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REVIEW

Role of auto-antibodies in the mechanisms of dengue pathogenesis and its progression: a comprehensive review

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Abstract

A complex interaction among virulence factors, host-genes and host immune system is considered to be responsible for dengue virus (DENV) infection and disease progression. Generation of auto-antibodies during DENV infection is a major phenomenon that plays a role in the pathophysiology of dengue hemorrhagic fever and dengue shock syndrome. Hemostasis, thrombocytopenia, hepatic endothelial dysfunction, and autoimmune blistering skin disease (pemphigus) are different clinical manifestations of dengue pathogenesis; produced due to the molecular mimicry of DENV proteins with self-antigens like coagulation factors, platelets and endothelial cell proteins. This review elaborately describes the current advancements in auto-antibody-mediated immunopathogenesis which inhibits coagulation cascade and promotes hyper-fibrinolysis. Auto-antibodies like anti-endothelial cell antibodies-mediated hepatic inflammation during severe DENV infection have also been discussed. Overall, this comprehensive review provides insight to target auto-antibodies that may act as potential biomarkers for disease severity, and a ground for the development of therapeutic strategy against DENV.

Keywords Dengue virus · Auto-antibodies · Molecular mimicry · Autoimmune disease

Introduction

Dengue fever (DF) exhibits an essential global public health concern which is leading to approximately 400 million cases and 22,000 fatalities per annum. It obtrudes extensive health burdens on both younger and adult groups in tropical and subtropical regions worldwide. The World Health Organization (WHO) has reported a remarkable increase in severe cases, ranging from 505,430 illnesses and 960 deaths in the year 2000 to 5.2 million illnesses and 4,032 deaths in 2019, with a particular impact in younger age groups. DF is currently accepted as an endemic disease in over 100 countries such as Africa, Eastern Mediterranean, USA, Southeast Asia, and Western Pacific regions (WHO 2023). Asian countries contribute approximately 70% of the entire estimated global cases of dengue infections, with Africa and America contributing 16% and 14% of cases, respectively (CDC 2015). Particularly in several Asian countries, including Bangladesh (101,000 cases), Malaysia (131,000 cases), Philippines (420,000 cases), and Vietnam (320,000 cases) have reported a higher occurrence of dengue infections (WHO 2023).

The DENV infection outbreak in the Abéché health district located in the Ouaddaï region of eastern Chad, was formally proclaimed on August 15, 2023, by the Ministry of Public Health and Prevention in the Republic of Chad and also reported by the WHO. This is the nation's first-ever dengue outbreak that has been recorded (CIDRAP 2023). DF was initially reported in India in 1956 in the Vellore district of Tamil Nadu (Chakravarti et al. 2012). A majority of Indian states consistently report annual dengue outbreaks and one of the major causes of hospitalizations (Ganeshkumar et al. 2018).

The development of DF is influenced by multiple factors, including climate variations, ecological shifts, fluctuations

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in mosquito vectors, and evolving demographics (Kakarlaet al. 2019). Regions in tropical and subtropical climates endure continuous DENV infections since the disease is closely linked to the rainy season, temperature variations, mosquito population dynamics, and changing seasons (Jing et al. 2019). Epidemics in different geographical areas occur at distinct times, often determined by the arrival of imported cases from endemic regions (Marques-Toledo et al. 2019). Central and South American countries, such as Brazil, witness DENV infection in peak position from February to May, while Puerto Rico experiences it from July to December (Wunderlich et al. 2017). In India, DENV infection reaches its peak during the rainy season, driven by elevated humidity that raises the proliferation of mosquito breeding sites (Raheel et al. 2010).

DENV infection, majorly classified as an arboviral disease, is attributed to the DENV who belongs to Flavivirus genus within the Flaviviridae family; it is characterized as a single-stranded positive-sense RNA virus. It consists of three distinct structural proteins, along with a group of seven non-structural (NS) proteins, including NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5. These proteins play a vital role in various aspects of virus activities, including evasion of the immune system, genome replication and assembly of viral particles, modulation of host responses, synthesis of the viral RNA genome and the complex composition of these proteins (NS) play a significant role in the ability of virus to cause disease (Chong et al. 2019). The pathogenesis of DENV infection is attributed to four distinct serotypes, namely DENV-1, DENV-2, DENV-3, and DENV-4 (Roy et al. 2021). Among these serotypes, DENV-2 and DENV-4 exhibit remarkably higher virulence compared to the others (Martina et al. 2009). In Malaysia, a fifth DENV serotype DENV-5was discovered in 2013 through genetic sequence analysis and isolation (Mustafa et al. 2015).

Although several mechanisms are involved in dengue pathogenesis, their relative importance remains uncertain. DENV infection becomes more perilous when auto-antibodies are generated; contributing to the development of various autoimmune diseases in infected patients (Fried et al. 2010). Auto-antibodies can develop in response to numerous viral infections, with their generation attributed to mechanisms such as molecular mimicry, epitope spreading, the presence of super-antigens, and the activation of multiple antibody types within the inflammatory context (Chuang et al. 2014).The DENV autoimmunity disease is caused by auto-antibodies that produce against self-antigens, such as platelets, endothelial cells, and coagulatory factors (Shih et al. 2023). This leads to several kinds of immunological disorders, severe and complex issues such as thrombocytopenia, coagulopathy, and vasculopathy (Chuang et al. 2014). In addition to the direct effects of the DENV infection and abnormal immune responses, including the production of pro-inflammatory cytokines (TNF-α, IL-6 and IFN-γ), chemokines (MCP-1and IL-8), and the activation of complement and immune cells may also play role in the disease pathogenesis (Srikiatkhachorn et al. 2017). In addition, elevated anti-platelet auto-antibody levels were linked to acute secondary infection and disease severity in DENV-infected patients (Vo et al. 2020).

