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Review

Influence of chemokines on the endothelial permeability and cellular transmigration during dengue

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ABSTRACT

During a pathogenic infection, an inflammatory process is triggered in which several inflammatory mediators, such as cytokines, chemokines, growth factors, complement system components, nitric oxide, and others induce integrity alteration on the endothelial barrier. Chemokines are responsible for regulating leukocyte trafficking under homeostatic conditions as well as activating immune system cells under inflammatory conditions. They are crucial molecules in the early stages of infection, leading to the recruitment of immune cells, namely neutrophils, monocytes, natural killer (NK) cells, natural killer T cells (NKT), dendritic cells (DC), T lymphocytes and all cells expressing chemokine receptors for inflammatory sites. Other functions, such as collagen production, tissue repair, a proliferation of hematopoietic precursors and angiogenesis, are also performed by these molecules. Chemokines, amongst inflammatory mediators, play a key role in dengue immunopathogenesis. Dengue fever is a disease caused by the dengue virus (DENV). It is characterized by a broad spectrum of clinical manifestations ranging from asymptomatic cases to mild and severe symptomatic ones. As for the latter, the appearance of hemorrhagic manifestations and changes in vascular permeability may lead the patient to develop cavitary effusions, organ involvement, and even death. As chemokines exert an influence on various homeostatic and inflammatory processes, acting vigorously on vascular endothelial activation and cell migration, the main purpose of this chapter is to discuss the influence of chemokines on the alteration of endothelial permeability and migration of T lymphocytes in DENV infection.

1. Immunopathogenesis of dengue: a brief review

1.1. Dengue virus

Dengue is considered a serious public health issue, stading within the 17 most neglected tropical diseases [1,2]. There is a hyper-endemicity of multiple dengue virus serotypes in many countries and the alarming impact both on human health and on global and national economies [3]. The World Health Organization (WHO) estimated a total of 390 million dengue infections per year, in which 96 million manifests clinically [4], with a 3.9 billion people prevalence, in 128 countries, at risk of infection [5]. According to the 2016 Global Burden of Disease Study, there was a significant increase in mortality from dengue between 2006 and 2016; from 20,800 deaths in 2006 to 37,800 deaths in 2016, whereas age-standardized rates increased from 0.3 deaths per 100,000 in 2006 to 0.5 deaths per 100,000 in 2016 [6]. Dengue epidemics have been expanding from tropical to subtropical regions in recent decades, partly fueled by urbanization and travel [7–9]. Dengue is now endemic in regions of Africa, the Americas, Eastern Mediterranean, Southeastern Asia and the Western Pacific. The Americas, Southeastern Asia and Western Pacific are the most seriously affected [3].

Dengue is a vector-borne viral acute infection caused by the dengue virus (DENV). The virus belongs to the *Flaviviridae* family which comprises a wide diversity of arboviruses of great impact for the world health, such as Yellow Fever virus (YF), Saint Louis Encephalitis virus (SLEV), West Nile virus (WNV) and the Zika virus (ZIKV) [10,11]. Since the isolation of the first DENV serotype in 1943, four antigenically distinct serotypes (DENV-1–DENV-4) are known with approximately 67–75% structural homology between them [12,13]. It is widely accepted that an infection by any serotype offers immunity to disease due to that same serotype, but only short-term heterologous immunity to other serotypes. In addition, a secondary infection is more likely to take place with more severe symptoms than the primary infection. Nevertheless, how exactly the previous infection history modulates the risk of subsequent infection outcome is not entirely clear, partly because of the

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difficulty in using the current methodology in retrospectively determining the entire individuals' infection history [14]. Differences between serotypes confer different genotypes. Five DENV-2 genotypes (Asian 1, Asian 2, Asian/American, American, Cosmopolitan and Wild) and four DENV-4 genotypes (I -III and Wild) are reported in the literature [15]. All serotypes are transmitted by female mosquitoes from genus Aedes, through their bite, in a human-mosquito-human cycle. DENVs are enveloped icosahedral viruses consisting of a single-strand, positive-sense RNA molecule of approximately 11 kb with a single open reading frame encoding a polyprotein that, when processed by viral proteases and cellular, gives rise to three structural proteins: capsid [C], Membrane [M] / transcribed in the form of its precursor [prM] and envelope [E] as well as seven primordial non-structural proteins for viral replication process: NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5. The infectious (mature) viral particle is approximately 50 nm long in diameter and contains the structural proteins C, M, E and the RNA genome [16].

1.2. Clinical manifestations of dengue

Dengue has a wide spectrum of clinical manifestations, often with unpredictable clinical outcome. Most patients have a mild, self-limited febrile condition. A small proportion progresses to the severe form of the disease, characterized by plasma extravasation and/or hemorrhage, which may evolve into shock [17]. There is no specific treatment for dengue and clinical management is aimed at symptom relief, fluid replacement and administration of analgesics following the recommendations of the WHO [3].

Until 1997, DENV infections were grouped into categories according to patients' clinical status: Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF). DHF was subdivided into four degrees of severity, with grades III and IV being defined as Dengue Shock Syndrome (DSS). With the spread of dengue in the world, it became evident that such classification was not applicable to all regions of the globe. In 2009, the study conducted by TDR/WHO (World Health Organization's Training and Research Program on Communicable Diseases) compared the clinical guidelines for the disease in different countries in order to evaluate variations of its classification in Latin America and Asia. The results suggested the need for new guidelines standardization. Thus, from 2009 the WHO adopted new classification criteria and divided the disease's clinical picture into dengue fever without (DF) or with signs of alarm (DFWS) and severe dengue fever [18]. A study by Barniol and colleagues in 2011 [19] compared the 1997 and 2009 classifications and came to the conclusion that the 1997 classification applicability was limited, since 13.7% of the evaluated cases did not fit into any of the DF, DHF and DSS frames, whilst in the current 2009 ranking, only 1.4% did not fit it.

Dengue symptoms begin abruptly, following three phases: acute, critical and recovery/convalescence. The acute phase lasts from 2 to7 days and is characterized by high viraemia, fever, and may present several symptoms, such as arthralgia, headache, retroorbital pain, diarrhea, facial erythema, myalgia, nauseas, and vomit. At this stage, the positive loop test is an important finding for the differential clinical diagnosis [20]. Other frequent laboratory findings are leukopenia and thrombocytopenia [21]. After the febrile period, most of the patients present clinical improvement, recovering in the defervescence phase. However, during the critical phase, a small portion of the patients may develop worsening of the clinical condition [18]. The critical phase occurs in the period near the recovery phase (24–48 h), where there may be an increase in plasma extravasation, resulting in metabolic acidosis, disseminated intravascular coagulation (DIC), hypovolemic shock (caused by loss of blood volume), organs' insufficiency and severe bleeding. They are manifestations accompanied by the marked increase in hematocrit leve as well as leucopenia and thrombocytopenia. In general, after this period the patient goes to a phase of rapid clinical improvement, defined as the convalescence phase. The recovery/convalescence phase is defined by the disappearance of clinical signs, restoration of normal platelet, leukocyte and hematocrit levels and gradual reabsorption of extravascular fluid. Notwithstanding, complications such as encephalopathy, bradycardia and, in rare cases, myocarditis and encephalitis may appear [22].

2. Immunological mechanisms enrolled in immunopathogenesis of dengue

Immunological clearance of DENV *in vivo* is coordinated by immune cells and immunological mechanisms. These include innate immune responses elicited by immune sentinels, including dendritic cells (DCs), Langerhans cells (LCs), macrophages and mast cells (MCs) directly infected with DENV at the mosquito bite site on the skin [23,24]. Moreover, the recruitment of cytotoxic cells subtypes, including natural killer (NK) cells and natural killer T (NKT) cells are involved in the production of type I and type II interferons, thus leading to direct killing of DENV-infected target cells [25–27]. Nevertheless, the induction of adaptive immunity, involving multiple antibodies' subclasses and various B and T cells subsets, may contribute to the resolution of primary infection, preventing symptomatic infection by homologous DENV strains during secondary infection [28]. We will briefly discuss how the adaptive immune response to DENV may contribute to the pathological responses.

Humans can acquire symptomatic DENV infection more than once in life, due to the circulation of four antigenically distinct serotypes, DENV1-DENV4. There is a consensus that antibodies (IgM and IgG) are likely to be critical effectors in viremia resolution and long-term immunity against DENV, a complex of four serotypes [29,30]. Immune memory responses are neutralizing and largely protective of same serotype viruses upon re-exposure. However, they are also cross-reactive against all 4 serotypes for only 2–3 months, after which the protection is specific to a given serotype [31]. When short-term cross-protection decreases, secondary DENV-infected patients showed an increased risk of severe disease [32], although this risk has not been observed universally [33]. The underlying mechanism for increased disease severity is explained by antibody-dependent enhancement (ADE).

