RESEARCH ARTICLE

Impact of elevated IgE in protective immunity and immunopathology of dengue

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ABSTRACT

Dengue is a mosquito-transmitted infection endemic in tropical and subtropical locations of the world where nearly half of the world's population resides. The disease may present as mild febrile illness to severe and can even be fatal if untreated. There are four genetically related but antigenically distinct dengue virus (DENV) serotypes. Immune responses to DENV infection are in general protective but under certain conditions, they can also aggravate the disease. The importance of the cellular immune responses and the antibody responses involving IgG and IgM has been well-studied. In contrast, not much has been described on the potential role of hypersensitivity reactions involving IgE in dengue. Several studies have shown elevated levels of IgE in patients with dengue fever, but its involvement in the immune response against the virus and disease is unknown. Activation of mast cells (MCs) and basophils mediated through dengue-specific IgE could result in the release of mediators affecting dengue virus infection. The present review explores the relationships between the induction of IgE in dengue virus infection, and the potential role of MCs and basophils, exploring both protective and pathogenic aspects, including antibody-dependent enhancement (ADE) of infection in dengue.

Keywords: Dengue; IgE; mast cells; ADE; immunity.

INTRODUCTION

Dengue is an important mosquito-borne disease caused by the dengue virus (DENV) from the genus *Flavivirus*. There are four serotypes of the virus dengue virus designated as DENV-1, DENV-2, DENV-3, and DENV-4 (Marshall *et al*., 2003; Appanna *et al*., 2012; St. John, 2013; Inokuchi *et al*., 2018). The occurrence of dengue fever outbreak has evolved from a sporadic disease to a serious public health concern with endemic status in over 100 countries. Dengue fever has become more widespread in recent years, posing a threat to almost half of the world's population (Guzman & Harris, 2015; Zainal *et al*., 2018; Roy & Bhattacharjee, 2021). DENV is estimated to cause approximately 400 million new infections each year. This statistic is likely to be underestimated due to the absence of effective surveillance networks in most tropical countries (Hasan *et al*., 2016; Tsheten *et al*., 2021).

DENV infection presents with different symptoms ranging from undifferentiated fever to dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) (Appanna *et al*., 2012; Roy & Bhattacharjee, 2021). The updated WHO classification (2009) separates dengue into two groups: non-severe and severe dengue (SDF); the non-severe categories are further separated into dengue with warning signals (D+W) and dengue without warning signs (D-W). To establish management standards and to make dengue reporting and surveillance easier, the new classification was created based on the degree of clinical severity (WHO, 2009; Katzelnick *et al*., 2017; Ajlan *et al*., 2019).

The mechanisms involved in the pathogenesis of dengue disease, especially the severe manifestations such as thrombocytopenia, hypotensive shock, haemorrhagic symptoms, and vascular leakage, which can result in organ failure and death are still unclear (Katzelnick *et al*., 2017). Due to the participation of DENV in both protective and pathogenic effects on the host, the immune reaction of the host towards DENV infection is complicated. Since the secondary heterologous infection carries a higher risk of severe dengue, people who have recovered from the original DENV infection generate a strong antibody that can prevent reinfection by the same serotype but not by heterologous serotype. The latter phenomenon, often referred to as antibody-dependent enhancement (ADE), occurs when heterotypic antibodies do not neutralise the virus but rather aid in its entry and multiplication instead (Abraham & St. John, 2010; Katzelnick *et al*., 2017). Other factors that may contribute to symptomatic or severe dengue include molecular mimicry between coagulation factors and DENV proteins resulting in anti-dengue antibodies, soluble factors such as high concentrations of chemokines, cytokines, and interleukins, and cellular immune responses such as T cells (Lin *et al*., 2011; Whitehorn & Simmons, 2011; Wan *et al*., 2013).

Previous studies on the maternal dengue-specific IgG antibodies obtained during pregnancy and breastfeeding from the mother in mice showed enhancement and protection against dengue (Lee *et al*., 2016; Mantri *et al*., 2021). In contrast, IgG antibodies have previously been demonstrated to boost DENV binding to Fc-gamma receptor IIIA (FcγRIIIA), which contributes to disease severity (Wang

et al., 2017). Another *in vivo* study showed that IgG from the serum of a dengue-seropositive monkey enhances infection, while IgM does not (Kurane *et al.*, 1991). In cases of initial dengue infection, the production of IgM and later IgG anti-dengue-specific antibodies is dependent on the activation of naïve B cells. In contrast, after a secondary infection, memory B cells serve as the main sources of dengue-specific antibodies, albeit IgM antibodies appear to be generated by the naïve cells (Vazquez *et al.*, 2014).