We hereby hypothesize that cross-reactive auto-antibody can hinder coagulation activation and may be induced by molecular mimicry between coagulatory molecules and DENV proteins. Furthermore, defects of coagulation activation, such as prolonged activated partial thromboplastin time and thrombin time have been detected in DENV-infected patients (Huang et al. 2001). Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) patients may also have decreased levels of fibrinogen and increased levels of fibrin degradation products, which indicate hyperfibrinolysis (Marchi et al. 2009; Sosothikul et al. 2005). As a result, DENV infection accelerates fibrinolysis which leads to a deficiency in coagulation activation. The pathogenic consequences of a few potential causes could upset the delicately balanced coagulation and fibrinolysis during DENV infection. Several disease developments are there because of the production of auto-antibodies against endothelial cells during host immune responses (Farsi et al. 2001; Hebbar et al. 2001; Song et al. 2000). Vasculopathy may be primarily caused by these anti-endothelial cell antibodies (AECA). Recent studies have shown that patients infected with DENV have acantholysis, one of the most prevalent auto-antibody-mediated mechanisms (Egu et al. 2022). The keratin filaments degrade and the intracellular connections erode. Desmosomes, the primary intracellular complex in this case, are unable to preserve cell adhesion in the mucous membrane and epidermis layer, which results in blister formation (Egu et al. 2022). In this review, we explained the production of auto-antibodies against desmogleins (DSG) and the cause of acantholytic intra-epidermal blisters in pemphigus diseases during dengue infection. Moreover, in DHF patients, there was a correlation found between the presence of IgG auto-antibodies against various components of the complement pathway, including Factor P and Complement C4, and coagulation pathways, including prothrombin protein, and platelet counts (Vo et al. 2020). This review summarizes the overview of the auto-antibody-mediated mechanisms underlying DENV infection and their correlation with the severity of the disease.

General mechanism of auto-antibodies production in dengue patients

The term 'molecular mimicry' is defined as the structural or sequence homology that exists between the host protein and that of the virus. For host immune cells to identify a pathogen as non-self, the homologous sequence or conformation of the pathogen molecules must differ adequately from that of the host (Davie et al. 1991). Molecular mimicry is characterized by the cross-reactivity between foreign antigens and self-antigens. This cross-reactivity can disrupt immune tolerance and lead to the development of autoimmune diseases.

Through sequence analysis of DENV proteins and coagulation molecules, a minimum of 12 distinct regions within DENV proteins such as core, prM, E, and NS1 exhibit amino acid sequence resemblance to various molecules, such as factors X, XI, VII (Lin et al. 2011). In the case of DENV infection, certain DENV proteins share similar amino acid sequences with coagulation factors, facilitating molecular mimicry demonstrated in Fig. 1 and initiation of autoimmune diseases. Additionally, auto-antibodies, that are produced by such cross-reactivity between DENV and host proteins can result in abnormal bleeding and there is a resultant imbalance between fibrinolysis and blood coagulation in dengue patients (Chuang et al. 2014).

It has been shown that serum from DENV-infected patients exhibit cross-reactivity with endothelial cells because auto-antibodies are induced by DENV predominantly during the acute phase which persist still 8 months of DENV infection. Patients with DHF or DSS show higher levels of anti-platelet antibodies and auto-antibodies targeting endothelial cells compared to those with DF (Wan et al. 2013). Experimental findings indicate that anti-NS1 antibodies exhibit partial cross-reactivity with endothelial cells, leading to apoptosis of endothelial cells. Consequently, autoimmune-related conditions such as thrombocytopenia, plasma leakage, abnormal bleeding, and liver injury are observed in DHF/DSS patients (Srikiatkhachorn et al. 2009).

Thrombocytopenia

In DF, thrombocytopenia can be associated with the destruction of platelets in the peripheral blood; otherwise platelet production is decreased in the bone marrow. Thrombocytopenia is a common abnormal condition frequently detected in DENV-infected patients and also commonly encountered

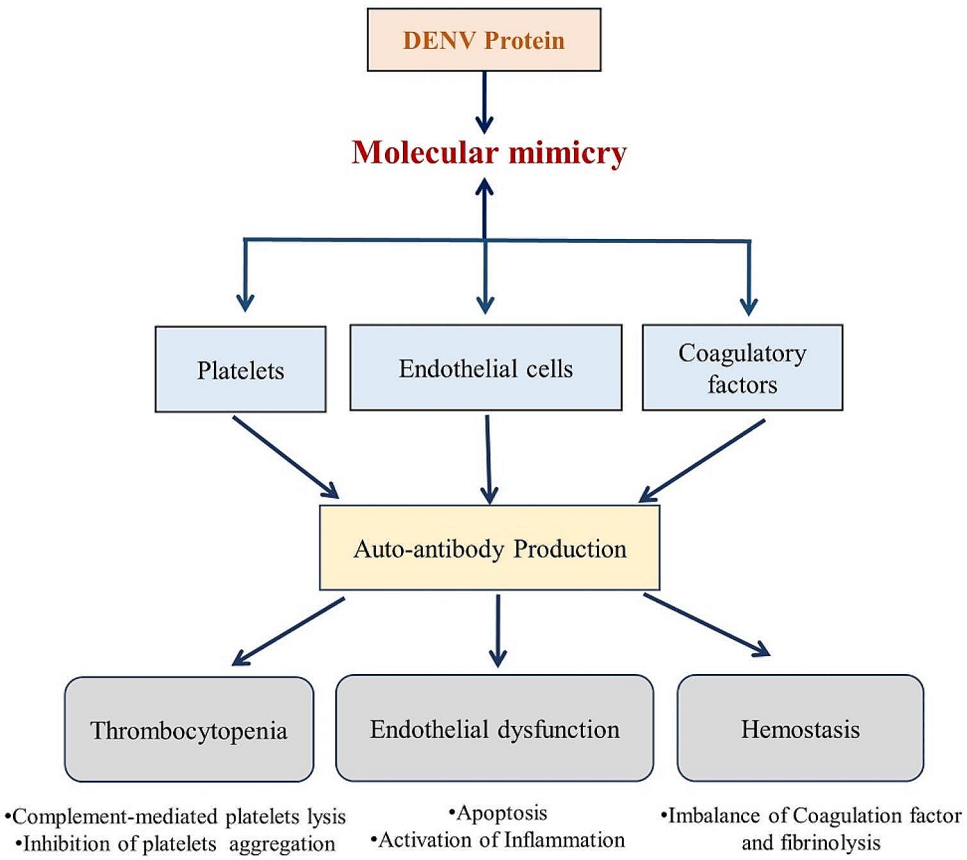

Fig. 1 Mechanism of auto-antibody production in dengue virus infection by molecular mimicry between platelets, endothelial cells and coagulatory molecules with DENV proteins

in cases of severe dengue, including DHF and DSS. The mechanisms underlying thrombocytopenia and bleeding in the context of DENV infection remain subtle. Particularly a high mean platelet volume is indicative of a significant destruction of platelet in DENV-infected patients and poses a substantial challenge in managing thrombocytopenia (Das et al. 2022). Evidence showed that cross-reactivity between antibodies against DENV-NS1 and platelets results in hemorrhage (Lin et al. 2001).

