global profiles of gene expression in Peripheral blood mononuclear cells from patients with DF and DHF/DSS also point to the complement system's role in the severity of the illness (249). There is still much to learn about complement activation and its part in DENV pathogenesis.

There has been a suggestion that NS1 plays a significant role in complement activation (122). Complement activation may occur when heterotypic antibodies bind to NS1 expressed on infected cells (8, 142). Furthermore, it's thought that complement factors in the fluid phase can be directly activated by NS1 released from infected cells (122). The synthesis of the C5b-C9 complex may subsequently set off biochemical processes and promote the release of inflammatory cytokines linked to the advancement of DHF/DSS (8). On the other hand, the C5b-C9 complex may independently cause additional local and ability to self-associate into multivalent complexes, which raises the possibility of C1q binding and functional affinity.

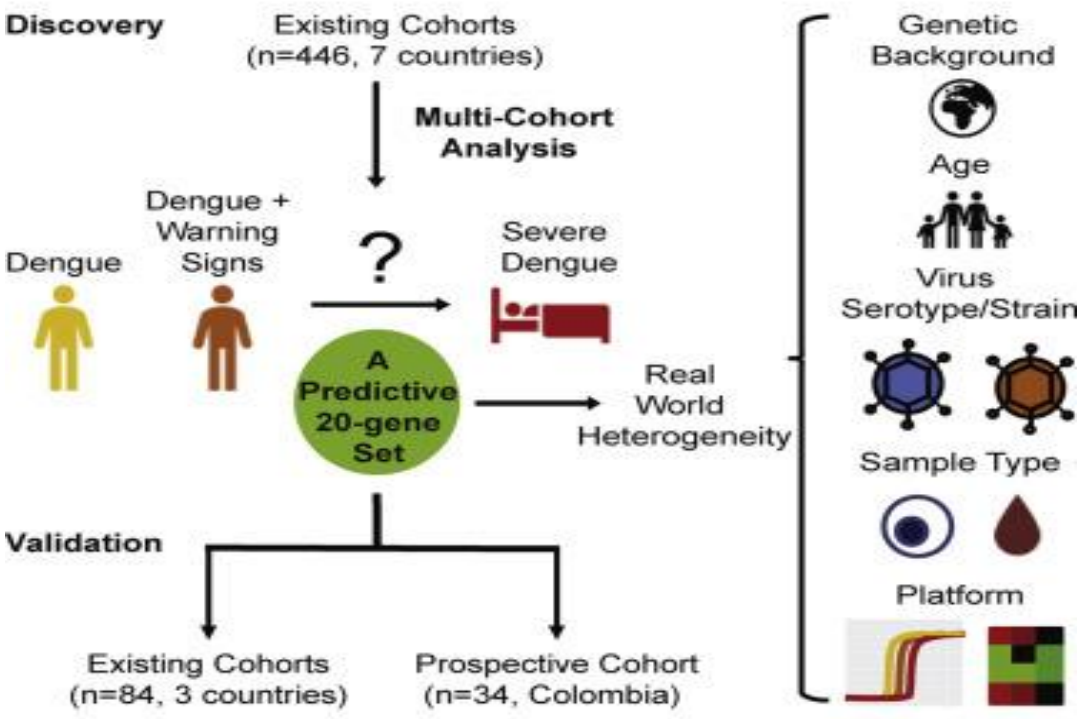
The complement-fixing abilities of IgG subclass glycans (100) and potentially their capacity to enhance infection (65, 163, 266) may also be impacted by the presence of sialic acid in those glycans. It's critical to comprehend what establishes the required activation threshold and how activation contributes to the development of DHF/DSS.

Temporary Autoimmunity



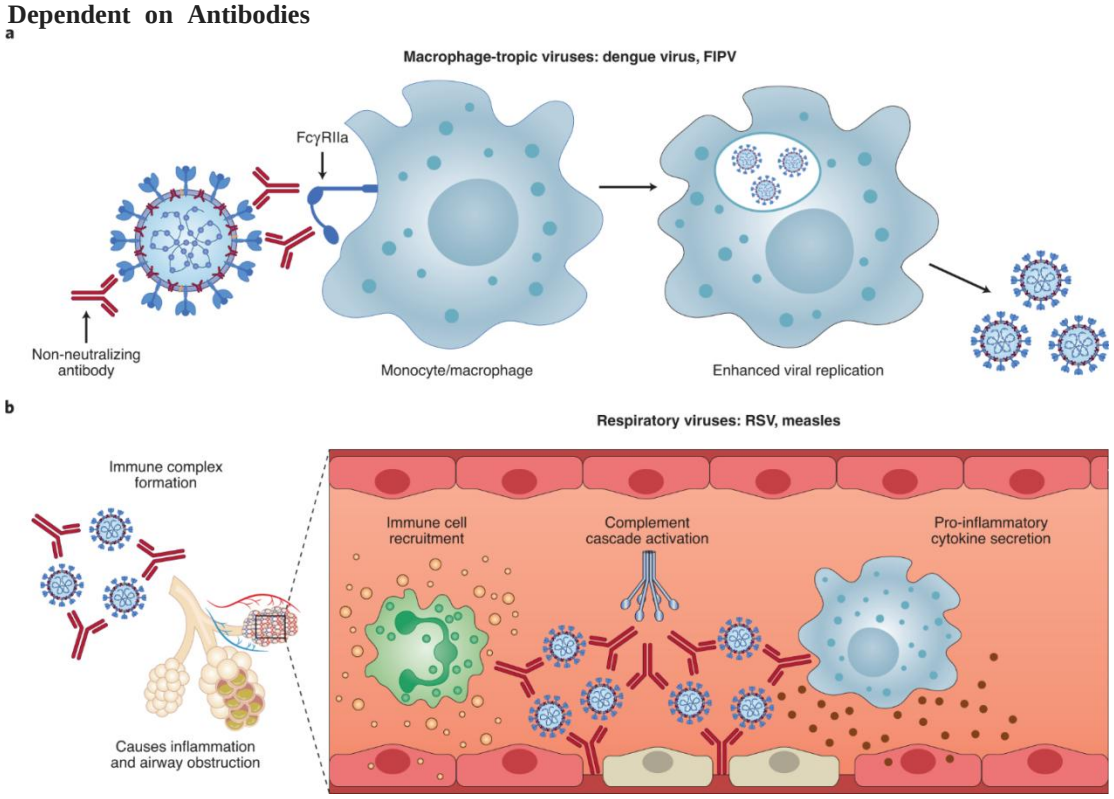
While it has been demonstrated that antibodies generated during a DENV infection can cross-react with certain self-antigens, it is unclear whether the generation of these antibodies is linked to subsequent DENV infections. For example, it has been demonstrated that antibodies that identify a linear epitope in the E protein can bind to human plasminogen and subsequently block plasmin activity (49, 64, 94, 159).