Extensive research has explored the diverse roles of IgG and IgM in DENV infection, encompassing both protective and potential pathological effects (St. John, 2013; Lee *et al.*, 2016; Wang *et al.*, 2017; St. John & Rathore, 2019; Jain *et al.*, 2021), while the role of IgE in this context remains undefine and warrants further research. Higher level of dengue-specific IgE antibody has been associated with severe dengue (Koraka *et al.*, 2003), while a study in mice showed that the mast cells (MCs) sensitized with serum containing IgE antibodies have increased degranulation following DENV infection (Avirutnan & Matangkasombut, 2013). This could be due to high-affinity thermolabile antibodies targeting MC receptors on their cellular surfaces, suggesting the possibility that IgE and MCs could play a pathogenic role in dengue through the release of histamine contents (Sanchez *et al.*, 1986). Histamine is responsible for inducing numerous inflammatory and hypersensitivity responses, such as vasodilation, oedema, increased vascular permeability, and contraction of smooth muscles (Krystel-Whittemore *et al.*, 2015; Yamauchi & Ogasawara, 2019). High levels of histamine are kept in MC granules, but it is assumed that during granule exocytosis, histamine is promptly solubilized to encourage increases in vascular permeability or hyperpermeability (Kunder *et al.*, 2011; Ashina *et al.*, 2015). As such, it is noted that histamine recruits more cells that induce plasma leakage (Parsons & Ganellin, 2006; Mikelis *et al.*, 2015; Yamauchi & Ogasawara, 2019). Diagram illustrating the role of histamine in dengue pathogenesis as depicted in Figure 1.

On the other hand, an earlier study demonstrated that sera of systemic lupus erythematosus (SLE) patients could neutralise DENV without having detectable levels of dengue-specific IgG, suggesting the possible role of cross-reacting IgE in the protective effects against dengue (Zainal *et al.*, 2018). Here, we will review the current knowledge related to protective and pathologic responses of IgE and MCs in dengue and explore the possible questions to be addressed in future studies.

Host immune responses in dengue
Hypothesized mechanisms through which DENV establishes infections include virus replication within macrophages, infection
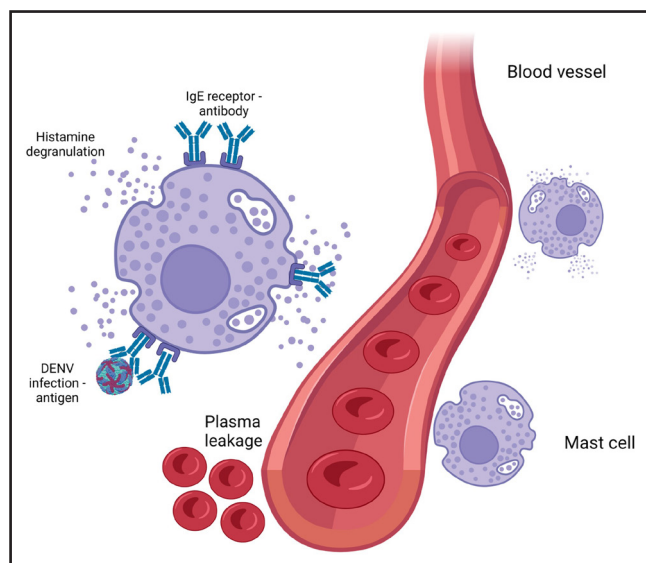
Figure 1. How histamine plays a role in dengue pathogenesis. Figure created using BioRender.

of human skin Langerhans, as well as immunological and chemical-mediated host-viral interactions (Bhamarapravati, 1980; Wu *et al.*, 2000). DENV is released into the body through the bite of an infected female *Aedes aegypti* or *Aedes albopictus* mosquito. The virus enters and passes through the lining of the epithelium (Makhluf & Shresta, 2015).