Thrombocytopenia may outcome from auto-antibodies attaching themselves to platelets. Furthermore, in auto-immune-mediated thrombocytopenic diseases caused by DENV, platelet-bound immunoglobulins (Ig) have been associated with platelet abnormalities and a higher rate of platelet clearance (Azeredo et al. 2015; Rasizadeh et al. 2024). The auto-antibodies targeting platelets in dengue patients are primarily of the IgM isotype rather than IgG (Lin et al. 2001). An investigation has suggested that the destruction of platelets in DENV may be linked to the DENV infection and immune-mediated reactions and ultimately occurring hemorrhage (Huang et al. 2000).

Endothelial dysfunction

In the case of DF, endothelial dysfunction causes leakage of plasma resulting from both direct viral impacts and immune-related alterations in vascular permeability. The scientists mentioned the presence of auto-antibodies against human endothelium in dengue infected individuals. Furthermore, when antibodies against DENV NS1 protein bind to vessel endothelial cells, it induces apoptosis in these cells through the nitric oxide (NO) pathway and disrupted the mitochondria. Afterward, the production of NO leads to increased p53 levels and reduced Bax, Bcl-2 and Bcl-xl levels, thereby triggers cytochrome c release from mitochondria and activates caspase-3 mediated apoptotic pathway (Lin et al. 2004). However, anti-DENV NS1 antibodies also correlate with inflammatory activation of vessel endothelial cells and producing higher level of IL-6, IL-8, and MCP-1. This activation is further evident in increased expression of the adhesion molecule ICAM-1 and enhanced adhesion capacity of peripheral blood mononuclear cells to endothelial cells (Lin et al. 2006). It is worth noting that anti-DENV NS1 has been shown to induce endothelial cell apoptosis and caused hepatitis-like pathological conditions in mouse model, which holds relevance to the hepatic injury observed in patients with DHF.

Hemostasis

Hemostasis is a highly organized and balanced system to prevent bleeding. In normal conditions, it is regulated by a number of mechanisms as well as pathways. A primary stage of hemostasis is involved in vascular constriction, platelet activation, aggregation and coagulation cascade activation, clot formation, followed by clot disintegration via fibrinolysis. These are also involved in secondary hemostasis (Chuang et al. 2013). DENV proteins have molecular similarities with coagulation and fibrinolytic factors. These similarities may cause auto-antibodies to impede hemostasis. Markoff et al. (1991) published the first report demonstrating auto-antibodies against coagulation factor in dengue patients. The molecular mimicry observed between DENV proteins and factors involved in coagulation and fibrinolysis has potential to trigger the production of auto-antibodies, potentially disrupting normal hemostasis. Profibrinolysis and hyperfibrinolysis caused by auto-antibody mechanisms, occurs during severe DENV infection. In profibrinolysis, auto-antibodies attach to plasminogen and break the fibrinogen. Conversely, hyperfibrinolysis occurs when these auto-antibodies bind to plasminogen, leading to the overproduction of fibrin degradation products and increased bleeding risk (Chuang et al. 2013). In several studies, the correlation between plasminogen cross-reactive antibodies and hemorrhage is observed in DENV-infected patients (Warter et al.2012).

Cross –reactive antibodies in dengue patients

DENV induced auto-antibody pathogenesis: coagulation and fibrinolysis

Several studies revealed a relation between DF and the production of auto-antibodies against platelets, endothelial cell, and coagulation factors (Lin et al. 2001; Oishi et al. 2003; Saito et al. 2004; Chuang et al. 2014; Zhou et al. 2007; Tracy et al. 2012). Molecular mimicry occurs in two approaches to ensure that auto-antibodies induced by DENV cross-react with coagulation factors. The initial approach involves directly comparing the linear amino acid sequences of the DENV proteins and the coagulation factors to determine a shared sequence. The other approach utilizes *in silico* conformational analysis to determine a shared motif or domain structure. Furthermore, for antibodies directed against the linear amino acid sequences region to attach to the target region and disrupt function, it must be made visible. Several amino acid sequences are common in DENV proteins and coagulation factors, such as prothrombin, fibrinogen, and plasminogen, as revealed by sequence analysis. DENV infection induces auto-antibodies via molecular mimicry (Chuang et al. 2014). During viral infection, a variety of mechanisms, such as polyclonal activation, epitope

spreading, and bystander activation, can cause autoimmunity. In the coagulation pathway, hemostasis may be caused by auto-antibodies resulting from the molecular mimicry between DENV proteins and coagulation factors and fibrinolytic factors. Moreover, throughout the proteomic studies and sequence analysis, it has been observed that the C-terminal region of the DENV NS1 shares sequence similarity with specific host-proteins. This schematic diagram demonstrated in Fig. 2, a specific amino acid sequence (WGNGCG) in the E protein bears sequence resemblance to factors XI (Lin et al. 2011).

The coagulation pathway can be activated by both intrinsic and extrinsic pathways to form thrombin and both pathways are joined at the activation point of factor X (Albert et al. 2010). Activated factor X forms a complex with the presence of activated factor V to activate prothrombin, after which thrombin is formed. Afterward, thrombin mediates the conversion of fibrinogen to fibrin and leads to clot formation. Prolonged thrombin time and activated partial thromboplastin time, in addition to a decline in the levels of fibrinogen and elevated levels of fibrinogen degradation products, are indicative of abnormal coagulopathy in DHF patients (Chuang et al. 2014). In the fibrinolysis mechanism, plasminogen is activated by an activator with the help of pro-activation in the presence of factor XII. Plasminogen is transformed into plasmin by tissue plasminogen activator (tPA) or Urokinase to prevent thrombosis (Chuang et al. 2013). Then plasmin can digest fibrin into a fibrin degradation product. Pro-coagulation and anti-coagulation factors tightly inhibited unwanted thrombosis or bleeding under normal conditions (Chuang et al. 2014). Several studies reported that the conversion of plasminogen to plasmin was inhibited when they use a monoclonal antibody (mAb) against DENV and identified 6H11 mAb was pre-incubated with DENV which enhanced the conversion of plasminogen to plasmin with or without Urokinase (Chuang et al. 2013).