First postulated by Hawkes in 1964 [34] and then by Halstead and colleagues [35,36], this model states that cross-reactive antibodies or sub-neutralizing concentrations of antibodies bind heterologous DENV to facilitate virus entry through FcγRII receptors expressed on target cells, such as monocytes and macrophages [36,37], as well as basophils and mast cells [38]. Mechanistically, ADE (Antibody-dependent enhancement) is a more efficient pathway for viral entry than cognate receptor-mediated endocytosis [39]. Moreover, virus-host interaction during ADE also enables the virus to evade host antiviral and immune responses which would otherwise limit infection [39,40]. Collectively, ADE thus results in a greater burden of infection that induces imbalanced pro-inflammatory and anti-inflammatory responses [41], which are thought to promote capillary endothelial pathology and vascular leakage [42]. This mechanism was also observed with anti-prM antibodies considered to be potent inducers of ADE. As mature viral particles do not express the prM protein, such particles are not neutralized by the specific prM antibodies. Partially mature viral particles are also generated and, by expressing the prM protein, they can be neutralized by specific prM antibodies [43]. In addition, antibodies against E proteins domains I and II and DENV NS1 protein are ADE inducers. Hence, preexisting IgG cannot exclusively predict the severity of the disease or more, the risk of ADE is not universal among all secondary DENV infections, but only in those who had baseline preinfection antibodies within a narrow range of titers [44,45]. Indeed, at the lower range of antibody concentrations, the DENV bound to the antibody will co-bind the more abundantly expressed activating Fc receptors, increasing viral entry into target cells [46]. Under other conditions, high concentrations of antibodies will form larger viral aggregates to co-bind the less abundant inhibitory Fcγ receptor, FcγRIIB

[47]. FcγRIIB signals inhibit phagocytosis, thus reducing viral entry into target cells [46]. Interestingly, Syenina et al. [48] showed that mast cells activation can be augmented by preexisting DENV-specific IgG that is dependent not on enhanced virus replication, but on FcγR-mediated augmented mast cells degranulation responses. Consequently, preexisting *in vivo* IgG during a natural infection IgG can enhance both mast cells degranulation and mast cells-dependent vascular leakage.

Several lines of evidence suggest that both CD4+ and CD8+ T cells are involved in resolving DENV infection. First, for specific serotypes, CD4+ and CD8+ T cell responses are observed in humans with primary DENV infection [49,50]. Secondly, DENV NS3-specific human CD4+ T cells proliferate, producing IFN-γ and lyse infected target cells [50,51]. Third, CD8+ T cells specific for NS1, NS3 and E can destroy infected target cells [25], suggesting that serotype-specific T cells are activated and functional in humans with primary DENV infection. Furthermore, higher frequencies of DENV-specific IFNγ-producing T cells are present in children who subsequently develop subclinical infection compared to those who develop symptomatic secondary DENV infection [52]. However, similarly to antibody responses, T cell responses may potentially exacerbate the immune pathology [53–55]. It has been proposed cross reactive T cells raised against the original infecting serotype dominate, during a secondary heterologous infection, a phenomenon that has been coined “original antigenic sin”. This term was first applied to the humoral response to influenza epidemics [56,57] and has also been observed in CD8+ T cell responses against lymphocytic choriomeningitis virus (LCMV) [58]. This hypothesis postulates that, during secondary infection expansion of pre-existing, lower avidity, cross-reactive memory T cells dominate the response over naive T cells that are of higher avidity for the new DENV serotype. It is further hypothesized that peptide variants derived from the secondary infection serotype can induce a response that is qualitatively different from the response induced by the original antigen, such as inducing a different pattern of lymphokine production [54,59]. Nonetheless, this hypothesis conflicts with the observation that heterologous T cell responses are not always needed to produce DHF in infants. Indeed, a study has shown a temporal mismatch between the CD8+ T cell response and commencement of capillary leakage, suggesting that CD8+ T cells are not responsible for early capillary leakage triggering in children with DHF [60]. Furthermore, studies have shown that different HLA alleles are associated with differential magnitude of anti-DENV responses as well as HLA alleles associated with increased risk of severe disease with DENV are associated with weaker CD8+ responses [61–64]. Thus, the absence of a multifunctional T cell response linked to individuals carrying non-protective HLA alleles, may be responsible for the immune pathogenesis linked in these individuals [65].

Finally, the Cytokine Storm described in 1993 by Ferrara et al. [66] associated a deregulated production of cytokines and chemokines such as IL-1β, IL-6, TNF and CXCL8/IL-8 to the development of graft-*versus*-host disease. Since then, the Cytokine Storm theory has been linked to a variety of infectious diseases (eg Cytomegalovirus, Epstein-Barr, Influenza, Smallpox, SARS) and non-infectious diseases (eg multiple sclerosis, pancreatitis, multiple dysfunction of organ, sepsis) [67].

3. Chemokines on alteration of vascular endothelium in dengue

3.1. Chemokines and their receptors: a brief review

Chemokines are low molecular weight proteins (7–12 kDa), constituting the largest family of cytokines. They are responsible for regulating of leukocyte traffic under homeostatic conditions as well as activating immune cells under inflammatory conditions, besides exerting several functionalities, such as collagen production, tissue repair, a proliferation of hematopoietic precursors and angiogenesis [68,69]. They are crucial molecules in early stage of infections and are generally produced after the onset of an infectious process in response to the activation of pattern recognition receptors (PRRs) by epithelial, stromal and immune cells. Chemokines lead to the recruitment of several immune cells, such as neutrophils, monocytes, natural killer (NK) cells, natural killer T cells (NKT), dendritic cells (DC) and all those which express chemokine receptors [70,71]. Currently, 50 distinct chemokine molecules are described and classified based on their structural organization in 4 subfamilies: C, CC, CXC and CX3C, according to cysteine residue positions (C) and the amino acid residues (X) present in its structure. According to their functionality, they can also be classified into 3 subfamilies: homeostatic, proinflammatory and mixed [71,72].

Proinflammatory chemokines (*e.g.* CCL2/MCP-1, CCL5/RANTES and CXCL8/IL-8) are produced by leukocytes and tissue cells in response to different stimuli, such as during pathogen-induced infectious processes, mechanical damage or released toxins by cellular components. Chemokines are chemoattractants of leukocytes to the inflamed region, contributing to the restoration of homeostasis [73]. However, homeostatic chemokines (*e.g.* CCL19/ELC, CCL21/SLC and CXCL13/MIP-3) are constitutively expressed by leukocytes and other cell types. They regulate cell the migration and their positioning. CCL19/ELC and CCL21/SLC chemokines, produced in lymph nodes, induce migration of immature dendritic cells expressing CCR7 from the dermis to regional lymph nodes [74]. Mixed chemokines (eg, CCL21/SLC, CCL27/CTACK and CXCL1/GRO-α) may assume homeostatic and proinflammatory functions, varying according to the tissue location in which it is secreted. For example, CCL27/CTAK is constitutively expressed in the skin and can also be induced during cutaneous inflammation, mediating T cell traffic [75].

Chemokine receptors belong to the ɣ-serpentine receptors subfamily, displaying 7 transmembrane domains coupled to a heterotrimer G protein. Twenty chemokine receptors are currently described. These receptors are present in all immune system cells as well as in other cell types, such as tumor ones [72]. Chemokine receptors can be grouped according to the presence or absence of an amino acid sequence: Aspartate-Arginine-Tyrosine-Leucine-Alanine-Isoleucine-Valine (DRYLAIV), positioned at the end of the transmembrane domain III of receptor, essential for the G protein coupling. This sequence is essential for the receptor signaling cascade initiation, thus activating several modified phospholipid enzymes, such as phosphatidyl inositol-3-kinase (PI3K), phospholipases A2 (PLA2) and D (PLD), tyrosine kinases (PTK) and proteins mitogen-activated kinases (MAPK). Binding-receptor interaction also leads to the activation of some low molecular weight molecules, such as Rac, Rho and cdc42, involved in cell migrating process. Interestingly, chemokines’ and their receptors’ interaction are quite "promiscuous," with a linker having the ability to bind to different chemokine receptors [76].

There is a second group of chemokine receptors lacking the DRYLAIV motif. Therefore, they do not signal through G proteins, thus not not inducing cell migration. The main functionality of these receptors is binding many chemokines with high affinity and, *via* β-arrestin signaling, mediate internalization of receptor-bound ligands and the degradation of chemokines [77]. Such receptors comprise chemokine receptors which have been described as scavengers, decoys, or chemokine-binding proteins. After a recent update of the chemokine receptor nomenclature, this subclass is now designated the atypical chemokine receptors (ACKRs) [71,76].

3.2. Participation of chemokines on cell migration

During the inflammatory process, neutrophils, monocytes, macrophages, immature dendritic cells and NK cells can be found at the initial site of inflammation. Expression of chemokine receptors and adhesion molecules on the immune cells provide these populations’ recruitment to target regions during the inflammatory process [70,73]. The initial stage of cell migration occurs through the interaction of leukocytes with activated endothelial cells of the venules near the inflamed region. The endothelium is then activated *via* pro-inflammatory mediators such as TNF-α and IL-1β produced by resident antigen presenting cells, infected

cells and / or neighboring cells. Thus, the endothelium increases adhesion expression molecules such as E-selectin (CD62E) and leukocytes increase P-selectin expression (CD62P), inducing cell adhesion to the endothelium. However, this adhesion is not strong enough to contain blood flow and it is constantly broken, leading to the rolling of these cells on the endothelium. In this step, in addition to chemotaxis induction, chemokines promote increased affinity of integrins, such as VLA-4 (very late antigen 4), present on the leukocyte surface and adhesion molecules present in the endothelium [78,79]. Among the chemokines, CX3CL1/Fraktalkine produced by activated endothelial cells, induce proteoglycans adhesion on endothelial surface cells and increase the affinity of these integrins. This leads to the promotion of firm adhesion of leukocytes to the endothelium [80]. Such interaction promotes a cellular cytoskeleton rearrangement, leading to the diapedesis of these leukocytes both through the transcellular and paracellular pathways [79]. The continuous migration of immune cells between lymphoid and non-lymphoid organs is an important immune system feature, as it ensures these components distribution to virtually all compartments of the body and chemokines plays a key role in this process [71].