Factors Genetically Host



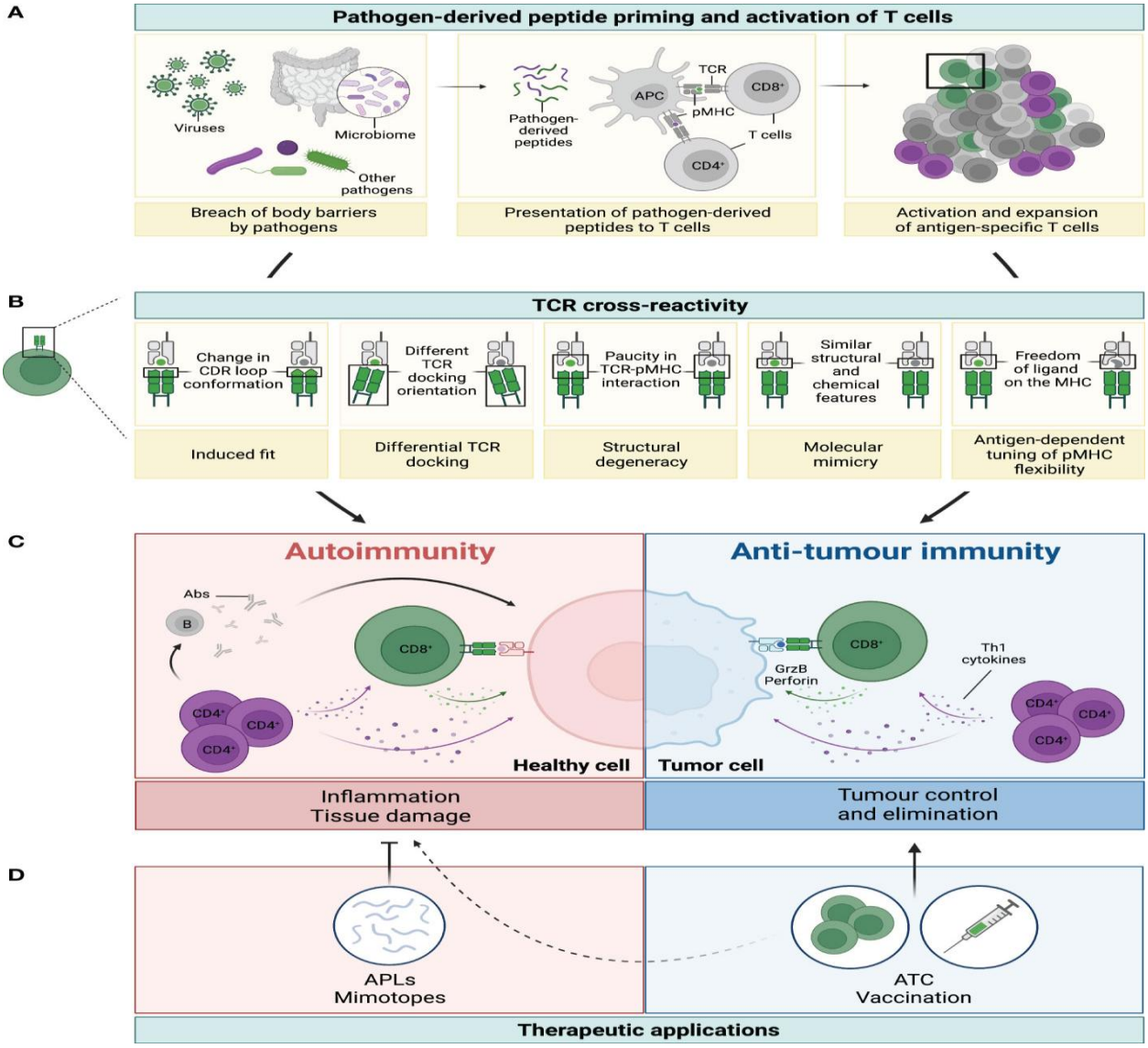
Disparities in the severity of diseases can be observed in populations as well as individuals. Numerous epidemiological investigations have demonstrated that genetic factors play a significant role in an individual's susceptibility to disease. The development of DHF is linked to multiple human HLA class I and II alleles (Table (Table1).1). The development of DHF/DSS has been linked to polymorphisms in the genes for transforming growth factor β (TGF-β), face receptor, vitamin D receptor, CTLA-4, and tumour necrosis factor alpha (TNF-α). A few host factors, like a lack of glucose-6-phosphate dehydrogenase (G6PD), may also be involved in the increased DENV replication in monocytes. The most common enzyme deficiency globally is a deficiency in G6PD, an X-linked enzyme that is widely distributed, with a high prevalence observed in the African population (175). A G6PD deficiency results in aberrant cellular redox, which influences nitric oxide production. Hydrogen peroxide and superoxide. By increasing the number of viral receptors on target cells or increasing the production of viral particles, oxidative stress is known to influence viral proliferation and virulence (264). While it is plausible that a G6PD deficiency creates a more favourable environment for viral replication, it is important to remember that studies carried out in Cuba and Haiti revealed a low incidence of severe disease in populations of African descent (54b, 54c). Mannose-binding lectin 2 (MBL2) gene polymorphism has been linked to thrombocytopenia and a higher risk of DHF development. As a member of the collection family, MBL is thought to be crucial for innate immune response and pattern recognition. A mutation in the MBL promoter region causes low serum levels of MBL, which can lead to a common immunodeficiency syndrome that affects up to 10% of Americans (243). A higher risk of developing DHF has also been linked to polymorphisms in transporters linked to antigen presentation and human platelet antigen (224). Following DENV infection, the likelihood of developing DHF and DSS is probably influenced by a number of common genetic traits, each of which has mild to moderate effects and predisposes to a more severe form of the disease. As has been found for a number of common pathogens, including pneumococci and mycobacteria, it is unknown if single gene defects that confer profound susceptibility to DENV infection exist (185). In this regard, people who experience DHF or DSS but are not Healthy individuals may be used as a pool to find polymorphisms and single-gene defects that increase the risk of developing the most serious DENV infection types.