In the case of pro-fibrinolysis demonstrated in Fig. 3, auto-antibodies bound to the plasminogen act on fibrinogen, and are tightly regulated to break fibrinogen. In another case of hyperfibrinolysis in DENV-infected patients, excessive fibrin degradation product is induced when auto-antibodies bind to the plasminogen complex and break down the fibrin clots. As a result, excessive activation of fibrinolysis will develop the tendency of bleeding, whereas the inhibition of fibrinolysis will result in thrombosis (Chuang et al. 2013). According to a study, DENV infection can cause auto-antibodies that are cross-reactive with plasminogen, which could enhance plasminogen activation (Srikiatkhachorn et al. 2009).

Furthermore, antibodies against NS1, along with the E protein have been demonstrated to interact with human fibrinogen (Chuang et al. 2014). However, the impact of this

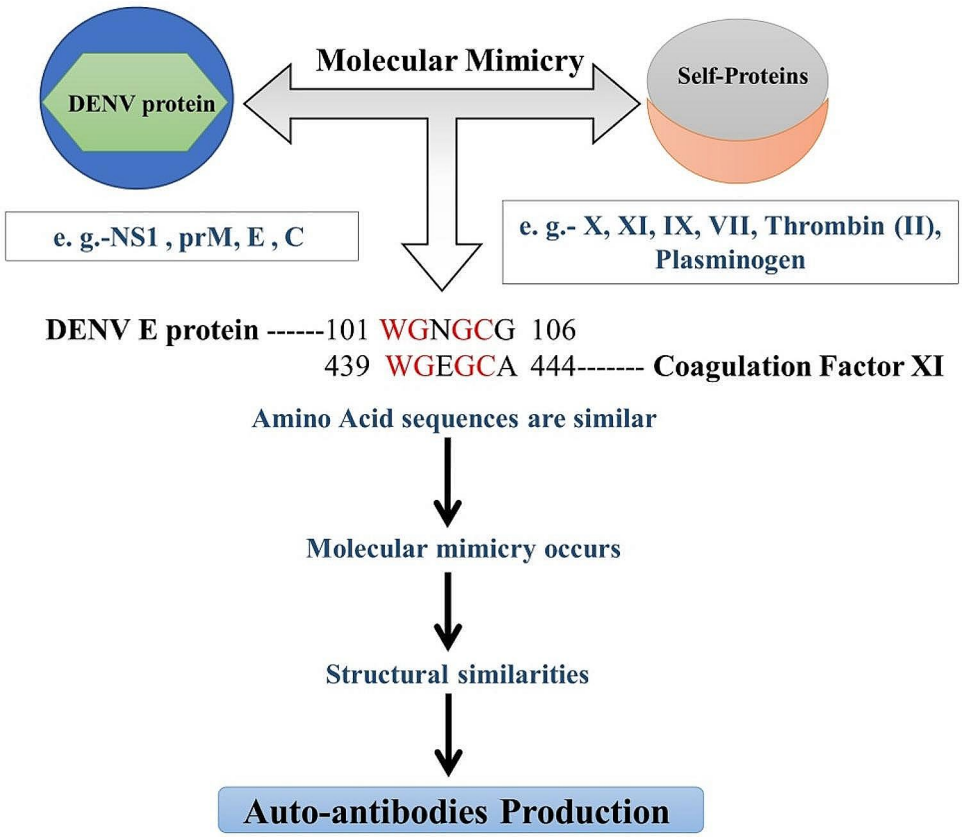

Fig. 2 A schematic model of general mechanism of molecular mimicry occurring between host-proteins and DENV proteins including NS1, core, prM and E proteins to induces auto-antibodies respectively. In addition, a specific amino acid sequence (WGNGCG) in the E protein bears sequence similarity to factors XI

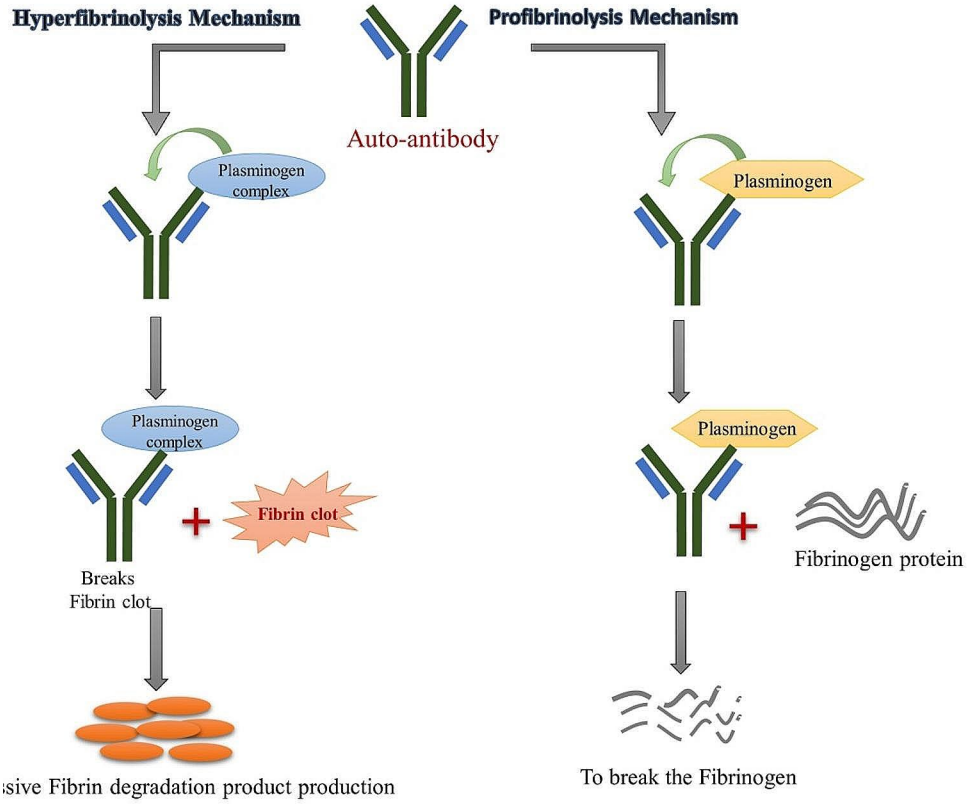

Fig. 3 Hyperfibrinolysis mechanism: The plasminogen complex is broken down by auto antibodies, which results in the production of an excess fibrin degradation product. Pro-fibrinolysis mechanism: Auto-antibodies attach to plasminogen and act on fibrinogen and degrade fibrinogen in a regulated manner