The ability to differentiate naive T lymphocytes to effectors and memory is one of the cellular immune response essential points. These T lymphocyte subpopulations are distinguished according to a receptor expression phenotype which will influence the migration and functionality of such cells [81]. We can mention naive T cells, whose CCR7 and CD62L expression keeps it re-circulating between blood and secondary lymphoid organs. Central memory T cells, on the other hand, also express CCR7, present a similar pattern to naive T cell traffic. CCR7 expression allows the entry of these two T cell populations into the peripheral node of the high endothelial venules by chemotaxis through the chemokines CCL19/ELC, CCL21/SLC and adressins. Resident memory T cells, regulatory T cells (Tregs) and effector T cells are also dependent on CCR7 to return to the secondary lymphoid organs. Thus, effector T cells differentiate by alternating the expression of chemokine receptors and thereby allowing recruitment to specific inflamed tissues [75].

Chemokine receptors are important pieces for the characterization and understanding of these T lymphocytes subpopulations [81,82]. As an example, the CCR5 and CXCR3 expression differentiates CD4 Th1 cells (IFN-γ and IL-2 producers), while CCR3 and CCR4 are expressed in Th2 cells subpopulations (producing IL-4, IL-5, IL-6, IL-10 and IL-13) [82–84]. Likewise, CXCR3 and CCR4 are expressed in CCR7+ central memory CD4 T cells subpopulations and characterize the pre-Th1 and pre-Th2 profiles [85].

Deregulated and compartmentalized chemokines' production can lead to excessive leukocyte migrating populations, increasing the local inflammatory process. T cells obtained from patients with multiple sclerosis, for example, have a higher migration capacity when stimulated with CCL5/RANTES and CCL3/MIP-1α. It suggests that the increase in T lymphocytes in the central nervous system is related to a higher chemokines' expression in these T cell populations [86].

Some chemokines, such as CXCL8/IL-8, CXCL10/IP-10, CCL2/MCP-1, CCL3/MIP-1α and CX3CL1/Fraktalkine are also produced in the central nervous system and have been described as increasing the invasive process of HIV-1 virus through the chemoattraction of infected leukocytes, allowing the virus to spread to other cells in the central nervous system [87–89].

3.3. Vascular endothelium: a brief review

The vascular system is vitally important in various activities of the organism, such as nutrient supply, elimination of metabolic residues, thermoregulation, oxygen and carbon dioxide transportation as well as in assisting the transport of antigens and traffic of immune system cells from peripheral tissues to secondary lymphoid organs and circulation to tissues. This vascular system is coated inside by endothelial cell monolayers which act as a semipermeable barrier regulating the molecule and fluids exchange between the circulation and body tissue compartments [90]. Such regulation occurs *via* paracellular transport (between cells through inter-endothelial junctions) or transcellular transport (through the endothelial cell), through interaction with receptors on endothelial cells, adhesion molecules and tight junctions [91].

In the transcellular route, albumin and other macromolecules are transported through the endothelial cell mostly by vesicles called caveolins. The caveolins vesicles, formed during transcellular transport, can reach up to 15% of the total endothelial cell volume, being formed *via* interaction between macromolecules and existing receptors on the endothelial surface. For instance, the gp60 receptor [90,91]. Regarding the paracellular transport, the interendothelial junctions are crucial in this process, also contributing to the maintenance of endothelial integrity and cell-cell communication. Interendothelial junctions contain complex junctional structures, namely adherens junctions (AJ), tight junctions (TJ) and gap junctions (GJ). They play pivotal roles in tissue integrity, barrier function and cell–cell communication, respectively. Claudin family members and occludin are the major TJ transmembrane constituents [92,93]. Gap junctions comprise connexins 21, 37, 40 and 43 [94]. VE-cadherin is a component of endothelial cell-to-cell adherent junctions [95]. These interendothelial junctions work together to aid the paracellular ions' and solutes' passage. In addition, tight junctions also act as linkers for these junctions to the adhesion molecules and to the actin cytoskeleton [96]. Adhesion molecules such as ICAM-1 (intercellular adhesion molecule 1) and VCAM-1 (vascular adhesion molecule 1) act in the interaction of endothelial cells and leukocytes, helping the migration process of these leukocytes to inflammatory sites [97]. Finally, other proteins and signaling pathways are also involved in keeping the endothelial barrier function, one of which involves the activity of the CD73 protein, an ectonucleotidase anchored to glycophosphatidyl inositol expressed in endothelial cells. It works increasing cyclic AMP intracellular levels and increasing expression of adhesion molecules and tight junctions [98–100].

The vascular endothelium presents different characteristics and diversity, and it can be divided into macrovasculature (arteries and veins) and microvasculature (arterioles, capillaries and venules). The macrovascular endothelium exhibits a lower porosity; it presents, in addition to the endothelial layer, a medium tunica layer consisting of smooth muscle cells and an adventitial tunica layer composed of connective tissue, which hinders and limits the vascular permeability process. While the microvascular endothelium can be either continuous or discontinuous, it consists only of an endothelial-cells monolayer adhered to an extracellular matrix [101,102]. These distinct characteristics between the types of endothelium influence molecular transport between the various compartments of the human body [102].

Endothelial cells are one of the major cells involved in the immune response and in different stages of the inflammatory process, such as regulation of leukocyte extravasation, angiogenesis, cytokine production, chemokines and proteases, extracellular matrix synthesis, vascular permeability and antigen presentation [103]. In addition to that, endothelial cells represent an important replicative niche for various viruses, bacteria and other parasitic organisms present in blood and/or lymph. For many pathogens, after initial invasion, the ability to access the vascular compartment is an essential step for its dissemination and perpetuation [101]. The inflammatory process begins when several inflammatory mediators, such as cytokines, chemokines, growth factors, complement system components and nitric oxide induce a dysfunction on the endothelial barrier [104–107]. This dysfunction can lead to plasma and hemorrhagic extravasation, as observed in several infectious processes caused by hantaviruses, arenaviruses and DENV [104].

4. Influence of chemokines on plasma leakage and cellular migration in the dengue

As previously described, dengue has a marked characteristic which is the increase in vascular permeability, more frequently observed in severe cases. This increase in permeability leads to plasma extravasation in vascular microvasculature target areas, such as the pericardial, pleural and abdominal cavity, mostly observed during the defervescence period [18,90]. There is consensus in the literature that the involvement of cytokines, chemokines and others inflammatory mediators excessively secreted by immune and non-immune cells can contribute to vascular leakage and endothelial permeability. That may lead to severe forms of dengue disease [108–110]. Notwithstanding, studies failed in showing DENV-infected ECs and have not demonstrated major morphological damage to the capillary endothelium [111,112]. Consequently, some *in vivo* evidences suggest ECs are poorly infected by DENV and are not important targets for DENV replication [113–115]. To evaluate the ability to induce transendothelial leakage and infectivity, a recent study tested *in vitro* two closely related DENV serotype-2 strains of the Cosmopolitan genotype. Remarkably, the less infective strain induced the more transendothelial cell leakage in ECs monolayer upon infection and secreted more non-structural protein (sNS1) from DENV into the culture supernatant. Two mutations within the NS1 protein coding region, F103S and T146I, that significantly changed amino acid properties, were found in the strain which secreted lower NS1 levels and caused less leakage [116]. Thus, some mechanisms have been described to report how secreted sNS1 triggers human ECs hyperpermeability *in vitro* as well as systemic vascular leakage *in vivo*. In primary human myeloid cells, NS1 was shown to activate toll-like receptor 4 signaling, thus leading to pro-inflammatory cytokines secretion and vascular leakage [117]. Furthermore, NS1 induces sialic acid degradation and heparan sulfate proteoglycans shedding disrupting the endothelial glycocalyx layer on human pulmonary microvascular ECs [118]. Recently, the macrophage migration inhibitory factor (MIF) directly participates in NS1-induced glycocalyx degradation and hyperpermeability *via* heparanase 1 and metalloproteinase 9 activation [119].

One of the interesting cells to actively take part in endothelial cell activation is mast cells. The authors showed an increase in VEGF plasma levels, tryptase proteases and chymase secreted by mast cells in patients with severe dengue [120]. In addition, DENV within mast cell granules results in increased production of VEGF-A and neuropilin, a co-receptor for VEGF [121]. VEGF and neuropilin participate in the activation and proliferation signaling of neighboring endothelial cells, in addition to facilitating viral transmission. It provides a lymphatic pathway by which DENV in extracellular granules can travel to the drainage of lymph nodes for systemic propagation [122].

On the other hand, *in vitro* studies have proposed that DENV infects human umbilical ECs through heparan sulfate-containing cell surface receptors. Consequently, several soluble mediators, including IL-6, IL-8, CXCL9, CXCL10 and CXCL11 involved in immune responses enhancement and capillary permeability, are released from DENV-infected ECs [123]. factor-α (TNF) tumor necrosis has been strongly associated with vascular infiltration [124,125]. TNF induces changes in adherent junctions and human DENV-infected ECs tight junctions, thus suggesting a synergistic role of TNF in relation to increased endothelial permeability in dengue [126].