Enhancement Dependent on Antibodies



The presence of neutralising and non-neutralizing antibodies is correlated with control, elimination, and ultimately protection in the majority of acute virus infection models. Nonetheless, a potential negative impact of virus-specific antibodies has been documented for multiple viruses based on the in vitro amplification of cell infection (72, 73, 93, 98, 189, 235, 238, 240, 255); this phenomenon is not exclusive to viral pathogens (150). An increased risk of developing DHF/DSS following a secondary DENV infection has been demonstrated by epidemiological studies (74, 111, 207, 245), and this in vitro phenomenon was also reported for DENV infection (86). Halstead and associates noted that in two groups of young children, the incidence of DHF and DSS peaked. A single peak was seen in babies. (between the ages of six and nine months) who contracted a different DENV serotype from their mothers. The most important finding was that infants whose mother antibodies had dropped to low, sub-neutralizing levels were the ones who suffered from severe disease. The other peak was seen in young children who had previously contracted a different DENV serotype and had an infection that was typically mild or subclinical. Based on these observations, it was concluded that infection with a different DENV serotype after immunisation could worsen the illness rather than improve it. This phenomenon was attributed to antibodies and was known as antibody-dependent enhancement (ADE) of disease (85). Additional circumstantial evidence for the significance of was provided by a number of later epidemiological studies. The pathophysiology of DHF involves PR immunity (25, 80, 82, 112). ADE may cause more target cells to become infected, which could account for the high viral load that has been reported in numerous studies (132, 221, 245, 251, 258, 259). The evidence supporting the involvement of ADE in human diseases, including DENV infections, is still circumstantial despite multiple clinical investigations. While certain research has indicated a connection between elevated serum activity, high viremia levels, and a higher risk of DHF/DSS (38), not all cases of severe illness are linked to antigen-specific infection, high viral loads, or ADE. When DHF/DSS is observed, viral RNA may sometimes become undetectable (132).However, a high viral load and the presence of the virus on the day of defervescence are generally considered to be significant risk factors for the progression of a severe illness. As previously mentioned, it is unclear if the absence of viremia always corresponds with the virus being removed from infected tissues (155, 199). An additional or alternative theory is that the antiviral immune response is suppressed by Facer-mediated entry. For instance, a study using the Ross River virus revealed that, whereas entry via the normal cellular receptor did not alter the antiviral environment, entry via the Facer pathway could suppress antiviral genes and increase IL-10 production in murine macrophages (135, 151). Moreover, it was demonstrated that IL-10 expression could not be promoted without viral replication. Regretfully, the Fc The receptor implicated in ADE was not found. Additionally, it was demonstrated that DENV infection of THP-1 cells via FCRA decreased transcription and production of IL-12, IFN-γ, TNF-α, and NO but increased expression of IL-6 and IL-10, two anti-inflammatory cytokines (36). This suggests that the environment created by ADE of DENV infection also encouraged viral replication. However, given that the impact of ADE of infection on gene expression might vary depending on the cell, these results need to be interpreted cautiously (20). Viral pathogens are not the only ones that experience this impact of Facer-mediated entry on the antiviral state.