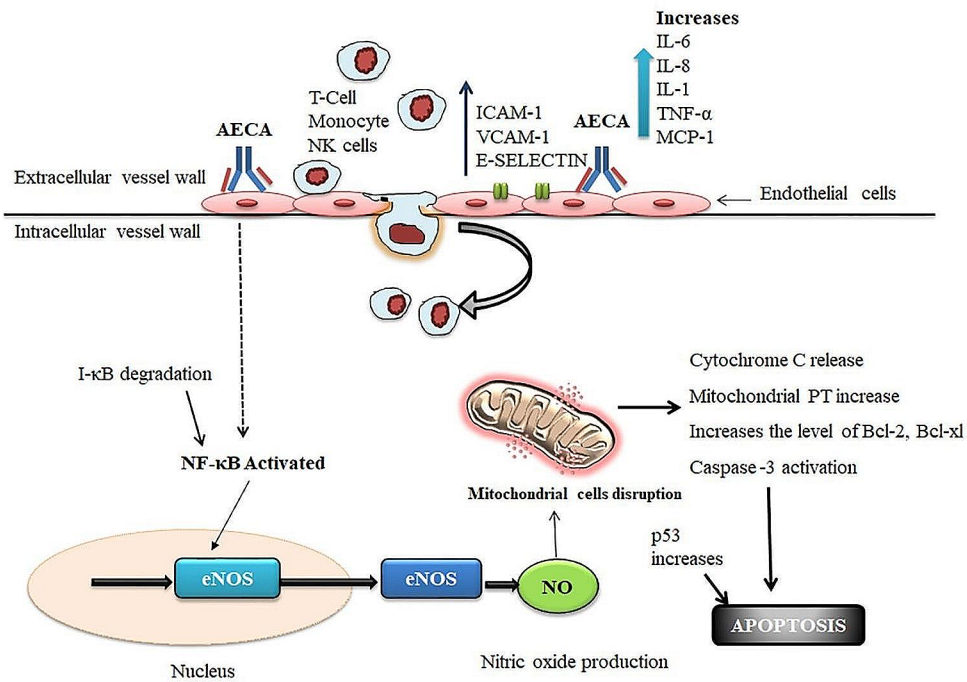

Fig. 4 Endothelium damage during the inflammatory responses caused by Anti-endothelial cell antibody (AECA) and activation of NF-κB as a result of endothelial cell degradation of I-κB. The procedure of signal transduction resulting in endothelial cell apoptosis caused by AECA is mediated by a nitric oxide (NO)-regulated pathway eNOS-endothelial nitric oxide synthase; ICAM-1- Intercellular adhesion molecule-1; IL -Interleukin; IFN - Interferon; MCP-1 - Monocyte chemotactic protein-1; NF-κB - Nuclear factor-kappa B; TNF-α-Tumour necrosis factor - α; VCAM-1 - Vascular adhesion molecule-1 ; NK - Natural killer cell

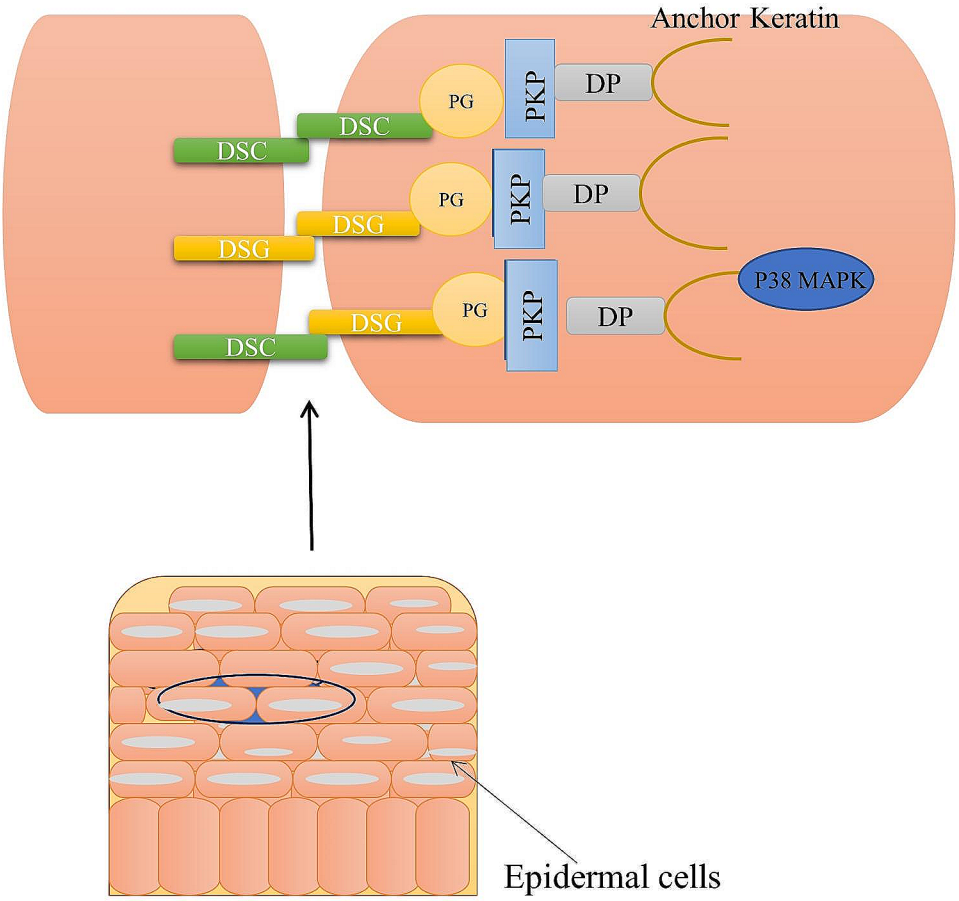

Fig. 5a Desmosomal proteins are necessary for maintaining intercellular adhesion in the epidermis. This adhesion is caused by the homophilic and heterophilic binding of desmogleins (DSG) and desmocollins (DSC). Desmoplakin (DP) interacts with proteins like plakoglobin (PG) and plakophilins (PKP) to attach itself to the intracellular tails of DSG and DSC. Keratins are anchored and desmosomes become stable by this process