Chemokines are important mediators present in DENV infection, influencing even the clinical patients' outcome. We report below a series of studies relating the participation of chemokines and their receptors in dengue. We highlight the chemokines CXCL8/IL-8 and CCL2/MCP-1, present at high levels in patients with DHF/DSS. Both influence on the transendothelial permeability of HMEC-1 (human mammary epithelial cells) and HUVEC (human umbilical vein endothelial cells) endothelial cell lines, demonstrated by regulating the tight junctions and cytoskeleton of these cells in *in vitro* assays. Pretreatment of DENV-infected monocyte supernatants with CXCL8/IL-8 and CCL2/MCP-1 blocking antibody resulted in partial reversal of permeability change in endothelial cell cultures with these monocytes supernatant. It indicates the role of such monocyte's chemokines in the process [127–129]. Recombinant chemokines CXCL8/IL-8, CXCL10/IP-10 and CCL5/RANTES induce filopodia protrusions formation in HBMEC (human brain microvascular endothelial cells), HMVEC (endothelial cells) and HUVEC endothelial cells, which, according to the authors, would contribute to leukocyte extravasation [103]. Moreover, TNF and CXCL8/IL-8 have already been found in supernatants DENV-infection THP-1 cells (monocytic cell line of acute leukemia cells). These supernatants were able to induce alteration of the permeability of HMVEC cells, demonstrated by the reduction of transendothelial electrical resistance (TEER) and increased expression of surface molecules, such as VCAM-1 and E-selectin [130].

Different molecules have been used as circulating vascular infiltration biomarkers. Increased levels of IL-12p70, TNF, IL-6, IL-1β, CXCL8/IL-8, CXCL10/IP-10, CCL2/MCP-1 and CXCL9/MIG were found in DSS patients when compared to DHF patients and patients with other febrile diseases. Only CCL5/RANTES chemokine was detected at decreased circulating levels in DSS patients compared to other patients, which led to an association between low levels of CCL5/RANTES with poor clinical prognosis in dengue [131]. Associations with the CCCCA haplotypes of the CXCL10/IP-10 gene and AGTTTAC of the CXCL11/I-TAC gene in DENV-infected patients from Malaysia were demonstrated in cases of severe dengue hospitalized patients that presented some type of vascular leakage during the epidemic [132]. Recently, the previous study conducted a meta-analysis covering 56 studies which analyzed different soluble mediators in DENV infected patients. This study compared levels of pro-inflammatory mediators between patients with DF and severe dengue patients, seeking to identify severity biomarkers. According to the authors' data, severe patients have elevated levels of CXCL8/IL-8, IL-10 and IL-18. On the other hand, CCL5/RANTES, IL-7, TGF-β and VEGFR2 were reduced in this same group. Thus, the authors concluded the influence of such mediators on dengue immunopathogenesis and suggested these mediators as biomarkers for severe dengue [133].

Altogether, proinflammatory mediators appear to influence vascular endothelium, promoting activation and deregulation of intercellular junctions (PECAM-1/CD31, ICAM-1/CD54 and VCAM-1/CD106). Elevated levels of ICAM-1/CD54 and VCAM-1/CD106 are present in severe patients and have already been associated with vascular damage. Endothelial permeability deregulation makes the vascular monolayer susceptible to leukocyte adhesion (increasing the cell migration process), exchange of macromolecules (such as albumin) and vascular lumen water for other tissues [134]. High albumin serum levels [135,136], hyaluronic acid, urinary heparan sulfate [135,137,138], syndecan-1 and chondroitin sulfate claudin-5 were associated with dengue shock syndrome (DSS) and plasma leakage cases. Thus, these molecules have been used as circulating vascular infiltration biomarkers [135]. Moreover, angiopoietin 1 and 2 (ang-1 and ang-2), VEGF, sVEGRF2 baseline levels are also found in the blood. Increased ICAM expression and VCAM is seen on the surface of endothelial cells [139].

Assessments in experimentally DENV-infected animal tissues and human fatal cases by natural dengue infection are extremely important to understand the leading mechanisms to vascular damage and its consequence. In 1972, authors have demonstrated the spread of dengue viruses in several tissues of experimentally infected rhesus monkeys [140] and in 1982 in infected mice tissues [141]. Similar approaches have been performed in human fatal cases which have developed severe dengue forms. In this context, Miagostovich et al. studied 5 fatal cases of dengue infection associated with encephalopathy. They showed DENV antigen in the cytoplasm of phagocytic mononuclear cells from liver, spleen, lung, and central nervous system (CNS). Furthermore, CD68+ macrophages and dengue antigen-positive cells share similar

morphology and localization. It suggests a unique identity of these cells and the infiltration of virus-infected macrophages could be one of the pathways by which viruses might enter the brain in dengue encephalitis [142]. Several works have discussed such topic, as Póvoa et al. observed hemorrhage, edema and other injuries in several tissues from dengue fatal cases. The authors detected DENV NS3 antigens and virus RNA negative strand in hepatocytes, type II pneumocytes and cardiac fibers, as well as in resident and circulating monocytes/macrophages and endothelial cells [143]. Afterwards, Póvoa et al. demonstrated an increased frequency of IFN-ɣ, TNF and CCL5 / RANTES expressing cells in association with increased cell infiltration and presence of viral antigens in liver, lung and kidney tissue samples from these same patients. It indicates the presence of inflammatory mediators in this tissue would be strongly related to severe cases [144]. Our group was able to present an increase in CCL5/RANTES+ cells frequency in liver tissue in fatal cases, as opposed to low circulating levels of CCL5/RANTES found in patients who developed mild forms of the disease. It might suggest the involvement of these inflammatory mediators in the migration of immune cells subpopulations from the blood to the tissues [145].

As far as immune cells migration from the blood to the tissues is concerned, we highlight the effector profile associated with increased chemokine receptors' expression of these blood immune cells in dengue. Our group portrayed a high frequency of CCR5-expressing CD4 and CD8 T cells, CXCR3-expressing CD4 T cells, and CCR4-expressing CD8 T cells in acute dengue patients. All these lymphocytes coexpressed activation/migration and cytotoxicity markers (CD44, CD29, CD127low e CD107a). Thus, it has been suggested T lymphocytes are activated and acquire migrating capacity since they increase the expression of chemokine receptors. Therefore, they would be able to control tissue viral infection to which they migrated [145]. Afterwards, Weiskopf et al. demonstrated that donors exposed to DENV showed high polarized DENV-specific CD4+ T cells, with a strong bias towards a CX3CR1+ cytotoxic T lymphocyte phenotype. Importantly, these cells were related to a protective HLA DR allele, having direct *ex vivo* DENV-specific cytolytic activity. The authors speculated cytotoxic dengue specific CD4+ T cells may play a role in the control of dengue infection *in vivo* [146].

Finally, in murine models, authors used CCR1, CCR2, CCR4 or CXCR3 and CXCL10 genetically deficient ($^{-/-}$) mice chemokine. CCR1$^{-/-}$ mice presented similar infection characteristics to WT (wild) mice, while CCR2$^{-/-}$ and CCR4$^{-/-}$ mice presented more attenuated clinical manifestations compared to WT mice [147]. CXCL10$^{-/-}$ mice were more susceptible to DENV infection with presence of CXCR3+ T lymphocyte infiltrates in the brain, like the group of infected WT mice, but with a high viral load in the brain region. This result demonstrates increased susceptibility of DENV-infected CXCL10$^{-/-}$ mice may be related to the antiviral capacity of the chemokine and not to increased recruitment of lymphocytes to the region [148]. In addition, CXCR3$^{-/-}$ mice are more susceptible to DENV infection, presenting higher mortality and high viral load compared to WT mice, indicating a protective effect of the CXCR3 receptor on DENV infection [149].

5. Conclusion

A small proportion of dengue patients develop poor clinical outcome characterized by severe bleeding and/or vascular effusions. Under homeostatic conditions, the vascular endothelium acts as a semi-permeable membrane, regulating molecules' exchange, fluids and cell migration. On the other hand, endothelial cells are involved in the immune response and in different stages of inflammatory process. Moreover, vascular endothelium may also represent an important replicative niche of pathogens, such as viruses. It plays a key role in spreading and perpetuating pathogens. Studies have divergent views on DENV ability to directly infect endothelial cells yet most of them agree that DENV stimulates cytokines and chemokines production by endothelial cells. In infectious and in inflammatory conditions, cytokines,