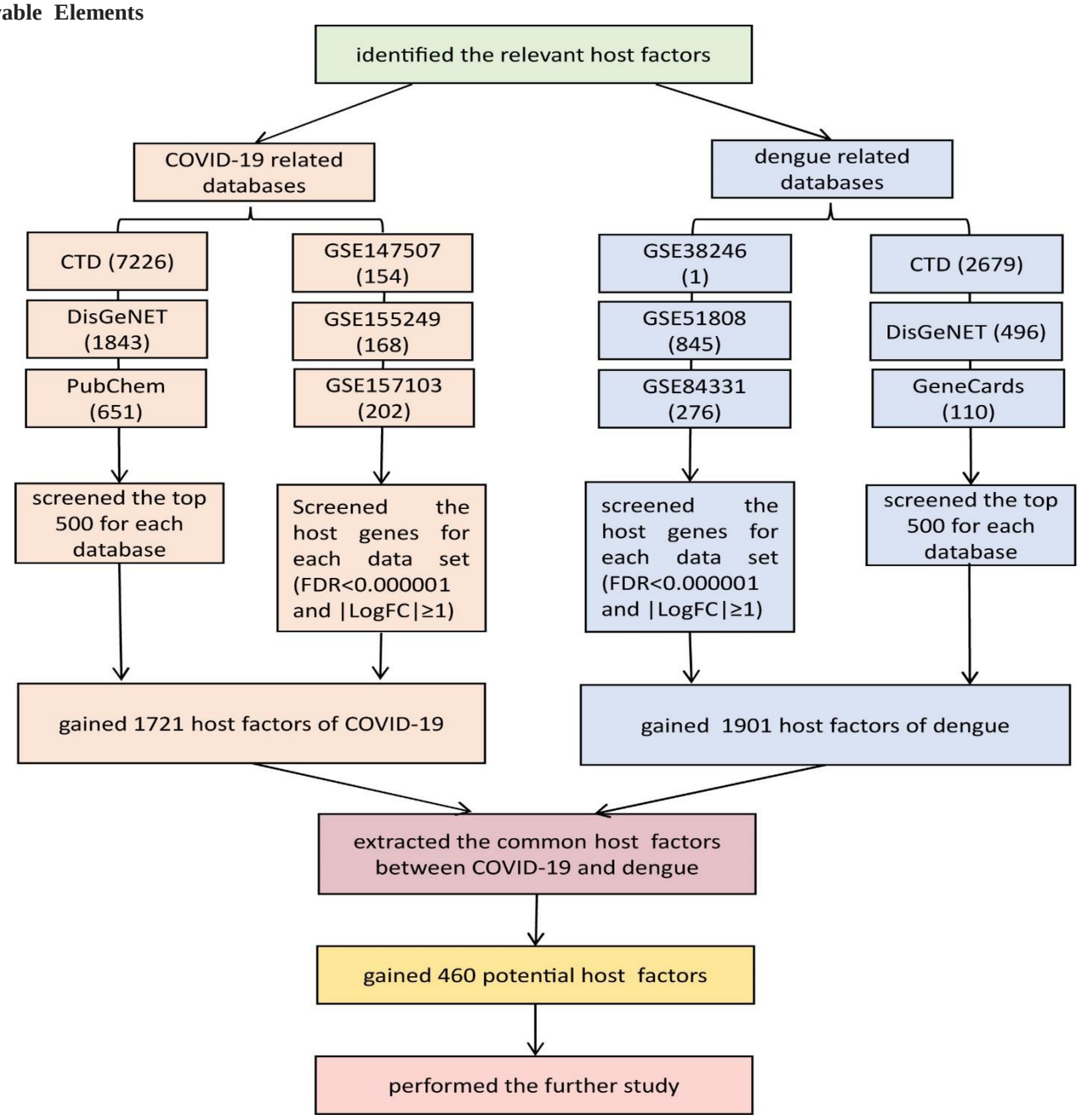
Response of Cross-Reactive T-Cells



Memory T cells that are cross-reactive with a heterologous virus can induce significant immunopathology in addition to partial protective immunity (210). Although their exact function during DENV infection is unknown, CD8+ T cells may contribute to immunopathogenesis and/or infection clearance (3, 166). It is noteworthy that morphological tissue damage due to cytolysis or inflammation caused by the high number of effector T cells is a consistent finding in all examples of T-cell-mediated pathology during acute or persistent viral infections. The avidity of the T-cell receptor (TCR) for the HLA-peptide complex (222) determines how well activated T cells remove virus-infected cells, and it is thought that cross-reactive T cells of low Heterologous virus avidity is not a defence (110). However, heterologous immunity has only been demonstrated to cause pathology in a small number of virus-animal models. These comprise the co-infections of influenza A virus (IAV) and murine cytomegalovirus (MCMV) (209), as well as lymphocytic choriomeningitis virus (LCMV) and vaccinia virus (VV) (209). In one study, respiratory VV challenge of LCMV-immune mice resulted in recruitment of LCMV-specific CD8+ T cells into the lung, causing bronchiolitis obliterans (40), while peripheral VV infection of LCMV-immune mice produced immune-mediated panniculitis (211). It has been demonstrated in the IAV-MCMV model that increased viral replication in the lungs caused severe consolidating mononuclear pneumonia in IAV-immune mice challenged with MCMV (41, 209). One instance of cross-reactivity that results in There have also been reports of human illness (250, 260). The two cases of fulminant hepatitis C virus infection linked to an exceptionally high frequency of CD8+ T cells were reported by the study's authors. It was demonstrated that these T cells could identify a single epitope on the NS3 hepatitis C virus, which also exhibited a cross-reaction with an epitope on the IAV neuraminidase protein. According to these data, memory T cells with cross-reactivity to different pathogens may alter both the initial immune response and the immunopathologic reaction.

High avidity for the infecting virus and highly cross-reactive CD8+ T cells are preferentially activated during the acute phase of a secondary infection in humans with heterologous DENV (58, 99). Most of these T cells that are reactive to cross-contamination produce large amounts ofPro- and anti-inflammatory cytokines include TNF-α, IL-13, and IFN-γ, but IL-10 levels are a little lower. These highly-avidity cross-reactive CD8+ T cells undergo apoptosis; however, it is unclear if this process is caused by activation-induced cell death or if cross-reactive epitopes specifically trigger apoptosis. According to additional research, epitopes may control the quantity of proinflammatory cytokines that T cells produce (146, 147). As an alternative, preferential expansion of low-avidity cross-reactive CD8+ T cells would occur (165, 166). These cross-reactive T cells produce large amounts of proinflammatory cytokines in response to heterologous epitopes, but they no longer have cytolytic activity. Such cross-reactive CD8+ T cell activation would be prolonged by delayed virus clearance, leading to the generation of high concentrations of soluble factors that influence vascular permeability, such as TNF-α, IL-6, or other cytokines. Original antigenic sin (OAS) is the term used to describe the phenomenon wherein cross-reactive memory T cells for the primary infecting virus are more efficiently activated, due to the increased frequency and higher activation state of memory cells. Mice with LCMV have also been reported to exhibit this phenomenon (110). Cross-reactive epitopes preferentially reactivate memory T cells against the priming virus more effectively than they activate naïve T cells during a secondary infection with a heterologous serotype. However, it's possible that during a heterologous DENV infection, only a very small subset of cross reactive memory T cells will be activated, in line with what has been reported for a number of other systems. A shrinking TCR repertoire will encourage cells to proliferate. Individuals would have distinct dominant responses as a result of this TCR repertoire narrowing and their distinct TCR specificity (private TCR) [52, 107]. This could account for the variation in disease prognosis observed following secondary infection with heterologous DENV. The CD4+ T-cell response during DENV infection is far less well understood. Nonetheless, there is proof that successive infection with distinct DENV serotypes can also modify the cytokine response of cross-reactive CD4+ T cells, leading to the generation of proinflammatory cytokines (154) that could potentially combine with the CD8+ T-cell response to cause a harmful cytokine release.

Dissolvable Elements



A "storm" of inflammatory cytokines and other mediators is thought to be triggered by a high viral load and activation of nonprotective T cells, which causes increased plasma leakage that is characteristic of DHF/DSS. This is a belief held by many scientists studying dengue pathogenesis. The discovery of soluble factors that can mediate, either independently or in concert, the functional alterations in EC that are linked to elevated plasma leakage is one of the most difficult problems facing DENV research. Referred to reference 15, numerous investigations have demonstrated that severe dengue infections lead to a significant increase in the concentrations of soluble receptors, a variety of cytokines, and other mediators. Higher amounts of TGF-1β, TNF-α, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-13, and IL-18 in the plasma found in patients with DSS in particular who had severe DENV infections (10, 23, 32, 103, 128, 169, 172, 183, 192, 194, 236). The samples from newborns, kids, and adults infected with various DENV serotypes were examined in these investigations. It makes sense to believe that these cytokines will work in concert with one another. Vascular endothelial growth factor (VEGF), granulocyte-macrophage colony-stimulating factor, monocyte chemoattractant protein 1 (MCP-1), macrophage migration inhibitory factor, thrombopoietin, soluble vascular cell adhesion molecule 1 (VCAM-1), soluble ICAM-1, von Willebrand factor antigen, thrombomodulin, E-selectin, tissue factor (TF), plasminogen activator inhibitor 1 (PAI-1), and tissue plasminogen activator are among the other mediators and soluble factors that have been found to be elevated in severe disease (23, 26, 27, 29, 44, 46, 115, 130, 153, 223, 229). evaluations of multiple Research findings are contradictory; although some studies report elevated plasma cytokine levels, others do not. The primary causes of these differences are the experimental setup and study design, the cytokine measurement lab tests, and the statistical tests used for the data analysis. Moreover, it is challenging to standardise the sampling time during infection, which could