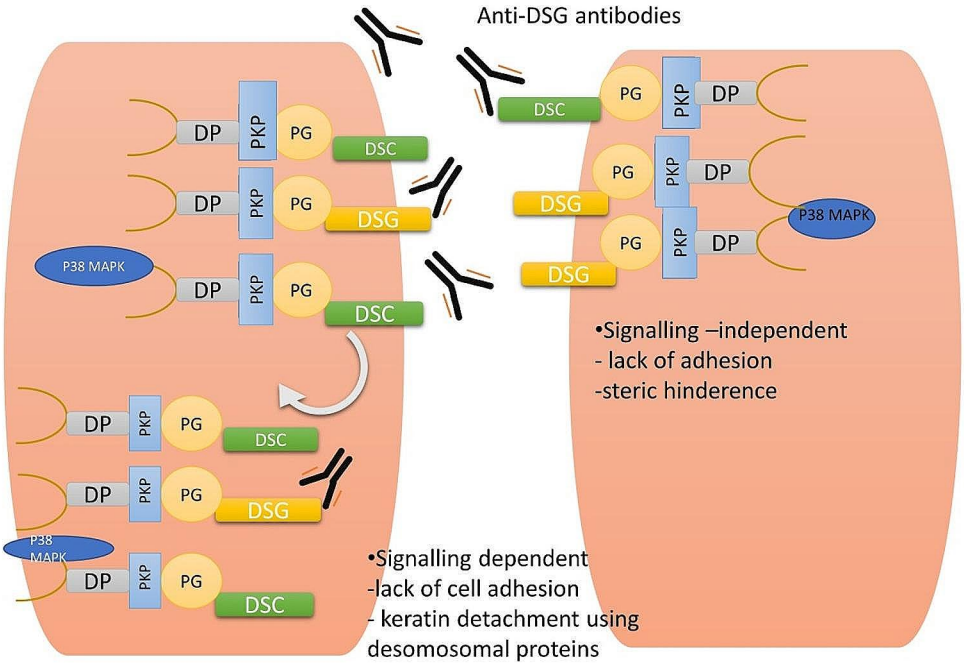

Fig. 5b Pathogenic auto-antibodies directed against DSG have specific targets in the N-terminal extracellular domain 1 (EC1) of the protein. For DSG to interact adhesively, this area is required. Steric hindrance is the term for the process by which keratinocytes separate without the need for cellular signalling due to the disruption of these interactions triggered by these auto-antibodies

cross-reactive fibrinogen is unknown how NS1 antibodies effect on fibrinogen activation. Serum samples typically consist of numerous components that may impede the process of coagulation, it is imperative to isolate the contributions of these elements from the effects of cross-reactive antibodies. Regarding this, using monoclonal antibodies might be useful. The effects of monoclonal antibodies on coagulation molecules may vary depending on their specificity, functionality or activation. Alternatively, recombinant single chain variable region (scFv) can be used to investigate how antibody affects coagulation function because it preserves the specificity of an antibody, but bacteriophages can also produce them (Chuang et al. 2014).

Chuang et al. (2014) generated scFv from NS1 immunized mice. Fibrinogen cross-reactive scFv antibodies were selected from the scFv library and their effect on fibrinogen activation and thrombin time was increased. In a few studies, recombinant scFv against NS1 can interfere with fibrin production which leads to prolonged thrombin time than normal thrombin time (Chuang et al. 2014). These results suggest that during DENV infection, coagulation factor cross-reactive auto-antibodies can be generated by molecular mimicry, which can lead to the pathophysiology of DHF/DSS.

Hepatic inflammation in dengue

Hepatic damage is an extremely important manifestation of DENV infection which is currently believed to transpire as a result of anti-DENV NS1 antibodies (Bhatt et al. 2021). Scientists suggest that normal liver function is disturbed during DENV infection as a result of production of auto-antibodies against the endothelial cells lining blood vessels (Lin et al. 2008). This, in turn, can lead to severe endothelial dysfunction, contributing to hepatic inflammation. Scientists have shown the action of anti-DENV NS1 antibodies in the murine model and found that these tend to cross-react with certain host components like endothelial cells, factors of blood clotting and various adhesion proteins (Lin et al. 2004). These antibodies were found to target the vascular endothelium of the central and portal hepatic veins in the murine model. After interaction with the anti-DENV NS1 antibodies, the liver showed drastic pathophysiological alterations in the histological architecture, which includes fatty liver, necrotic body, liver fibrosis, development of vesicles and cellular infiltration. Enhanced infiltration of mononuclear phagocytic cells was observed in the liver when these tissues were passively inoculated with anti-DENV NS1 antibodies thereby causing liver injury (Lin et al. 2008). Immune activation in liver endothelial cells might occur upon cross reactivity with anti-DENV NS1 antibodies through the activation of cellular signal transduction pathways and tyrosine phosphorylation of cellular proteins.

AECA like anti-DENV NS-1 antibodies play a crucial role in destruction of liver function as discussed, there are few experiments that have been done to establish the same in other organs. Upon activation of AECA there is an upregulates the expression of pro-inflammatory cytokines including IL-1, IL-6, IL-8, MCP-1, and tumor necrosis factor- α (TNF-α), which are associated with tissue injury during DENV infection (Lei et al. 2001). Severe liver damage might also be a result of such upregulation due to auto-antibody production during DENV infection. In Fig. 4, it can be seen that NF-κB is activated through the degradation of I-κB which could be involved in triggering the pro-inflammatory responses (Lin et al. 2004). This activation has been observed when anti-DENV NS-1 protein cross-reacts with non-infected endothelial cells, inducing apoptosis in these cells (Lin et al. 2004). Research have demonstrated that both sera from dengue patients and mouse antibodies against DENV activate multiple signaling pathways, leading to the expression of iNOS (inducible nitric oxide synthetase) and the production of NO following stimulation by anti-NS1 antibodies (Lin et al. 2004). In the Fig. 4, eNOS is believed to undergo a similar process of disproportionate NO production upon stimulation by anti-NS1 antibodies; thereby causing changing of mitochondrial potential, leaking cytochrome C into the cytosol, and finally mitochondrial disruption; which, in turn, might cause acute liver failure. The production of NO further induces the expression of p53 and Bax, along with the down regulation of Bcl-2/Bcl-XL, which results in the activation of caspase-3 and further intrinsic pathway of apoptosis after the mitochondrial cell disruption. These processes disrupt the critical balance of pro-apoptotic and anti-apoptotic factors, ultimately leading to endothelial cell death and activation via NO-mediated inflammatory pathways (Lin et al. 2004).