Clinical manifestations of DENV infections range from asymptomatic, mild febrile to severe illness that could be fatal if not properly treated. Symptoms of dengue fever manifest after 5–7 days of incubation period. The illness progresses through three stages: febrile, critical, and convalescent. The fever is usually biphasic and lasts 2–7 days (Kalayanarooj, 2011). After infection, the virus begins to replicate itself in skin cells such as Langerhans cells and keratinocytes. Virus invasion induces several host's innate immune responses (Uno & Ross, 2018). When an infection occurs, innate immune cells such as dendritic cells (DC), macrophages, and monocytes are the first to fight it off by using their pattern recognition receptors (PRRs) to find the pathogen-associated molecular patterns (Kao *et al.*, 2018; Uno & Ross, 2018). An antiviral state will be produced as a result of the release of cytokines and chemokines in response to PRR identification. In addition to endosomal Toll-like receptor 3 (TLR3) and TLR7, the PRRs melanoma differentiation-associated protein 5 (MDA5) and a cytoplasmic retinoic acid-inducible gene I (RIG-1) are connected to DENV recognition (Uno & Ross, 2018). The type 1 interferon (IFN) responses are induced when these receptors are activated by DENV recognition. RIG-1 and MDA5 are RIG-1-like receptors (RLRs) with similar RNA helicases expressed in MC types (Makhluf & Shresta, 2015; Kao *et al.*, 2018; Uno & Ross, 2018; Lee *et al.*, 2022). Type I IFN is the dominant innate immune response, and the virus's principal evasion technique is to target the type I IFN response. Complement activation, apoptosis, autophagy, and RNA interference (RNAi) are examples of innate immune responses known in dengue virus infection (Kao *et al.*, 2018; Uno & Ross, 2018).

The innate and adaptive immune systems cooperate to combat the virus when a person has dengue. B cells in the immune system produce antibodies as the adaptive immune response to combat dengue infection (Janeway Jr., 2001; Lee *et al.*, 2022). Additionally, crucial in tying together the innate and adaptive immune responses is the complement activation (Mellors *et al.*, 2020). Antigen and activated antigen-presenting cells (APCs) are delivered to the draining lymphoid tissues to initiate adaptive immunity when the innate immune response fails to eradicate an infection (Janeway Jr., 2001; Lee *et al.*, 2022). Virus-infected cells are recognised and destroyed by cytotoxic T lymphocytes. The complement system is activated by the innate immune response, aiding in the removal of the virus by white blood cells and antibodies. The innate and adaptive immune responses cooperate to neutralise the DENV infection, helping with dengue fever recovery (Guzman & Vazquez, 2010). Dengue-specific CD4+ T cells and CD8+ T cells played a critical role in controlling the virus and preventing severe disease. The presence of pre-existing dengue-specific antibodies could enhance the adaptive immune response and protect against future infections (Mathew & Rothman, 2008).

Dengue symptoms include thrombocytopenia, leukopenia, and increased vascular permeability, exhibiting a spectrum that ranges from mild fever to severe manifestations. While the initial infection activates immune responses against DENV serotypes, the severity of the illness is heightened by subsequent heterotypic DENV infections with different serotypes (Roy & Bhattacharjee, 2021). The body's immune response worsens the clinical symptoms of dengue and increases the risk of developing severe dengue in people who become infected with a different strain of the virus a second time, through mechanisms of antibody-dependent enhancement (ADE). ADE occurs when rather than protecting the body against infections, the antibody level at sub-neutralizing concentration magnifies and exacerbates the virus infection (Marshall *et al.*, 2003; Rothman, 2003; Martina *et al.*, 2009). The virus cannot be neutralised by the