account for some of the inconsistent findings. The question of whether plasma levels of cytokines and mediators actually reflect concentrations in different compartments is justified by the observation that plasma leakage primarily occurs in the peritoneal and pulmonary cavities. When seasonal IAV (H1N1 or H3N2) infected humans or animals, the infection site's levels of cytokines and chemokines were significantly higher than within serum or plasma (68, 71, 88). On the other hand, H5N1 causes fulminant disease in humans, which progresses to multiorgan dysfunction and diffuse damage to the alveoli. Here, there is a strong correlation between the severity of the disease and the levels of cytokines both locally and systemically (54a, 129). For example, multiorgan dysfunction seen in patients with confirmed H5N1 fatal infections has been linked to hemophagocytic syndrome (247, 268). Notably, high cytokine production has been linked to hemophagocytic syndrome in fulminant viral infections or autoimmune diseases and macrophage activation syndrome in hematopoietic cell transplantation (127, 193, 227). Thus, the environment in which cytokines are produced and act has a crucial role in determining their behaviour. Further research with more focused designs is required to analyse the connections between different levels of In cases of severe DENV infections, there are more cytokines in the peritoneal (ascites) and pulmonary (pleural fluid) regions than in the plasma or serum. It is possible that variations in the damage caused by viruses and selective EC in vivo will result in a different cytokine profile and vascular permeability patterns.

Animal models of increased vascular permeability and haemorrhage during DENV infections provide some evidence for the potential involvement of cytokines (39, 217). Serum from DENV-infected mice has been shown to contain high levels of TNF-α, IL-1β, IL-6, and IL-10 (6). Furthermore, numerous in vitro studies have shown that the culture supernatants of DENV-infected (primary) DC (20), monocytic cells (47, 162), and EC (11) contain high concentrations of cytokines. When anti-NS1 antibodies are present, EC release MCP-1. IL-6, IL-8, and in vitro (138). In addition, TNF-α, IFN-γ, IL-4, and/or IL-10 may be produced by T cells interacting with DENV-infected cells (91).

TABLE i2. Summary iof isoluble ifactors ithat iare ior iare ilikely ito ibe iassociated iwith idevelopment iof iDHF/DSS.

Soluble factor	Biological function in relation to pathogenesis
Thrombin	Thrombin is thought to act near the site at which it is produced. Thrombin converts circulating fibrinogen to fibrin and triggers platelet activation, which results in platelet aggregation. Thrombin activates EC and increases EC permeability, leading to plasma leakage and edema formation. Thrombin is chemotactic for monocytes and is mitogenic for lymphocytes and mesenchymal cells. Activated platelets release several soluble factors with inflammatory, antimicrobial, and immune modulating activity, such as MMP-9, which enhances EC permeability. Activated platelets also secrete soluble CD40 ligand, which can induce EC to produce reactive oxygen species, adhesion molecules, chemokines, and TF. Thrombin also inhibits IL-12 production by mononuclear cells.
C3a and C5a	C3a activates platelets and enhances their activation and adhesion properties. C5a enhances blood thrombogenicity by upregulating TF and PAI-1 expression on various cell types. C5a stimulates monocytes to produce IL-1, IL-6, IL-8, and TNF-α. Activation of these complement factors is enhanced by thrombin, which cleaves C3 and C5 to C3a/b and C5a/b, respectively. Activated platelets are also involved in C3 cleavage, which induces activation of the classical complement pathway.
C4b	C4b binds to protein S and thereby inhibit the anticoagulant properties of activated protein C-protein S complexes.
IL-1	IL-1β is major mediator of platelet-induced activation of EC, causing enhanced chemokine release and upregulation of VCAM-1. VCAM-1 promotes adhesion of monocytes to the endothelium. IL-1 increases the expression of TF on EC and suppresses the cell surface anticoagulant activity of EC. Depending on its concentration, it may upregulate TNF-α production or downregulate TNF-receptors. IL-1 stimulates the hypothalamus and, as a consequence, the pituitary gland to produce anti-inflammatory mediators such as endorphins, melanocyte-stimulating hormone, and adrenocorticotropic hormone.
IL-6	Together with other proinflammatory cytokines, IL-6 potentiates the coagulation cascade. It can downregulate production of TNF-α and TNF receptors. IL-6, together with IL-1, is a potent inducer of fever.
IL-8	IL-8 is a chemokine that is abundantly produced by monocytes, EC, and hepatocytes. EC damage in the liver may elevate systemic concentrations. Activation of the coagulation system results in increased expression of IL-6 and IL-8 by monocytes, while the APC-PS anticoagulation pathway downregulates production of IL-8 by EC.
IL-10	IL-10 is produced by monocytes and regulatory T helper cells and may cause platelet decay. Thrombin can stimulate IL-10 production by monocytes. The cytokine downregulates the inflammatory response and creates a parvoviral survival milieu. IL-10 promotes OAS by inhibiting development of effector T cells to new epitopes. IL-10 also inhibits the expression of TF and inhibits fibrinolysis.
TNF-α	TNF-α in a potent activator of EC and enhances capillary permeability. TNF-α upregulates expression of TF