Pemphigus as a pathomechanism of acantholysis in dengue

Pemphigus disorders are associated with the generation of auto-antibodies against DSG, which trigger acantholytic intra-epidermal blisters. The two primary clinical manifestations of autoimmune skin blisters are Pemphigus vulgaris (PV), which affects mucous membranes and the skin through the generation of anti-DSG-1 and anti-DSG-3 antibodies, and Pemphigus foliaceus (PF), which affects the skin by producing anti-DSG-1 (Zenzo et al. 2017; Ahmed et al. 2016; Machado et al. 2017; Mihailidou et al. 2016; Maderal et al. 2014). Because auto-antibodies against DSG are frequently developed, the precise etiologic of pemphigus is still unknown and depends on the interaction of both genetic

and environmental factors (Qian et al. 2016; Miguel et al. 2022; E. Ruocco et al. 2014). Viral infections such as the DENV, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex viruses 1 and 2 (HSV1/2) may trigger or exacerbate pemphigus (Senger et al. 2012; Kurata et al. 2014; Machado et al. 2017).

Acantholysis may result from the development of auto-antibodies against desmosomal proteins in DENV disease (Delva et al. 2009). Acantholysis disrupts intercellular connections and causes the keratin filament to collapse. One of the intercellular complexes in the mucous membrane and epidermis that provides strong cell-to-cell adhesion is the desmosome. These five protein types— DSG, desmocolins (DSC), desmoplakin (DP), plakophilins (PKP), and plakoglobin (PG)—make the structure of desmosomes. DSG, DSC and PKP have multiple isoforms within the epidermal layer. These are the following: DSG 1 to 4, DSC 1 to 3, and PKP 1 to 3 (Thomason et al. 2010; Broussard et al. 2015; Osmani et al. 2015).

Several studies have associated patients with DHF and DF with PV and PF, the two major autoimmune diseases (Furue et al. 2017; Saito et al. 2012). The mucous membranes and epidermal layer are the main targets of these autoimmune diseases. In these studies, patients infected with DENV developed epidermal blisters as a result of passively transferring anti-DSG antibodies to new born mice (Spindler et al. 2013). Desmosome cell adhesion is disrupted in pemphigus diseases because of the homophilic and heterophilic binding of DSG and DSC. PKP and PG, which subsequently bind to DP proteins, are linked to the intracellular tails of both DSG and DSC proteins. This process anchors the tissue keratins (Furue et al. 2017).

Furthermore, as an outcome of auto-antibody binding, the keratin fibres collapse inward and the desmosome complex internalizes into the cytoplasm. During this procedure, the essential component of the signaling-dependent pathway, P38 mitogen-activated protein kinase (P38 MAPK), is activated (Furue et al. 2017). Both signaling-dependent and signaling-independent pathways must play a part in the development of acantholysis and demonstrated in Fig. 5a and b. In the case of dengue, anti-DSG antibodies directly bind to the N-terminal extracellular domain 1 (EC1) of DSG protein, which is essential for the adhesive trans-interaction of DSG. This binding leads to steric hindrance, resulting in the dissociation of keratinocytes in a signaling-dependent manner (Saito et al. 2012). Some researchers have confirmed that both signaling-independent and signaling-dependent pathways play role in the progression of acantholysis (Spindler et al. 2013).

Additionally, binding of anti-DSG auto-antibodies to the cell surface of DSG-3, both EC-1 non-targeting and EC-1 targeting polyclonal pemphigus vulgaris auto-antibodies, induces clustering and endocytosis of DSG-3, with P38 MAPK activation leading to the breakdown of keratin filaments (Vielmuth et al. 2015). DSG-3 internalization is associated with the decline in cell adhesion when P38 MAPK inhibitors prevent auto-antibody-mediated clustering and endocytosis of DSG-3, along with the loss of cell adhesion through the signaling pathway (Furue et al. 2017). It is worth noting that the degeneration of cell adhesion due to monoclonal anti-DSG-3 antibodies does not depend on P38 MAPK activation, clustering, or endocytosis of DSG-3, but a recent study suggests that DSG-3 disassembly alone is insufficient for keratinocyte dissociation in PV (Heupel et al. 2008; Delva et al. 2008). Another important factor to consider is cholesterol rafts, which lead to the depletion of cell surface DSG-3 (Resnik et al. 2011; Saleh et al. 2015). The pathogenic effects of polyclonal PV auto-antibodies vary in each PV autoimmune disease observed in DHF patients (Kamiya et al. 2015). In cases of low pathogenicity, anti-DSG-3 auto-antibodies can induce mucosal erosions in infected patients (Kamiya K et al. 2016). Conversely, mucosal involvement can be induced by highly pathogenic anti-DSG-3 auto-antibodies, even at undetectable low levels of DSG-3 assembly and the subsequent formation of desmosomes appeared to be dependent on calcium (Chuang YC et al. 2004; Stahley et al. 2014). Furthermore, auto-antibodies that target of DSG-3calcium-dependent epitopes are more deleterious (Kamiya et al. 2013). However, the involvement of anti-DSG auto-antibodies as a primary pathogenic factor in pemphigus is highlighted by the fact that DSG-specific auto-antibodies result in altered distribution, which is followed by internalization of desmosomal proteins and is sufficient to cause skin blistering (Furue et al. 2017). Accordingly, the ability of IgG fractions to induce blistering was eliminated upon immune adsorption of pathologic auto-antibodies from PV sera by the complete extracellular domains of DSG-1 and DSG-3 (Hofrichter et al. 2018; van et al. 2010).