main infection's antibodies. Instead, the Fc-gamma receptors (FcγRs) on circulating monocytes serve as receptors for the antibody-virus complex that leads to the virus effectively infecting and replicating in the monocytes and other FcγR-bearing cells. This phenomenon increases virus titre in the host and elevates the likelihood of developing severe dengue (Rothman, 2003; Martina *et al.*, 2009; Abraham & St. John, 2010; Krystel-Whittemore *et al.*, 2015). There are two parts to the ADE phenomenon: intrinsic and extrinsic ADE (Halstead, 2014; Narayan & Tripathi, 2020). While intrinsic ADE increases viral generation by inhibiting type 1 IFN and activating interleukin-10, extrinsic ADE promotes a T helper type 2 (Th2) type immune response by helping to increase virus entrance. Comparative to extrinsic ADE, intrinsic ADE contributes more to promoting DENV reproduction (Narayan & Tripathi, 2020). Extrinsic ADE, also described as greater antibody-mediated cell binding and the entrance of both mature and (partially) immature DENV particles, as well as higher virus generation per infected cell due to inhibition of the innate antiviral response, which are the two main drivers of ADE of dengue infection. Although further study is needed, intrinsic ADE primarily resulted from reduced TLR-signalling causing a decrease in host antiviral activity (Flipse *et al.*, 2013). Extrinsic and intrinsic ADE have been found to contribute threefold or one hundredfold, respectively, to an increase in virus production (Halstead, 2014). The severity of dengue fever is linked to an increase in immunological activity (Appanna *et al.*, 2012; Inokuchi *et al.*, 2018). The failure of the immune response to inhibit DENV replication due to ADE resulted in elevated viral levels and the subsequent activation of more pro-inflammatory cytokines and chemokines. This, in turn, can trigger a phenomenon known as a 'cytokine storm'. A cytokine storm represents a profound immune reaction characterized by the excessive release of pro-inflammatory cytokines and chemokines. This immune response can significantly contribute to the severity of dengue. It affects the vascular endothelium, resulting in heightened vascular permeability, causing plasma to leak from blood vessels into surrounding tissues, leading to shock (Chen *et al.*, 2008; Kelley *et al.*, 2012; Modhiran *et al.*, 2015). In addition to the shock, severe plasma leakage can also lead to organ failure (Srikiatkhachorn *et al.*, 2017).

Activation of IgE, mast cells, and basophils

IgE has long been considered to be the notable immunoglobulin responsible for type I hypersensitivities and illnesses such as allergic rhinitis, anaphylaxis, and asthma (Luker *et al.*, 2019). In allergy and inflammatory disorders, IgE receptors are considered to be critical components of the immunological cascade (Novak *et al.*, 2001). FcεR1, a high-affinity IgE receptor produced by MCs and basophils, as well as DCs and Langerhans cells in the skin, is one of two IgE receptors. Due to its high affinity for monomeric IgE, FcεR1 efficiently functions as an antigen receptor on the surface of FcεR1-expressing cells. FcεR1-expressing cells may bind a range of IgE antibodies, each of which may have a varied level of specificity, in contrast to B cells, which can only produce one kind of immunoglobulin. Monocytes, B cells, and DCs express CD23, the FcεR2 low-affinity IgE receptor. There are proposed regulatory roles for CD23 that are both beneficial and harmful (Stone *et al.*, 2010). CD23 can prevent IgE from binding to the FcεR1 in its soluble state and acts as a buffer to prevent the production of excessive amounts of IgE. There is disagreement about whether CD23 promotes or inhibits IgE synthesis, despite the possibility that it regulates IgE production (Engeroff & Vogel, 2021). Immunocompetent cells (B and T lymphocytes) and cytokines (IL-4, IFN gamma, IL-2, IL-5, IL-6) released by T cells in response to antigenic stimuli influence IgE synthesis. IL-4 regulates the expression of the CD23+ receptor (FcεR2) on the surfaces of monocytes-macrophages, eosinophils, platelets, epidermis Langerhans cells, and B lymphocytes (Di Monaco *et al.*, 1992). IFN-gamma, on the other hand, inhibits IL-4-mediated T-dependent activities. Atopic diseases, such as ocular rhinitis, dermatitis, and hyper-IgE syndrome, are characterized by elevated IgE levels, eosinophils, and a large number of CD23+ cells in the blood suggesting that the IgE system is hyperactive and that IL-4 production is high (Poole & Rosenwasser, 2005; Stone *et al.*, 2010). Although IgE-mediated degranulation is an efficient way to initiate a protective immune response, it may also inflict considerable tissue damage. Furthermore, FcεR1 on MCs and basophils mediates classic IgE-mediated activation of multivalent antigens cross-linking receptor-bound IgE causing degranulation and the release of pre-formed mediators. This pro-inflammatory environment attracts immune cells and triggers a Th2 immune response (Abraham & St. John, 2010).