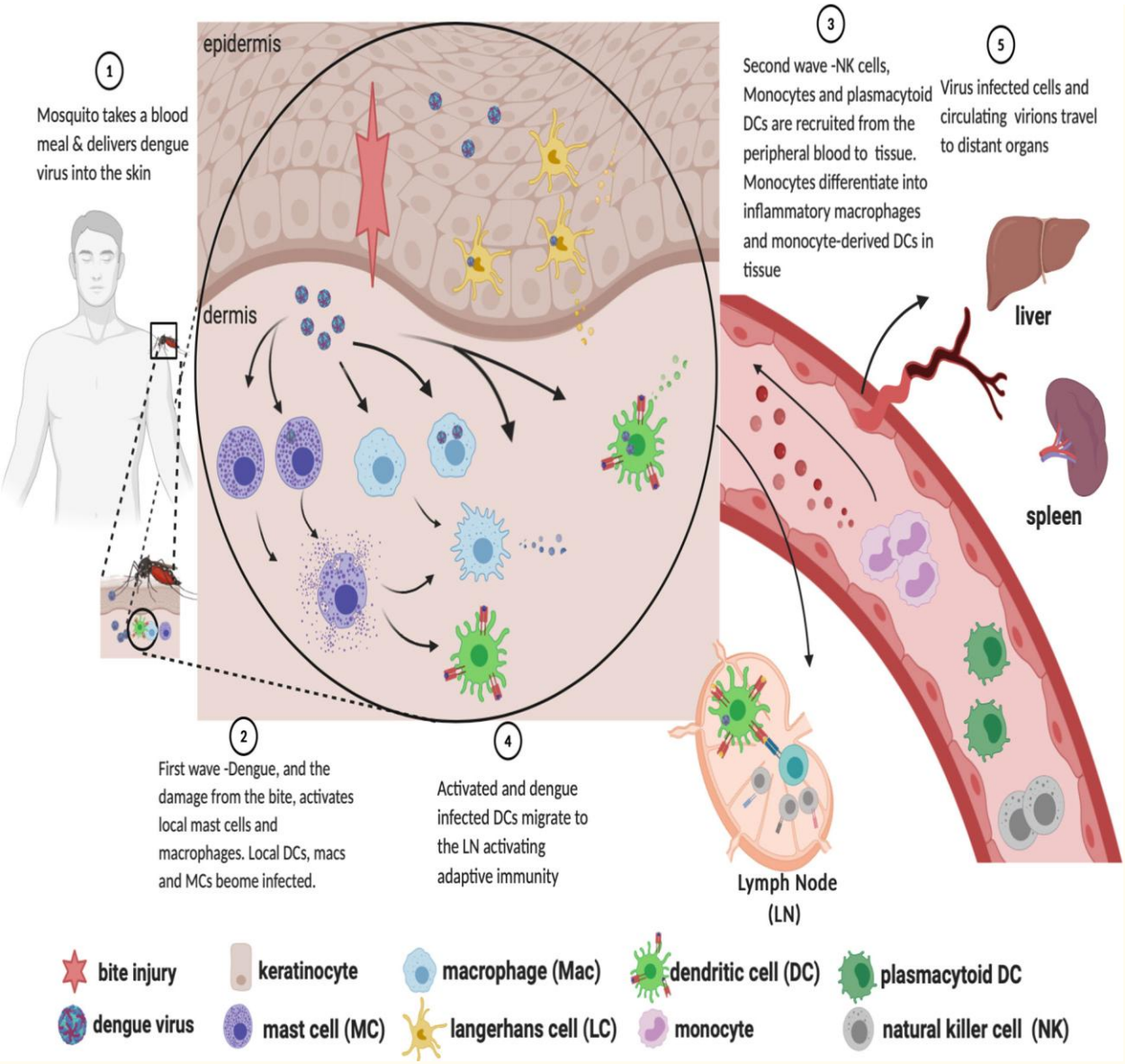
Soluble factor	Biological function in relation to pathogenesis
	on monocytes and EC and downregulates expression of thrombomodulin on EC. It also activates the fibrinolysis system. TNF-α enhances expression of NO and mediates activation-induced death of T cells, and it has therefore been implicated in peripheral T-cell deletion.
TGF-β	TGF-β may act as a proinflammatory or anti-inflammatory cytokine, depending on its concentration. Early in infection, low levels of TGF-β may trigger secretion of IL-1 and TNF-α. However, later in infection, the cytokine inhibits the Th1 response and enhances production of Th2 cytokines such as IL-10. TGF-β increases expression of TF on EC and upregulates expression and release of PAI-1.
NO	NO has a multifaceted role in inflammatory reactions. It enhances vasodilatation and formation of edema. It upregulates TNF-α production in monocytes. At low concentrations it protects cells from apoptosis, while at high concentrations it induces apoptosis. NO downregulates expression of MHC class II and suppresses expansion of Th1 cells. Maintenance of the EC barrier requires a basal level of NO. Both a lack of NO and high NO levels destabilize EC junctions.
VEGF	VEGF is a key driver of vascular permeability. It reduces EC occluding, claudins, and VE-cadherin content, all of which are components of EC junctions. Upon activation, VEGF stimulates expression of ICAM-1, VCAM-1, and E-selectin in EC.

It is evident that there is significant overlap in the functions of cytokines, making it challenging to explain the pathophysiology of DHF/DSS using just one cytokine. In other words, the absence of one particular cytokine may be made up for by the presence of another cytokine. It is more likely that a variety of cytokines work in concert to cause DHF/DSS at the same time. It is reasonable to assume that cytokines and other soluble mediators of the functional pathology and, to a lesser extent, the morphological pathology characteristic of DHF/DSS are also necessary for effective viral clearance, independent of any other factors. The remarkably quick recovery of DSS patients following appropriate fluid therapy implies that, in contrast to many immunopathology models, cytokines cause a reversible EC rather than tissue destruction.

INTERGRATED PERSPECTIVE

Although the exact mechanisms causing the severe DENV infection symptoms are still unknown, they most likely involve multiple factors (Fig. 1).1. The host's genetic background affects how the immune system responds to a DENV infection. The primary targets of DENV infection in the dermis are keratinocytes and Langerhans cells. After that, the virus spreads through blood (primary viremia) and infects tissue macrophages in various organs, most notably the splenic macrophages. The viral load measured in blood is determined by the combined effects of DENV's replication efficiency in DC, monocytes, and macrophages, as well as its tropism for and replication efficiency in EC, bone marrow stromal cells, and liver cells. This virus count is a significant risk factor for onset of a serious illness. Basically, the immune and hemostatic reactions to DENV are influenced by the infection of EC, hepatocytes, and macrophages. Apoptosis is the primary method of infection cell death; necrosis is used less frequently. The release of toxic products during necrosis triggers the activation of the fibrinolytic and coagulation systems. Reduced blood thrombogenicity is the result of hemopoiesis being suppressed, which is dependent on the degree of infection of bone marrow stromal cells and the levels of IL-6, IL-8, IL-10, and IL-18.