IgG and IgM auto-antibody activity during DENV infection

Primary DENV infections usually cause mild symptoms, but secondary infections can manifest a spectrum of symptoms, from DF to DHF or DSS (Bhatt et al. 2021). Patients with DENV infection can be distinguished from those with other Flaviviridae family members including Japanese encephalitis virus and hepatitis C by the presence of serum-induced platelet lysis (Linet al. 2001). Additionally, IgM and IgG antibodies against the NS1 protein were discovered to be platelet-specific IgM auto-antibodies in DENV-infected individuals. These antibodies cross-reacted with

platelet antigens and were correlated with the severity of the infection (Lin et al. 2001; Oishi et al. 2003; Jayathilaka et al. 2018). Research studies show that complement pathway elements (C5, C8, C9, factor B, factor H, and factor P) are targeted by auto-antibodies produced in DENV-infected patients. Strong complement activation is considered to play a role in blood vessel disruption and vascular leakage during infection. Patients with DHF have increased C3 convertase (C3bBb) complex formation, leading to the alternative complement cascade, whereas patients with DF have reduced factor H expression (Kouser et al. 2013). Auto-antibodies against factors H and P were identified, especially in cases of primary infections. Low levels of anti-prothrombin IgG, anti-complement C4 IgG, and anti-factor P IgG have been related to low platelet counts in DHF patients. These points to a possible immune complex-mediated clearance of these auto-antibodies, which would accelerate the development of DHF by interfering with the complement cascade. Additionally, auto-antibodies directed against complement or coagulation proteins and matrix proteins are less prevalent in DF and DHF patients (Vo et al. 2020). Studies discovered a correlation between platelet count, anti-complement C4 IgG auto-antibodies, and anti-factor P IgG. Primary DENV infection has been connected to these auto-antibodies that bind nuclear proteins like autoimmune diseases. DENV-specific IgGs were significantly elevated in secondary infections, whereas IgG auto-antibodies were more common in primary infections. IgG auto-antibodies, a sign of a compromised tolerance mechanism; promote the growth of auto-antigen-binding B cells and their subsequent differentiation into plasma cells that secrete antibodies (Balakrishnan et al. 2011; Koraka et al. 2001; Yurasov et al. 2007).

Future perspectives

Many parts of the world are facing a serious health threat from viral diseases, with dengue fever standing out as one of the prominent examples. The present study focuses on the potential involvement of anti-DENV antibodies in the pathophysiology of DHF and DSS. These results might open up new avenues for future study on auto-antibodies, which could transform our understanding of dengue infection and lead to the incorporation of auto-antibody-mediated consequences into vaccine development strategies.

Understanding the specificity and function of auto-antibodies

Further investigation is required to recognize the precise auto-antibodies produced after DENV infection and comprehend their functional properties. This entails delineating their binding targets, neutralizing capacities, and potential contributions to immune dysregulation including inflammation and autoimmunity.

Investigating the implications of auto-antibodies on disease outcome

The subsequent research ought to focus on understanding the association between clinical results and auto-antibody profiles in DENV-infected individuals. Determine whether specific auto-antibody signatures correlate with the intensity of disease and susceptibility to severe clinical manifestations such as DHF, DSS, and long-term complications. Based on the current status of epidemiology, mathematical models have the prospective to be an advantageous tool in diagnosing strategies of dengue throughout the population. It is highly significant to promote the integration of experimental and epidemiological data with fundamental studies and genomic studies, along with the application of highly essential cutting-edge technologies such as ‘omics’, nanotechnology, biosensors, and molecular modelling.

Development of biomarkers and therapeutic targets

More investigations may concentrate on identifying auto-antibodies that act as biomarkers for disease severity, prognosis, or response to treatment in DENV-infected individuals. Additionally, there is potential to discover auto-antibodies as therapeutic targets for the development of novel immunomodulatory or antibody-based therapies aimed at mitigating disease progression and improving outcomes. Various approaches, particularly antibody engineering and nanobodies derivatives, are interesting concepts for creating particular and sensitive biomarker indicators. Additional approaches involve the use of structural analysis, molecular mimicry, the identification of antigenic cryptic epitopes, and inhibitory mechanisms. DENV NS1 antigen can be targeted by numerous biomarker indicators, and also NS1 may emerge as a potential biomarker for DENV detection. Additionally, in order to decrease the burden of this infection, therapeutic monoclonal antibody (mAb) preparations may neutralize DENV without rising antibody-dependent enhancement and early diagnostic testing. Comprehensive auto-antibody profiling studies are also anticipated to simplify progress in high-throughput screening systems and bioinformatics tools. These will be enable the detection of new auto-antibody markers and the validity of those that already exist across a range of communities. Eventually, the therapy of DENV infection could be improved by introducing auto-antibody profiling into standard clinical practice. These would enhance patient outcomes and decrease the prevalence of vector-borne viral disease worldwide.

Analyzing auto-antibody reactions in various dengue endotypes

Further studies should investigate the differences in auto-antibody responses across the different dengue endotypes, such as primary versus secondary infections, various virus serotypes, and specific host immune profiles, considering the heterogeneity of outcomes and clinical manifestations of DENV infection.

Most importantly, there is a need for enhanced collaboration between clinicians, scientists, and public health authorities to upgrade knowledge and effectively utilize the significance of dengue auto-antibodies in the ongoing effect of this crucial global health burden. By utilizing auto-antibodies as biomarker, the gap between DF and its therapeutic interventions may be effectively bridged, thereby reducing the worldwide impact of the dengue epidemic.

Conclusion

Globally, dengue cases have surged and are currently documented in over 100 countries. It's critical to control and prevent dengue. However, among the potentially fatal side effects experienced by severe dengue patients is the development of autoimmune disease. In DENV infection, auto-antibodies may cause abnormalities through an array of mechanisms. Recognizing these pathways can help prevent mild-to-severe diseases like autoimmune diseases, DHF, and DSS. Moreover, DENV-induced cytokines and auto-antibodies may be involved in the disturbance of the equilibrium between coagulation and fibrinolysis, as well as in the operations of platelets and endothelial cells. The pathophysiology of autoimmune disease may also be significantly influenced by cross-reactive auto-antibodies. At various stages of DENV infection, each of them might have a distinct pathogenic function. In order to prevent any adverse reactions, dengue vaccine designers should avoid using epitopes that mimic coagulation factors. Additionally, AECA-induced endothelial cell apoptosis plays a significant role in vasculopathy. The idea that auto-antibody-associated immunopathogenesis contributes to DHF raises questions about vaccine development because autoimmune memory can make a person more susceptible to a more severe case of dengue later on. A number of candidate vaccines are currently under evaluation; the majority of which make use of chimeric or live attenuated viruses. Future research into the development of a secure and reliable dengue vaccine may need to take auto-antibody-mediated complications into consideration. Clinical trials shall be conducted to assess the development of all these concepts in the future, which will substantially improve the therapeutic options used to treat DENV infection.

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Declarations

Competing interests The authors declare no competing interests.

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