MCs are leukocytes linked with connective tissue that are found at places of external contact, such as the skin and mucous membranes (Brown *et al.*, 2006; Amin, 2012). They are a type of white blood cell that can be found in the connective tissues of the body, specifically in the lungs and intestines, surrounding blood vessels and lymphatic arteries, in nerves, and under the skin (Krystel-Whittemore *et al.*, 2015). MCs develop from blood-circulating, bone marrow-derived progenitors that then differentiate once they enter tissues (Abraham & St. John, 2010). They have a long lifespan of several months to years, and despite being terminally differentiated, they can multiply in response to the right signals (Abraham & St. John, 2010; Amin, 2012). All mature MCs have a similar basic morphology and conspicuous electron-dense granules in their cytoplasm (Abraham & St. John, 2010). MCs play a critical role in the immune system's response to pathogens and parasites as well as in the control of other immune reactions. They also contain compounds including histamine, heparin, cytokines, and growth factors (Marshall *et al.*, 2003; Abraham & St. John, 2010; Amin, 2012; St. John & Abraham, 2013). They create these chemicals during allergic reactions and following immunological responses. Numerous effects of these substances include angiogenesis and the growth of blood vessels. During an allergic response, they might cause itching and flushing (a heated, red face). They can also cause shock, low blood pressure, muscle pain, nausea, vomiting, and stomach cramps. MCs are innate immune cells that live in the tissues surrounding blood arteries and lymphatic vessels and constitute the body's first line of defence against infections. They can be triggered by particular antibodies attaching to receptors on their surface, and they can also directly identify pathogens and inflammatory proteins (Avirutnan & Matangkasombut, 2013; St. John & Abraham, 2013). MCs, in general, contain a high number of granules that are abundant in components including histamine, tryptase, chymase, and tumour necrosis factor, and these substances are released when MCs are triggered to degranulate within seconds of the MCs being triggered (Krystel-Whittemore *et al.*, 2015). These cells are activated by FcRs, pathogen-associated substances, and endogenous inflammatory factors (Abraham & St. John, 2010). MCs that have been activated start producing leukotrienes, prostaglandins, cytokines, and other inflammatory mediators (Marshall *et al.*, 2003; Krystel-Whittemore *et al.*, 2015). The release of these substances enhances blood vessel permeability and attracts immune cells to the infection site. It also causes non-immune cells like smooth muscle cells and mucous glands to become activated, which aids in the removal of allergens and infections from the body (Avirutnan & Matangkasombut, 2013; St. John & Abraham, 2013). The integrity, tone, and function of the vascular system are well-established cellular regulators by MCs. They coat the inside of blood vessels and generate a large number of redundant vasoactive mediators (St. John *et al.*, 2013). The involvement of MCs in viral infections is more intriguing and less thoroughly researched. Many viral products can activate MCs, especially to stimulate the generation of cytokines; however, the degree of MC degranulation in response to viral infection and any potential functional ramifications are less known (Abraham & St. John, 2010).

Basophils, in addition to mast cells, are a part of the innate immunity family that has many characteristics in common with MCs (Stone *et al.*, 2010). Basophils, however, are the least common granulocytes, and due to their rarity and resemblance to tissue-

resident MCs, they have long been neglected in immunological studies (Miyake *et al.*, 2022). The segmented condensed nucleus of basophils, which ranges in size from 5 to 8 μm, is a characteristic of cells. Basophils are created from CD34+ progenitors, differentiate, and mature in the bone marrow, which then circulates in the peripheral circulation, where they make up less than 1% of all leukocytes. They are thought to have a few-day half-life. To develop stem cells into basophils, IL-3, the main cytokine driving basophil differentiation is required (Stone *et al.*, 2010). Basophil-derived IL-4 has recently been demonstrated to have a variety of roles in allergic inflammation by interacting with a wide range of cell types, including macrophages, innate lymphoid cells, fibroblasts, and endothelial cells (Miyake & Karasuyama, 2017). Basophils are capable of acting as antigen-presenting cells that bind antigens on their surface and stimulate humoral immune responses, resulting in the development of Th2 cells. Lower humoral memory activation and increased infection susceptibility are the effects of their depletion (Murdaca *et al.*, 2021). Basophil infiltration into inflammatory sites has been associated with a variety of allergic inflammations, including atopic dermatitis, allergic rhinitis, and asthma. Through their migration to the site of inflammation and production of several mediators, including cytokines, chemokines, and proteases, basophils play significant roles in both IgE-dependent and IgE-independent allergic inflammation (Miyake & Karasuyama, 2017). However, as basophils have similar characteristics to MCs, their roles are not very much studied in other areas.