In order to preserve vascular stability, a normal quantity of functional platelets is required. Platelets and EC interact closely. Increased capillary fragility, which is clinically characterised by petechiae, easy bruising, and gastrointestinal mucosal inflammation, may be caused by a high viral load in blood and potentially viral tropism for EC, severe thrombocytopenia, and platelet dysfunction. bleeding (170), a defining feature of DHF. In addition, infection promotes the growth of particular antibodies and DENV-specific cellular immune responses. Increased production of IgM antibodies that cross-react with EC, platelets, and plasmin amplifies the loop responsible for coagulopathy and increased vascular permeability. Enhancing IgG antibodies also aid in the binding of heterologous viruses during secondary infection and promote APC infection, which in certain cases results in an increased viral load during secondary viremia. Moreover, a high viral load overstimulates T cells that are cross-reactive with low and high avidities. When cross-reactive T cells are exposed to specific HLA haplotypes, they produce high quantities of proinflammatory cytokines and other mediators but also delay the removal of the virus. In the end, these elevated quantities of soluble components, numerous of which yet to be discovered, cause alterations in EC that result in the coagulopathy and plasma leakage that characterise DSS.


1
Mosquito takes a blood meal & delivers dengue virus into the skin
epidermis
dermis
2
First wave -Dengue, and the damage from the bite, activates local mast cells and macrophages. Local DCs, macs and MCs beome infected.
3
Second wave -NK cells, Monocytes and plasmacytoid DCs are recruited from the peripheral blood to tissue. Monocytes differentiate into inflammatory macrophages and monocyte-derived DCs in tissue
4
Activated and dengue infected DCs migrate to the LN activating adaptive immunity
5
Virus infected cells and circulating virions travel to distant organs
liver
spleen
Lymph Node (LN)
bite injury
keratinocyte
macrophage (Mac)
dendritic cell (DC)
plasmacytoid DC
dengue virus
mast cell (MC)
langerhans cell (LC)
monocyte
natural killer cell (NK)

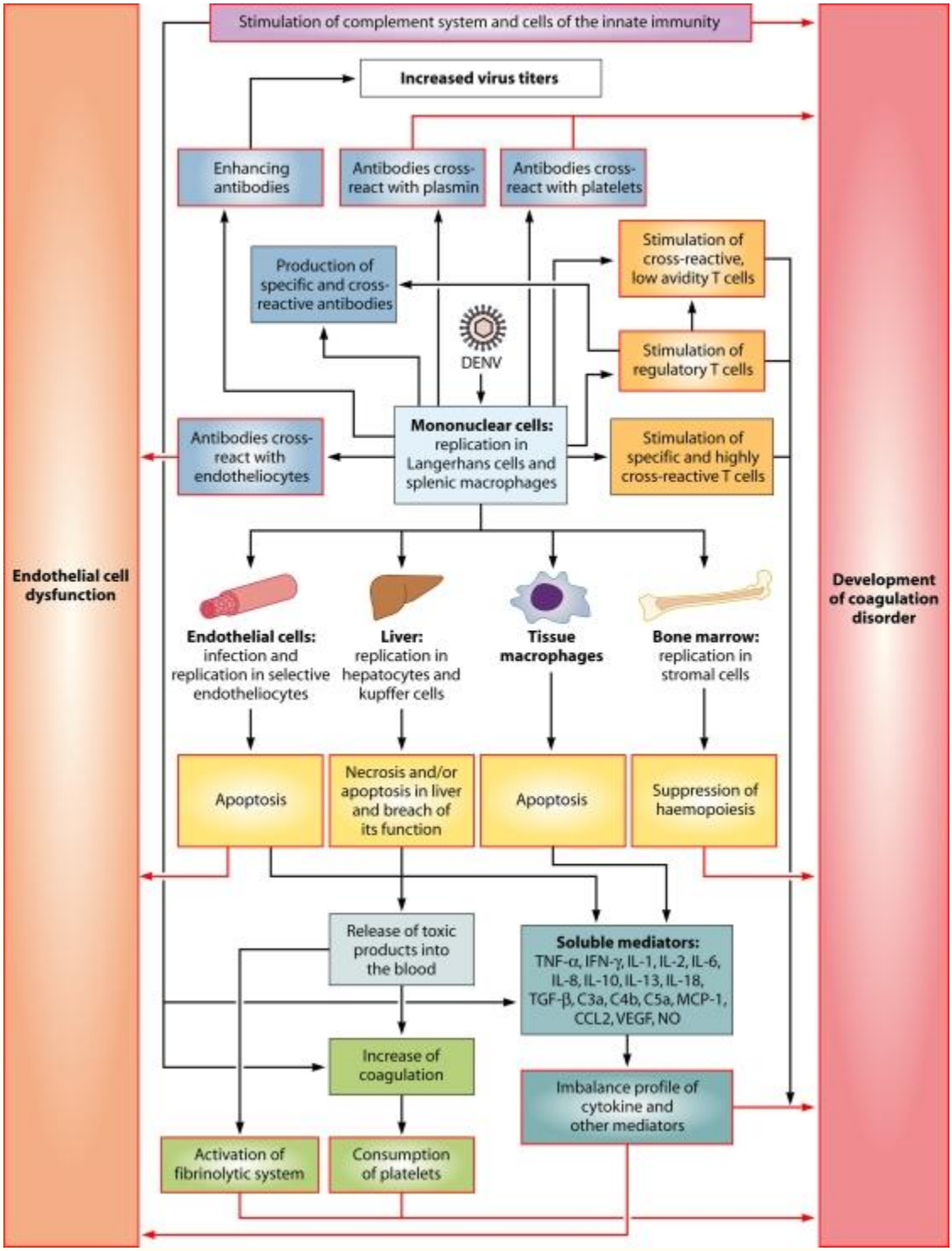


FIG. 1.
Proposed model for the pathogenesis of DF, DHF, and DSS, based on an integrated view of the data presented (see section The Integrated View in the text). Black arrows, processes leading to the indicated event; colored boxes with white centers, pathological events. Each event will ultimately affect the EC or the hemostatic system (purple arrows).