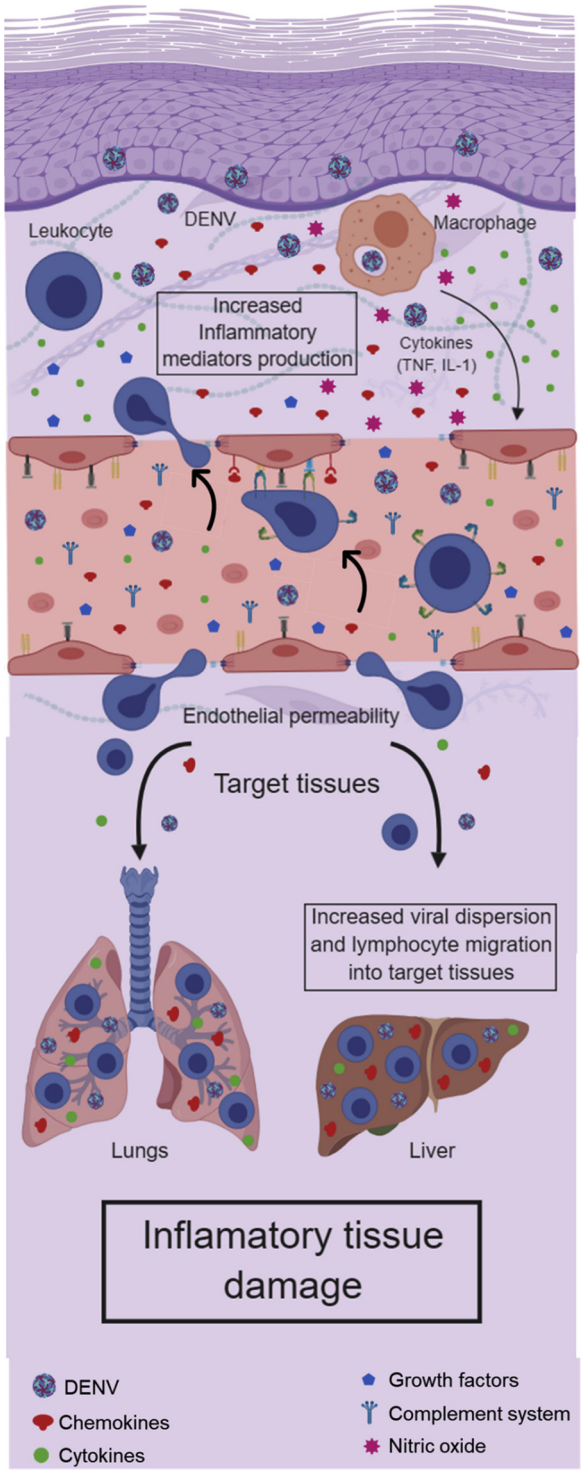

Fig. 1. Under infectious and in inflammatory conditions, cytokines, chemokines, growth factors, components of the complement system, nitric oxide, among others, induce an endothelial barrier dysfunction and may lead to plasma extravasation as observed in severe cases of dengue. Vascular endothelium represents an important replicative niche of viruses, playing a key role in their spread and perpetuation. Nevertheless, studies disagree on DENV ability to directly infect endothelial cells yet most of them agree DENV stimulates the cytokines' and chemokines' production by endothelial cells. Furthermore, an increase in endothelial permeability favors viral dispersion and migration of immune cells to target tissues. Under intense and persistent inflammatory conditions, chemokines have an important role in activating and migrating immune cells to different target tissues, which can lead to tissue damage in the dengue patient.

chemokines, growth factors, components of the complement system, nitric oxide, among others, induce an endothelial barrier dysfunction and may lead to plasma extravasation, as observed in dengue severe cases. Furthermore, an increase in endothelial permeability favors viral dispersion and migration of immune cells to target tissues. Under intense and persistent inflammatory conditions, chemokines participate in immune cells' activation and migration to different target tissues, which can lead to tissue damage in the patient. This conclusion is described in Fig. 1.

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References

[1] WHO/TDR, Technical Handbook for Dengue Surveillance, Dengue Outbrake Prediction/Detection and Outbrake Responses ("Model Contingency Plan"), World Health Organization, 2016, https://www.who.int/tdr/publications/year/2016/tech_handbook_dengue/en/.

[2] M.G. Guzman, E. Harris, Dengue, Lancet 385 (2015) 453–465, https://doi.org/10.1016/S0140-6736(14)60572-9.

[3] WHO, Dengue and Severe Dengue, World Health Organization, 2019, https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue.

[4] S. Bhatt, P.W. Gething, O.J. Brady, J.P. Messina, A.W. Farlow, C.L. Moyes, J.M. Drake, J.S. Brownstein, A.G. Hoen, O. Sankoh, M.F. Myers, D.B. George, T. Jaenisch, G.R. Wint, C.P. Simmons, T.W. Scott, J.J. Farrar, S.I. Hay, The global distribution and burden of dengue, Nature 496 (2013) 504–507, https://doi.org/10.1038/nature12060.

[5] O.J. Brady, P.W. Gething, S. Bhatt, J.P. Messina, J.S. Brownstein, A.G. Hoen, C.L. Moyes, A.W. Farlow, T.W. Scott, S.I. Hay, Refining the global spatial limits of dengue virus transmission by evidence-based consensus, PLoS Negl. Trop. Dis. 6 (2012) e1760, https://doi.org/10.1371/journal.pntd.0001760.

[6] GBD 2016 Causes of Death Collaborators, Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet 390 (2017) 1151–1210, https://doi.org/10.1016/S0140-6736(17)32152-9.

[7] T.P. Endy, K.B. Anderson, A. Nisalak, I.K. Yoon, S. Green, A.L. Rothman, S.J. Thomas, R.G. Jarman, D.H. Libraty, R.V. Gibbons, Determinants of inapparent and symptomatic dengue infection in a prospective study of primary school children in Kamphaeng Phet, Thailand, PLoS Negl. Trop. Dis. 5 (2011) e975, https://doi.org/10.1371/journal.pntd.0000975.

[8] N.M. Ferguson, D.A. Cummings, How season and serotype determine dengue transmissibility, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 9370–9371, https://doi.org/10.1073/pnas.1407648111.

[9] J.P. Messina, O.J. Brady, T.W. Scott, C. Zou, D.M. Pigott, K.A. Duda, S. Bhatt, L. Katzelnick, R.E. Howes, K.E. Battle, C.P. Simmons, S.I. Hay, Global spread of dengue virus types: mapping the 70-year history, Trends Microbiol. 22 (2014) 138–146, https://doi.org/10.1016/j.tim.2013.12.011.

[10] J.S. Mackenzie, D.J. Gubler, L.R. Petersen, Emerging flaviviruses: the spread and resurgence of Japanese encephalitis, West Nile and dengue viruses, Nat. Med. 10 (2004) S98–S109, https://doi.org/10.1038/nm1144.

[11] M.R. Holbrook, Historical perspectives on flavivirus research, Viruses 9 (2017), https://doi.org/10.3390/v9050097 pii: E97.

[12] M.G. Guzman, D.J. Gubler, A. Izquierdo, E. Martinez, S.B. Halstead, Dengue infection, Nat. Rev. Dis. Primers 2 (2016) 16055, https://doi.org/10.1038/nrdp.2016.55.

[13] S. Hotta, Experimental studies on dengue. II. A skin reaction observed during the epidemic of Osaka, Japan, in 1944, J. Infect. Dis. 90 (1952) 10–12, https://doi.org/10.1093/infdis/90.1.10.

[14] T.K. Tsang, S.L. Ghebremariam, L. Gresh, A. Gordon, M.E. Halloran, L.C. Katzelnick, D.P. Rojas, G. Kuan, A. Balmaseda, J. Sugimoto, E. Harris, I.M. Longini Jr., Y. Yang, Effects of infection history on dengue virus infection and pathogenicity, Nat. Commun. 10 (2019) 1246, https://doi.org/10.1038/s41467-019-09193-y.

[15] S.C. Weaver, N. Vasilakis, Molecular evolution of dengue viruses: contributions of phylogenetics to understanding the history and epidemiology of the preeminent arboviral disease, Infect. Genet. Evol. 9 (2009) 523–540, https://doi.org/10.1016/j.meegid.2009.02.003.

[16] B.R. Murphy, S.S. Whitehead, Immune response to dengue virus and prospects for a vaccine, Annu. Rev. Immunol. 29 (2011) 587–619, https://doi.org/10.1146/annurev-immunol-031210-101315.

[17] A. Srikiatkhachorn, A.L. Rothman, R.V. Gibbons, N. Sittisombut, P. Malasit, F.A. Ennis, S. Nimmannitya, S. Kalayanarooj, Dengue—how best to classify it, Clin. Infect. Dis. 53 (2011) 563–567, https://doi.org/10.1093/cid/cir451.

[18] WHO Library Cataloguing-in-Publication Data, Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control – New Edition. ISBN 978 92 4 154787 1.

[19] J. Barniol, R. Gaczkowski, E.V. Barbato, R.V. da Cunha, D. Salgado, E. Martínez, C.S. Segarra, E.B. Pleites Sandoval, A. Mishra, I.S. Laksono, L.C. Lum, J.G. Martínez, A. Núnez, A. Balsameda, I. Allende, G. Ramírez, E. Dimaano, K. Thomacheck, N.A. Akbar, E.E. Ooi, E. Villegas, T.T. Hien, J. Farrar, O. Horstick, A. Kroeger, T. Jaenisch, Usefulness and applicability of the revised dengue case classification by disease: multi-centre study in 18 countries, BMC Infect. Dis. 11 (2011) 106, https://doi.org/10.1186/1471-2334-11-106.

[20] M. Mayxay, R. Phetsouvanh, C.E. Moore, V. Chansamouth, M. Vongsouvath, S. Sisouphone, P. Vongphachanh, T. Thaojaikong, S. Thongpaseuth, S. Phongmany, V. Keolouangkhot, M. Strobel, P.N. Newton, Predictive diagnostic value of the tourniquet test for the diagnosis of dengue infection in adults, Trop. Med. Int. Health 16 (2011) 127–133, https://doi.org/10.1111/j.1365-3156.2010.02641.x.