Roles of IgE and mast cells in the protective aspects of dengue
There are presently limited research and articles regarding the role of IgE in dengue. The link between higher IgE levels and dengue infection might be due to IgE's involvement in maintaining immune homeostasis. IgE antibody responses to infectious agents, such as viruses, are more sensitive and specific than IgG, IgM, or IgA antibody responses suggesting that monitoring IgE levels may help determine the severity of an infection (Koraka *et al.*, 2003). When patients were examined according to their age and sex, there were no differences in their DENV-specific IgE levels (Machain-Williams *et al.*, 2023). A balanced immune response, rather than the development of a specific T-helper cell pathway, may lead to illness resolution in patients with present or previous DENV infection, according to abnormally high IgE levels. Furthermore, the DENV has been shown to trigger the creation of IL-6, which is implicated in the synthesis of IgE in humans. The presence of a specific IgE response and the maintenance of high IgG levels after recovery from dengue infection (IgG response) may suggest the presence of a specific IgE

response and perhaps represent immunological memory (Miguez-Burbano *et al.*, 1999). However, earlier studies have suggested that initial infections with any of the four DENV serotypes result in the production of protective type-specific antibodies as well as ADE when such antibodies are directed against non-viral entry surface epitopes (Halstead, 2014).

Due to their capacity to retain preformed mediators and release them almost immediately into an infection site when triggered, MCs have a kinetic advantage over other sentinel cells in the initiation of both innate and adaptive immune responses. In addition to influencing the immediate innate processes that eliminate infections, they could also affect the long-term host responses to pathogens (Abraham & St. John, 2010). Pro-inflammatory cytokine production is started by MCs, although they can also block them when necessary. This may accomplish several objectives, including facilitating wound healing, restoring homeostasis following pathogen clearance, and preventing tissue damage from protracted inflammation (St. John & Abraham, 2013). MCs can be stimulated by the DENV and although DENV clearance *in vivo* has been linked to cells such as the natural killer (NK) cells and T cells, which can kill DENV-infected cells, the cell types involved in initial surveillance for DENV are less well understood (St. John *et al.*, 2011). Since MCs are common in the skin, they are most likely to be among the first immune cells to encounter the mosquito bite-mediated subcutaneous-injected DENV. Due to the fact that MCs are involved in a variety of innate immune responses, there are numerous potential avenues for their contribution to host defence during the first few hours after DENV infection. There may be an MC-dependent recruitment of different subsets of NK and/or T cells to the infection sites. As soon as DENV is injected subcutaneously into the skin, MCs undergo degranulation and release preformed mediators, aiding in the immune surveillance for DENV. Degranulation is also induced by UV-inactivated viruses, suggesting that this release is a result of viral structural proteins. In response to viral activation, *in vivo* degranulation has never been recorded before (St. John, 2013). A brief summary of the roles of IgE and mast cells in the protective aspects of dengue can be found in Table 1.

Role of IgE and mast cells in the pathological aspects of dengue
Peripheral blood mononuclear cell cultures from dengue-immune as opposed to non-immune subhuman primates showed increased DENV infection. This phenomenon was later explained by the existence of non-neutralizing enhancing dengue antibodies, which led to increased DENV infection of primary monocytes and macrophages (Halstead, 2014). When pre-existing, non-neutralizing

Table 1. Protective aspects of IgE in dengue

Topic	Protective aspects of dengue	Reference
IgE	− Higher IgE levels may be linked to dengue infection. IgE antibody responses to viruses are more sensitive and specific than other antibody responses.	− (Koraka *et al.*, 2003)
	− Monitoring IgE levels may help determine disease severity.	− (Koraka *et al.*, 2003)
	− DENV triggers the production of IL-6, which is implicated in IgE synthesis.	− (Miguez-Burbano *et al.*, 1999)
	− The presence of a specific IgE response may represent immunological memory.	− (Miguez-Burbano *et al.*, 1999)
Mast cells	− Have a kinetic advantage in initiating immune responses and influence both innate and adaptive immune responses.	− (Abraham & St. John, 2010)
	− Can produce or block pro-inflammatory cytokines.	− (St. John & Abraham, 2013)
	− May be the first immune cells to come into contact with DENV.	− (St. John *et al.*, 2011)
	− Aid in immune surveillance for DENV by releasing preformed mediators upon contact with the virus. MC-dependent recruitment of NK and/or T cells may occur.	− (St. John *et al.*, 2011)
	− *In vivo* degranulation in response to viral activation has not been recorded.	− (St. John *et al.*, 2011)