CONVERSATION

Here, we examine and talk about the many theories regarding the pathophysiology of DHF and DSS that have been put forth in the literature. The majority of these theories do not conflict with one another, and when taken as a whole, they contain a number of components that, when taken into account, may account for the majority of the phenomena seen in the various DENV infection presentations. The main objections to the theories presented in this review are addressed in Table Table 33. Both DHF grades I/II and DSS have a complex, multifactorial pathophysiology that involves both host and viral factors. Nevertheless, the factors that are necessary and/or sufficient have not yet been determined. One may wonder if there are any factors that explain the pathophysiology of DHF and DSS in every patient. The course of a disease may be significantly influenced by genetic predisposition. Few research have looked at host genetics in relation to DENV infection severity. The majority of genetic variations that are clinically significant are single-nucleotide polymorphisms in genes that alter disease pathways. Numerous polymorphisms frequently interact with other polymorphisms and environmental risk factors, and many have modest and independent effects on the course of a disease (24). In the end, this leads to intricate and diverse medical consequences. To find specific molecular markers of DHF/DSS, studies combining single-nucleotide polymorphism genotyping, careful phenotypic disease characterization in well-defined cohorts, and genomics (transcriptomics, proteomics, and metabolomics) should be used.

Both host-specific and viral components are involved in the pathways leading to DHF, as this review discusses. You can sum up the following points here.

Contrary to popular belief, the involvement of EC and the liver seems to be a significant component in the pathogenesis of dengue in various organ systems. Understanding the impact on the EC lining the thoracic and peritoneal cavities is crucial in this regard. It is noteworthy that although both DHF and DSS patients (16) have higher vascular permeability values, there is no evidence of widespread edoema and plasma leakage is largely confined to the pleural and peritoneal cavities. In DENV infections that result in death, no particular vascular lesions are discovered. Additionally unrelated to EC are viruses that are known to cause hemorrhagic fever, including those from the families Arenaria (which includes the Junin and Lassa viruses), Filoviridae (which includes the Ebola and Marburg viruses), Universiade (which includes the Hanta and Rift Valley viruses), and Flaviviridae (which includes the yellow fever virus). injury (43, 70). In these situations, severe liver damage that results in decreased albumin and coagulation protein production is the pathogenesis of hemorrhagic diathesis. As is evident in severe cases of Lassa fever, increased vascular permeability from hypertyrosinemia and a decrease in plasma osmotic pressure from severe liver damage lead to the formation of edoema (67). Moreover, hypotension and sodium loss are caused by the majority of these viruses replicating in the adrenal gland, which adds up to hypovolemic shock. However, the shock syndrome linked to DSS is specific to DENV infection, and it is crucial to comprehend how the EC lining the peritoneal and thoracic cavities are impacted.

The hemorrhagic symptoms observed in DHF and DF Grades I and II are typically mild and show up as skin-wide petechiae that are more likely to bleed when bruised. These symptoms appear soon after the fever starts and correspond with the viremia window and thrombocytopenia degree (121). The increased capillary fragility resulting from thrombocytopenia or platelet dysfunction, virus infection of EC, and high concentrations of cytokines that compromise vascular integrity could be the pathogenesis of the mild haemorrhages observed in DF and DHF grades I/II (54, 170, 257). Retraction of EC and opening of intercellular gaps are caused by most mediators that increase vascular permeability because they alter the structure of adherents junctions (AJ), a complex network of adhesion proteins connected to the intracellular cytoskeleton (54). On the other hand, the stability of There could be a weakening of the junctions, leading to vascular fragility. The fact that internalisation of VE-cadherin or phosphorylation of AJ proteins reduces junction stability without the opening of intercellular gaps is an example of how weakening of the junctions is not reflected by morphological changes (4, 62). Remarkably, intercellular gaps in the rich in AJ postcapillary venules are the main anatomical sites of bleeding in patients with severe thrombocytopenia (170). As a result of fluid shear stress, platelets constitutively release a variety of factors, including sphingosine-1-phosphate and platelet-activating factor, which contribute to the integrity of AJ (5). Consequently, increased vascular fragility may result from disruption of the platelet-EC interaction caused by severe thrombocytopenia or platelet dysfunction. resulting in bleeding or a greater propensity to bleed.

A number of investigations have demonstrated that plasma leakage happens prior to hemoconcentration or defervescence. As previously stated, pathogenesis studies should not use the WHO case definition as a selection criterion because it is primarily intended for clinical diagnostic purposes. The differences between (I) no bleeding tendencies, (ii) increased bleeding manifestations or tendencies for bleeding, and (iii) plasma leakage as determined by sonography and hemoconcentration should be the focus of pathogenesis studies. Understanding the pathophysiological basis of plasma leakage and the reasons it is localised to or more prominent in peritoneal and thoracic regions requires an examination of the pleural fluid

i. Antibody-mediated enhancement of infection is responsible for type 2 cytokine responses or a high viral load.
ii. In certain viral systems, pathological alterations during a subsequent infection with a related but heterologous virus are facilitated by cross-reactive CD8+ T-cell responses. On the other hand, DENV cross-reactive T cells produce a lot of proinflammatory cytokines and other mediators but lose their ability tocytolyze. It is important to look into the part that preexisting immunity to other flaviviruses plays in the development of severe dengue.

A key role for soluble host factors appears to play in the pathophysiology of DSS and DHF grades I–II. Despite the fact that a number of these have been linked to serious illness, their concentrations are also raised in other viral infections without producing plasma seepage. Patients suffering from anaphylaxis, meningococcal sepsis, and Jarish Herxheimer reaction have been linked to capillary leakage and the development of hypovolemic shock when high concentrations of cytokines, including TNF-α, IL-6, and IL-8, are present (105, 176, 233). Similarly, adverse results from infections with filovirus (253), arenavirus (89, 160), and yellow fever virus (241) have been linked to high cytokine concentrations. Nevertheless, under these circumstances, the shock syndrome linked to DSS does not materialise. As a result, it is possible to hypothesise that the soluble factors linked to the elevated vascular permeability observed in DSS must differ from those implicated in the previously mentioned conditions both qualitatively and quantitatively.

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