[21] C.L. De Oliveira, E.R.J.C. Pontes, R.V. Da Cunha, B. Fróes, D. Do Nascimento, Alterações hematológicas em pacientes com dengue, Rev. Soc. Bras. Med. Trop. 42 (2009) 682–685, https://doi.org/10.1590/S0037-86822009000600014.

[22] D.A. Muller, A.C. Depelsenaire, P.R. Young, Clinical and laboratory diagnosis of dengue virus infection, J. Infect. Dis. 215 (2017) S89–S95, https://doi.org/10.1093/infdis/jiw649.

[23] A.S. Janssens, R. Heide, J.C. den Hollander, P.G. Mulder, B. Tank, A.P. Oranje, Mast cell distribution in normal adult skin, J. Clin. Pathol. 58 (2005) 285–289, https://doi.org/10.1136/jcp.2004.017210.

[24] L.C. Zaba, J. Fuentes-Duculan, R.M. Steinman, J.G. Krueger, M.A. Lowes, Normal human dermis contains distinct populations of CD11c+BDCA-1+ dendritic cells and CD163+FXIIIA+ macrophages, J. Clin. Invest. 117 (2007) 2517–2525, https://doi.org/10.1172/JCI32282.

[25] A. Mathew, I. Kurane, A.L. Rothman, L.L. Zeng, M.A. Brinton, F.A. Ennis, Dominant recognition by human CD8+ cytotoxic T lymphocytes of dengue virus nonstructural proteins NS3 and NS1.2A, J. Clin. Invest. 98 (1996) 1684–1691, https://doi.org/10.1172/JCI118964.

[26] V.V. Costa, W. Ye, Q. Chen, M.M. Teixeira, P. Preiser, E.E. Ooi, J. Chen, Dengue virus-infected dendritic cells, but not monocytes, activate natural killer cells through a contact-dependent mechanism involving adhesion molecules, MBio 8 (2017), https://doi.org/10.1128/mBio.00741-17.DOI: 10.1128/mBio.00741-17 pii: e00741-17.

[27] S.J. Gagnon, F.A. Ennis, A.L. Rothman, Bystander target cell lysis and cytokine production by dengue virus-specific human CD4(+) cytotoxic T-lymphocyte clones, J. Virol. 73 (1999) 3623–3629 PMID: 10196254.

[28] A.L. St John, A.P.S. Rathore, Adaptive immune responses to primary and secondary dengue virus infections, Nat. Rev. Immunol. 19 (2019) 218–230, https://doi.org/10.1038/s41577-019-0123-x.

[29] G. Screaton, J. Mongkolsapaya, S. Yacoub, C. Roberts, New insights into the immunopathology and control of dengue virus infection, Nat. Rev. Immunol. 15 (2015) 745–759, https://doi.org/10.1038/nri3916.

[30] F.A. Rey, K. Stiasny, M.C. Vaney, M. Dellarole, F.X. Heinz, The bright and the dark side of human antibody responses to flaviviruses: lessons for vaccine design, EMBO Rep. 19 (2018) 206–224, https://doi.org/10.15252/embr.201745302.

[31] A.B. Sabin, Research on dengue during world war II, Am. J. Trop. Med. Hyg. 1 (1952) 30–50 PMID: 14903434.

[32] N. Sangkawibha, S. Rojanasuphot, S. Ahandrik, S. Viriyapongse, S. Jatanasen, V. Salitul, B. Phanthumachinda, S.B. Halstead, Risk factors in dengue shock syndrome: a prospective epidemiologic study in Rayong, Thailand. I. The 1980 outbreak, Am. J. Epidemiol. 120 (1984) 653–669, https://doi.org/10.1093/oxfordjournals.aje.a113932.

[33] D.H. Libraty, L.P. Acosta, V. Tallo, E. Segubre-Mercado, A. Bautista, J.A. Potts, R.G. Jarman, I.K. Yoon, R.V. Gibbons, J.D. Brion, R.Z. Capeding, A prospective nested case-control study of dengue in infants: rethinking and refining the antibody-dependent enhancement dengue hemorrhagic fever model, PLoS Med. 6 (2009) e1000171, https://doi.org/10.1371/journal.pmed.1000171.

[34] R.A. Hawkes, Enhancement of the infectivity of arboviruses by specific antisera produced in domestic fowls, Aust. J. Exp. Biol. Med. Sci. 42 (1964) 465–482 PMID: 14202187.

[35] S.B. Halstead, Observations related to pathogensis of dengue hemorrhagic fever. VI. Hypotheses and discussion, Yale J. Biol. Med. 42 (1970) 350–362 PMID: 5419208.

[36] S.B. Halstead, E.J. O'Rourke, Dengue viruses and mononuclear phagocytes. I. Infection enhancement by non-neutralizing antibody, J. Exp. Med. 146 (1977) 201–217, https://doi.org/10.1084/jem.146.1.201.

[37] K. Boonnak, B.M. Slike, G.C. Donofrio, M.A. Marovich, Human FcγRII cytoplasmic domains differentially influence antibody-mediated dengue virus infection, J. Immunol. 190 (2013) 5659–5665, https://doi.org/10.4049/jimmunol.1203052.

[38] Y.T. Fang, S.W. Wan, Y.T. Lu, J.H. Yao, C.F. Lin, L.J. Hsu, M.G. Brown, J.S. Marshall, R. Anderson, Y.S. Lin, Autophagy facilitates antibody-enhanced dengue virus infection in human pre-basophil/mast cells, PLoS One 9 (2014) e110655, https://doi.org/10.1371/journal.pone.0110655.

[39] K.R. Chan, E.Z. Ong, H.C. Tan, S.L. Zhang, Q. Zhang, K.F. Tang, N. Kaliaperumal, A.P. Lim, M.L. Hibberd, S.H. Chan, J.E. Connolly, M.N. Krishnan, S.M. Lok, B.J. Hanson, C.N. Lin, E.E. Ooi, Leukocyte immunoglobulin-like receptor B1 is critical for antibody-dependent dengue, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 2722–2727, https://doi.org/10.1073/pnas.1317454111.

[40] E.Z. Ong, S.L. Zhang, H.C. Tan, E.S. Gan, K.R. Chan, E.E. Ooi, Dengue virus compartmentalization during antibody-enhanced infection, Sci. Rep. 7 (2017) 40923, https://doi.org/10.1038/srep40923.

[41] A.L. Rothman, Immunity to dengue virus: a tale of original antigenic sin and tropical cytokine storms, Nat. Rev. Immunol. 11 (2011) 532–543, https://doi.org/10.1038/nri3014.