antibodies cross-react with an antigenically unique heterologous DENV serotype, ADE-promoting immune complexes are formed. These weak connections allow viruses to adhere to antibodies without being destroyed, which leads to immune complexes attaching to cells and promoting virus uptake (Syenina *et al.*, 2015). When antibodies and antigens combine to form immunological complexes, Fc-receptor-bearing cells are effectively able to bind IgG through the Fc portion of the antibody. Similar to other Fc-receptor-bearing cells, MCs are also susceptible to infection via the ADE process when immune complexes containing unneutralized DENV are picked up by Fc receptor-mediated endocytosis (King *et al.*, 2000; Syenina *et al.*, 2015).

IgE levels are considerably greater in people with a history of DENV infection and notably raised in those in the primary or secondary acute phase of dengue illness, compared to the baseline of people with previous dengue exposure (Miguez-Burbano *et al.*, 1999). The IgE response may be important for how severe DENV infection manifests. Elevated levels of histamine in the blood and urinary histamine release have been linked to the severity of dengue infection. This could imply the potential role of IgG-mediated mast cell degranulation in severe dengue (AbuBakar *et al.*, 1997). Together with the earlier findings of serum IgE, measuring total and DENV-specific IgE serum antibodies could be explored as a possible predictive predictor in the development of severe DENV complications. Furthermore, the presence and development of DENV-specific IgE serum antibodies in DENV infection suggest that IgE may have a pathogenetic role in the haemostatic abnormalities seen in dengue haemorrhagic fever and dengue shock syndrome (Koraka *et al.*, 2003).

In vivo study of DENV has been hampered due to the unavailability of a suitable animal model. DENV from human clinical isolates generally do not efficiently infect or replicate in mice, making it challenging to establish a mouse model. However, for the study of immunity and DENV, several modifications have been made such as DENV was administered to mice through the skin of their ears to start understanding the pathogenic function of MCs. The mice showed symptoms of capillary leakage and localised activation of MCs, which implies that mice can be used for certain types of research on DENV (St. John *et al.*, 2011). There are limitations to every animal model of DENV, but in this instance, it is crucial to underline that mouse MCs only have the activating FcγRIII (Syenina *et al.*, 2015). As mentioned earlier, dengue fever symptoms may also include DHF and DSS, both of which could involve increased vascular permeability, plasma leaking into tissues, and internal organ bleeding (Appanna *et al.*, 2012; Hasan *et al.*, 2016; Roy & Bhattacharjee, 2021). Although DENV has not been shown to infect MCs *in vivo*, several clinical studies suggest that MCs are involved in severe dengue illness (Brown *et al.*, 2011).

MC can exhibit diverse responses to the DENV, which may include a favourable reaction, aiding in virus inhibition and reducing its severity, or an unfavourable response, characterized by excessive or unregulated release of immune mediators that can initiate adverse reactions. MC responses in dengue seem to be selective, pointing to the potential involvement of MC in the initial chemokine-dependent host defences against viral infection (Marshall *et al.*, 2003). In terms of the pathophysiology of dengue, MC participation has not yet been studied. MCs have FcεR1 and a few other Fcγ receptors. They are therefore potential targets for a viral infection that is worsened by antibodies, as well as for the subsequent production of potent vasoactive cytokines. In addition, a study demonstrates that MCs can become infected with the DENV, particularly in cases when pre-existing antibodies from an earlier infection are present (King *et al.*, 2000). The graphical abstract of the manuscript is presented in Figure 2.
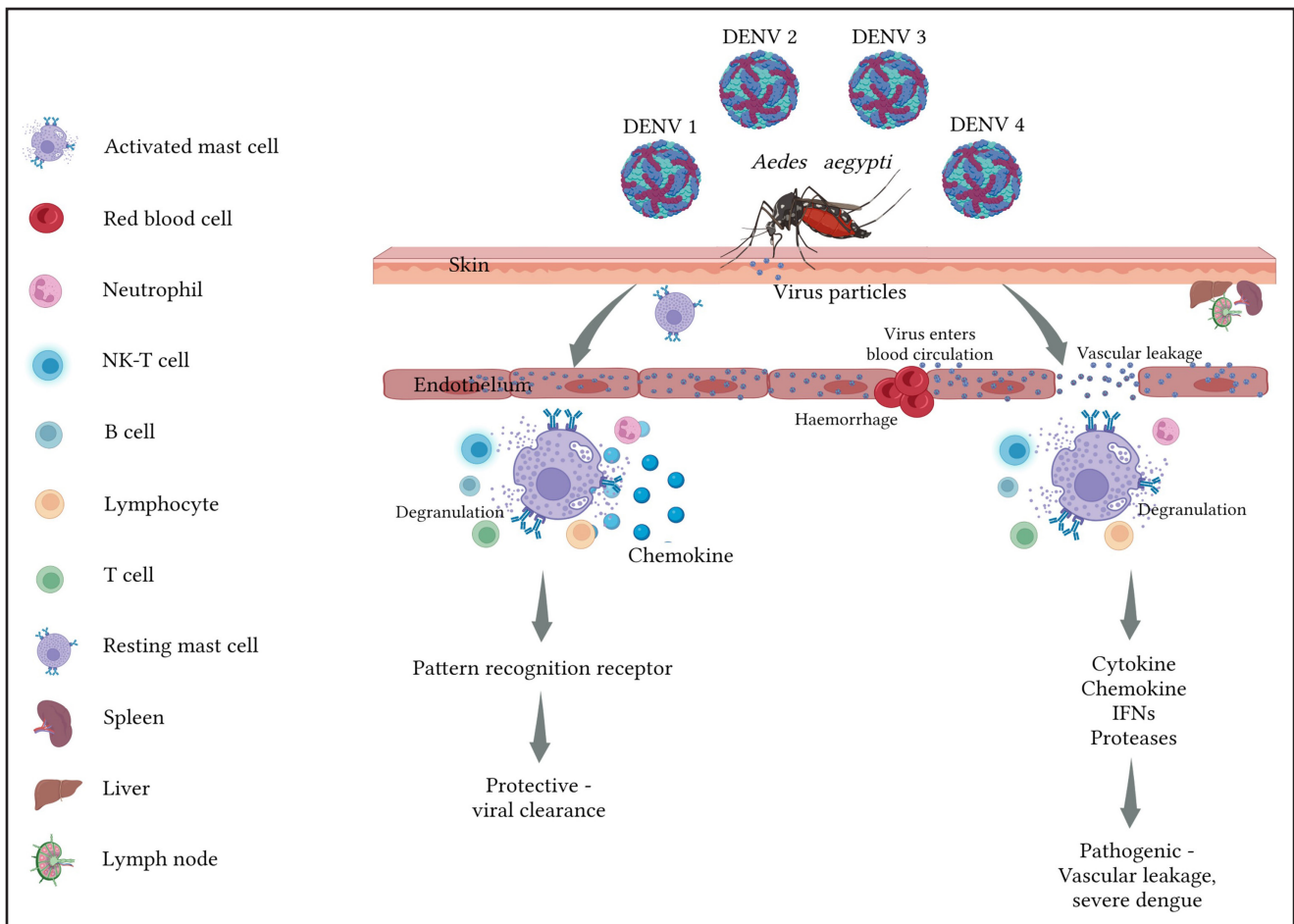

Figure 2. Graphical abstract. Figure created using BioRender.

CONCLUSION

Dengue remains a major health concern as currently there are no effective treatments and widely acceptable effective vaccines. Understanding the mechanisms of how dengue infection could present as asymptomatic or mild febrile illness and how it could become severe, could lead to more effective measures to treat dengue. The potential role of IgE responses in the prevention or increasing the severity of dengue is highlighted in this review. From the review, it is indicated that IgE plays crucial roles in protective immunity and immunopathology of dengue. Nonetheless, much more research is needed to delineate the contribution of IgE and MC activation in the pathogenesis and protection against dengue.

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