[42] S. Yacoub, H. Wertheim, C.P. Simmons, G. Screaton, B. Wills, Microvascular and endothelial function for risk prediction in dengue: an observational study, Lancet 385 (2015) S102, https://doi.org/10.1016/S0140-6736(15)60417-2.
[43] W. Dejnirattisai, A. Jumnainsong, N. Onsirisakul, P. Fitton, S. Vasanawathana, W. Limpitikul, C. Puttikhunt, C. Edwards, T. Duangchinda, S. Supasa, K. Chawansuntati, P. Malasit, J. Mongkolsapaya, G. Screaton, Cross-reacting antibodies enhance dengue virus infection in humans, Science 328 (2010) 745–748, https://doi.org/10.1126/science.1185181.
[44] L.C. Katzelnick, L. Gresh, M.E. Halloran, J.C. Mercado, G. Kuan, A. Gordon, A. Balmaseda, E. Harris, Antibody-dependent enhancement of severe dengue disease in humans, Science 358 (2017) 929–932, https://doi.org/10.1126/science.aan6836.
[45] H. Salje, D.A.T. Cummings, I. Rodriguez-Barraquer, L.C. Katzelnick, J. Lessler, C. Klungthong, B. Thaisomboonsuk, A. Nisalak, A. Weg, D. Ellison, L. Macareo, I.K. Yoon, R. Jarman, S. Thomas, A.L. Rothman, T. Endy, S. Cauchemez, Reconstruction of antibody dynamics and infection histories to evaluate dengue risk, Nature 557 (2018) 719–723, https://doi.org/10.1038/s41586-018-0157-4.
[46] K.R. Chan, S.L. Zhang, H.C. Tan, Y.K. Chan, A. Chow, A.P. Lim, S.G. Vasudevan, B.J. Hanson, E.E. Ooi, Ligation of Fc gamma receptor IIB inhibits antibody-dependent enhancement of dengue virus infection, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 12479–12484, https://doi.org/10.1073/pnas.1106568108.
[47] A. Syenina, C.J. Jagaraj, S.A. Aman, A. Sridharan, A.L. St John, Dengue vascular leakage is augmented by mast cell degranulation mediated by immunoglobulin Fcγ receptors, Elife 4 (2015), https://doi.org/10.7554/eLife.05291.
[48] P.G. Livingston, I. Kurane, L.C. Dai, Y. Okamoto, C.J. Lai, R. Men, S. Karaki, M. Takiguchi, F.A. Ennis, Dengue virus-specific, HLA-B35-restricted, human CD8+ cytotoxic T lymphocyte (CTL) clones. Recognition of NS3 amino acids 500 to 508 by CTL clones of two different serotype specificities, J. Immunol. 154 (1995) 1287–1295 PMID: 7529799.
[49] I. Kurane, A. Meager, F.A. Ennis, Dengue virus-specific human T cell clones. Serotype crossreactive proliferation, interferon gamma production, and cytotoxic activity, J. Exp. Med. 170 (1989) 763–775, https://doi.org/10.1084/jem.170.3.763.
[50] S.J. Gagnon, F.A. Ennis, A.L. Rothman, Bystander target cell lysis and cytokine production by dengue virus-specific human CD4(+) cytotoxic T-lymphocyte clones, J. Virol. 73 (1999) 3623–3629 PMCID: PMC104137.
[51] S. Hatch, T.P. Endy, S. Thomas, A. Mathew, J. Potts, P. Pazoles, D.H. Libraty, R. Gibbons, A.L. Rothman, Intracellular cytokine production by dengue virus-specific T cells correlates with subclinical secondary infection, J. Infect. Dis. 203 (2011) 1282–1291, https://doi.org/10.1093/infdis/jir012.
[52] H. Friberg, H. Bashyam, T. Toyosaki-Maeda, J.A. Potts, T. Greenough, S. Kalayanarooj, R.V. Gibbons, A. Nisalak, A. Srikiatkhachorn, S. Green, H.A. Stephens, A.L. Rothman, A. Mathew, Cross-reactivity and expansion of dengue-specific T cells during acute primary and secondary infections in humans, Sci. Rep. 1 (2011) 51, https://doi.org/10.1038/srep00051.
[53] J. Mongkolsapaya, W. Dejnirattisai, X.N. Xu, S. Vasanawathana, N. Tangthawornchaikul, A. Chairunsri, S. Sawasdivorn, T. Duangchinda, T. Dong, S. Rowland-Jones, P.T. Yenchitsomanus, A. McMichael, P. Malasit, G. Screaton, Original antigenic sin and apoptosis in the pathogenesis of dengue hemorrhagic fever, Nat. Med. 9 (2003) 921–927, https://doi.org/10.1038/nm887.
[54] A. Culshaw, K. Ladell, S. Gras, J.E. McLaren, K.L. Miners, C. Farenc, H. van den Heuvel, E. Gostick, W. Dejnirattisai, A. Wangteeraprasert, T. Duangchinda, P. Chotiyarnwong, W. Limpitikul, S. Vasanawathana, P. Malasit, T. Dong, J. Rossjohn, J. Mongkolsapaya, D.A. Price, G.R. Screaton, Germline bias dictates cross-serotype reactivity in a common dengue-virus-specific CD8+ T cell response, Nat. Immunol. 18 (2017) 1228–1237, https://doi.org/10.1038/ni.3850.
[55] F.M. Davenport, A.V. Hennessy, T. Francis Jr., Epidemiologic and immunologic significance of age distribution of antibody to antigenic variants of influenza virus, J. Exp. Med. 98 (1953) 641–656, https://doi.org/10.1084/jem.98.6.641.
[56] T. Francis Jr., Preventive medicine in 1985 and a reemphasis on the preservation of health, Whats New 220 (1960) 26–27 PMID: 24545611.
[57] P. Klenerman, R.M. Zinkernagel, Original antigenic sin impairs cytotoxic T lymphocyte responses to viruses bearing variant epitopes, Nature 394 (1998) 482–485, https://doi.org/10.1038/28860.
[58] S.B. Halstead, S. Rojanasuphot, N. Sangkawibha, Original antigenic sin in dengue, Am. J. Trop. Med. Hyg. 32 (1983) 154–156, https://doi.org/10.4269/ajtmh.1983.32.154.
[59] N.T. Dung, H.T. Duyen, N.T. Thuy, T.V. Ngoc, N.V. Chau, T.T. Hien, S.L. Rowland-Jones, T. Dong, J. Farrar, B. Wills, C.P. Simmons, Timing of CD8+ T cell responses in relation to commencement of capillary leakage in children with dengue, J. Immunol. 184 (2010) 7281–7287, https://doi.org/10.4049/jimmunol.0903262.
[60] H. Loke, D.B. Bethell, C.X. Phuong, M. Dung, J. Schneider, N.J. White, N.P. Day, J. Farrar, A.V. Hill, Strong HLA class I–restricted T cell responses in dengue hemorrhagic fever: a double-edged sword? J. Infect. Dis. 184 (2001) 1369–1373, https://doi.org/10.1086/324320.
[61] R. Appanna, T.L. Huat, L.L. See, P.L. Tan, J. Vadivelu, S. Devi, Cross-reactive T-cell responses to the nonstructural regions of dengue viruses among dengue fever and dengue hemorrhagic fever patients in Malaysia, Clin. Vaccine Immunol. 14 (2007) 969–977, https://doi.org/10.1128/CVI.00069-07.
[62] T.P. Nguyen, M. Kikuchi, T.Q. Vu, Q.H. Do, T.T. Tran, D.T. Vo, M.T. Ha, V.T. Vo, T.P. Cao, V.D. Tran, T. Oyama, K. Morita, M. Yasunami, K. Hirayama, Protective and enhancing HLA alleles, HLA-DRB1*0901 and HLA-A*24, for severe forms of dengue virus infection, dengue hemorrhagic fever and dengue shock syndrome, PLoS Negl. Trop. Dis. 2 (2008) e304, https://doi.org/10.1371/journal.pntd.0000304.
[63] B. Sierra, R. Alegre, A.B. Pérez, G. García, K. Sturn-Ramirez, O. Obasanjo, E. Aguirre, M. Alvarez, R. Rodriguez-Roche, L. Valdés, P. Kanki, M.G. Guzmán, HLA-A, -B, -C, and -DRB1 allele frequencies in Cuban individuals with antecedents of dengue 2 disease: advantages of the Cuban population for HLA studies of dengue virus infection, Hum. Immunol. 68 (2007) 531–540, https://doi.org/10.1016/j.humimm.2007.03.001.
[64] D. Weiskopf, M.A. Angelo, E.L. de Azeredo, J. Sidney, J.A. Greenbaum, A.N. Fernando, A. Broadwater, R.V. Kolla, A.D. De Silva, A.M. de Silva, K.A. Mattia, B.J. Doranz, H.M. Grey, S. Shresta, B. Peters, A. Sette, Comprehensive analysis of dengue virus-specific responses supports an HLA-linked protective role for CD8+ T cells, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) E2046–E2053, https://doi.org/10.1073/pnas.1305227110.
[65] J.L.M. Ferrara, Cytokine dysregulation as a mechanism of graft versus host disease, Curr. Opin. Immunol. 5 (1993) 794–799, https://doi.org/10.1016/0952-7915(93)90139-J.
[66] J.R. Tisoncik, M.J. Korth, C.P. Simmons, J. Farrar, T.R. Martin, M.G. Katze, Into the eye of the cytokine storm, Microbiol. Mol. Biol. Rev. 76 (2012) 16–32, https://doi.org/10.1128/MMBR.05015-11.
[67] X. Blanchet, M. Langer, C. Weber, R. Koenen, P. von Hundelshausen, Touch of chemokines, Front. Immunol. 3 (2012) 1–18, https://doi.org/10.3389/fimmu.2012.00175.
[68] A. Zlotnik, O. Yoshie, The chemokine superfamily revisited, Immunity 36 (2013) 705–716, https://doi.org/10.1016/j.immuni.2012.05.008.
[69] K. Matsushima, Y. Terashima, E. Toda, F. Shand, S. Ueha, Chemokines in inflammatory and immune diseases, Inflamm. Regen. 31 (2011) 11–22, https://doi.org/10.2492/inflammregen.31.11.
[70] O. Schulz, S.I. Hammerschmidt, G.L. Moschovakis, R. Förster, Chemokines and chemokine receptors in lymphoid tissue dynamics, Annu. Rev. Immunol. 34 (2016) 203–242, https://doi.org/10.1146/annurev-immunol-041015-055649.
[71] A.E.I. Proudfoot, M. Uguccioni, Modulation of chemokine responses: synergy and cooperativity, Front. Immunol. 7 (2016) 1–6, https://doi.org/10.3389/fimmu.2016.00183.
[72] P. López-Cotarelo, C. Gómez-Moreira, O. Criado-García, L. Sánchez, J.L. Rodríguez-Fernández, Beyond chemoattraction: multifunctionality of chemokine receptors in leukocytes, Trends Immunol. 38 (2017) 927–941, https://doi.org/10.1016/j.it.2017.08.004.
[73] B. Nedoszytko, M. Sokolowska-Wojdylo, K. Ruckemann-Dziurdzinska, J. Roszkiewicz, R.J. Nowicki, Chemokines and cytokines network in the pathogenesis of the inflammatory skin diseases: atopic dermatitis, psoriasis and skin mastocytosis, Postep Dermatol. Alergol. 31 (2014) 84–91, https://doi.org/10.5114/pdia.2014.40920.
[74] J.W. Griffith, C.L. Sokol, A.D. Luster, Chemokines and chemokine receptors: positioning cells for host defense and immunity, Annu. Rev. Immunol. 32 (2014) 659–702, https://doi.org/10.1146/annurev-immunol-032713-120145.
[75] F. Bachelerie, A. Ben-Baruch, A.M. Burkhardt, C. Combadiere, J.M. Farber, G.J. Graham, R. Horuk, A.H. Sparre-Ulrich, M. Locati, A.D. Luster, A. Mantovani, K. Matsushima, P.M. Murphy, R. Nibbs, H. Nomiyama, C.A. Power, A.E. Proudfoot, M.M. Rosenkilde, A. Rot, S. Sozzani, M. Thelen, O. Yoshie, A. Zlotnik, International Union of Basic and Clinical Pharmacology. LXXXIX Update on the extended family of chemokine receptors and introducing a new nomenclature for atypical chemokine receptors, Pharmacol. Rev. 66 (2014) 1–79, https://doi.org/10.1124/pr.113.007724.
[76] R.J. Nibbs, G.J. Graham, Immune regulation by atypical chemokine receptors, Nat. Rev. Immunol. 13 (2013) 815–829 PMID: 24319779.
[77] M. Garcia, M. Wehbe, N. Lévêque, C. Bodet, Skin innate immune response to flaviviral infection, Eur. Cytokine Netw. 28 (2017) 41–51, https://doi.org/10.1684/ecn.2017.0394.2017.
[78] V. González-Motos, K.A. Kropp, A. Viejo-Borbolla, Cytokine & growth factor reviews chemokine binding proteins: an immunomodulatory strategy going viral, Cytokine Growth Factor Rev. 30 (2016) 71–80, https://doi.org/10.1016/j.cytogfr.2016.02.007.
[79] H. Umehara, E.T. Bloom, T. Okazaki, Y. Nagano, O. Yoshie, T. Imai, Fractalkine in vascular biology: from basic research to clinical disease, Arterioscler. Thromb. Vasc. Biol. 24 (2004) 34–40, https://doi.org/10.1161/01.ATV.0000095360.62479.1F.
[80] M. Locati, K. Otero, T. Schioppa, P. Signorelli, P. Perrier, S. Baviera, S. Sozzani, A. Mantovani, The chemokine system: tuning and shaping by regulation of receptor expression and coupling in polarized responses, Allergy Eur. J. Allergy Clin. Immunol. 57 (2002) 972–982, https://doi.org/10.1034/j.1398-9995.2002.02166.x.
[81] V. Appay, R.A.W. van Lier, F. Sallusto, M. Roederer, Phenotype and function of human T lymphocyte subsets: consensus and issues, Cytom. Part A 73A (2008) 975–983, https://doi.org/10.1002/cyto.a.20643.
[82] P. Salgame, J.S. Abrams, C. Clayberger, H. Goldstein, R.L. Modlin, B.R. Bloom, Differing lymphokine profiles of functional subsets of human CD4 and CD8 t cell clones, Science 254 (1991) 279–282, https://doi.org/10.1126/science.1681588.
[83] P. Romagnani, M.-P. Piccinni, F. Annunziato, S. Romagnani, Th1/Th2 cells, their associated molecules and role in pathophysiology, Eur. Cytokine Netw. 11 (2000) 510–511 PMID: 11203198.
[84] L. Rivino, M. Messi, D. Jarrossay, A. Lanzavecchia, F. Sallusto, J. Geginat, Chemokine receptor expression identifies pre–T helper (Th)1, pre–Th2, and non-polarized cells among human CD4 + central memory T cells, J. Exp. Med. 200 (2004) 725–735, https://doi.org/10.1084/jem.20040774.
[85] Y.C. Zang, A.K. Samanta, J.B. Halder, J. Hong, M.V. Tejada-Simon, V.M. Rivera, J.Z. Zhang, Aberrant T cell migration toward RANTES and MIP-1 alpha in patients with multiple sclerosis. Overexpression of chemokine receptor CCR5, Brain 123 (2000) 1874–1882, https://doi.org/10.1093/brain/123.9.1874.

[86] Y. Becker, The spreading of HIV-1 infection in the human organism is caused by fractalkine trafficking of the infected lymphocytes-a review, hypothesis and implications for treatment, Virus Genes 34 (2007) 93–109, https://doi.org/10.1007/s11262-006-0056-x.
[87] C.C. Clay, D.S. Rodrigues, Y.S. Ho, B. Fallert, K. Janatpour, T.A. Reinhart, U. Esser, Neuroinvasion of fluorescein-positive monocytes in acute simian immunodeficiency virus infection, J. Virol. 81 (2007) 12040–12048, https://doi.org/10.1128/JVI.00133-07.
[88] S.A. Kolb, B. Sporer, F. Lahrtz, U. Koedel, H.-W. Pfister, A. Fontana, Identification of a T cell chemotactic factor in the cerebrospinal fluid of HIV-1-infected individuals as interferon-gamma inducible protein 10, J. Neuroimmunol. 93 (1999) 172–181, https://doi.org/10.1016/S0165-5728(98)00223-9.
[89] C. Chanthick, A. Suttitheptumrong, N. Rawarak, Transcytosis involvement in transport system and endothelial permeability of vascular leakage during dengue virus infection, Viruses 10 (2018) E69, https://doi.org/10.3390/v10020069.
[90] D. Mehta, A.B. Malik, Signaling mechanisms regulating endothelial permeability, Physiol. Rev. 86 (2006) 279–367, https://doi.org/10.1152/physrev.00012.2005.
[91] M. Furuse, S. Tsukita, Claudins in occluding junctions of humans and flies, Trends Cell Biol. 16 (2006) 181–188, https://doi.org/10.1016/j.tcb.2006.02.006.
[92] T. Hirase, J.M. Staddon, M. Saitou, Y. Ando-Akatsuka, M. Itoh, M. Furuse, K. Fujimoto, S. Tsukita, L.L. Rubin, Occludin as a possible determinant of tight junction permeability in endothelial cells, J. Cell. Sci. 110 (Pt. 14) (1997) 1603–1613 PMID: 9247194.
[93] M.S. Nielsen, L.N. Axelsen, P.L. Sorgen, V. Verma, M. Delmar, N.H. Holstein-Rathlou, Gap junctions, Compr. Physiol. 2 (2012) 1981–2035, https://doi.org/10.1002/cphy.c110051.
[94] M. Giannotta, M. Trani, E. Dejana, VE-cadherin and endothelial adherens junctions: active guardians of vascular integrity, Dev. Cell 26 (2013) 441–454, https://doi.org/10.1016/j.devcel.2013.08.020.
[95] Y. Wallez, P. Huber, Endothelial adherens and tight junctions in vascular homeostasis, inflammation and angiogenesis, Biochim. Biophys. Acta Biomembr. 1778 (2008) 794–809, https://doi.org/10.1016/j.bbamem.2007.09.003.
[96] A. Mantovani, R. Bonecchi, M. Locati, Tuning inflammation and immunity by chemokine sequestration: decoys and more, Nat. Rev. Immunol. 6 (2006) 907–918, https://doi.org/10.1038/nri1964.
[97] J.H. Mills, L. Alabanza, B.B. Weksler, P.-O. Couraud, I.A. Romero, M.S. Bynoe, Human brain endothelial cells are responsive to adenosine receptor activation, Purinergic Signal. 7 (2011) 265–273, https://doi.org/10.1007/s11302-011-9222-2.
[98] M.S. Bynoe, C. Viret, A. Yan, D.G. Kim, Adenosine receptor signaling: a key to opening the blood-brain door, Fluids Barriers CNS 12 (2015) 1–12, https://doi.org/10.1186/s12987-015-0017-7.
[99] C. Konradt, C.A. Hunter, Pathogen interactions with endothelial cells and the induction of innate and adaptive immunity, Eur. J. Immunol. 10 (2018) 1607–1620, https://doi.org/10.1002/eji.201646789.
[100] K.Y.Y. Fung, G.D. Fairn, W.L. Lee, Transcellular vesicular transport in epithelial and endothelial cells: challenges and opportunities, Wiley Traffic (2018) 5–18, https://doi.org/10.1111/tra.12533.
[101] C. Whittall, O. Kehoe, S. King, A. Rot, A. Patterson, A chemokine self-presentation mechanism involving formation of endothelial surface microstructures, J. Immunol. 190 (2013) 1725–1736, https://doi.org/10.4049/jimmunol.1200867.
[102] N.A. Dalrymple, E.R. MacKow, Virus interactions with endothelial cell receptors: implications for viral pathogenesis, Curr. Opin. Virol. 7 (2014) 134–140, https://doi.org/10.1016/j.coviro.2014.06.006.
[103] H.F. Dvorak, Vascular permeability to plasma, plasma proteins, and cells: an update, Curr. Opin. Hematol. 17 (2010) 225–229, https://doi.org/10.1097/MOH.0b013e3283386638.
[104] D.B. Cines, E.S. Pollak, C.A. Buck, J. Loscalzo, G.A. Zimmerman, R.P. McEver, J.S. Pober, T.M. Wick, B.A. Konkle, B.S. Shwartz, E.S. Barnathan, K.R. McCrae, B.A. Hug, A.M. Schmidt, D.M. Stern, Endothelial cells in physiology and in the pathophysiology of vascular disorders, Blood. 91 (1998) 3527–3561.
[105] W.C. Aird, Endothelium as an organ system, Crit. Care Med. 32 (2004) S271–S279, https://doi.org/10.1097/01.CCM.0000129669.21649.40.
[106] D.G. Nielsen, The relationship of interacting immunological components in dengue pathogenesis, Virol. J. 6 (2009) 211, https://doi.org/10.1186/1743-422X-6-211.
[107] A. Srikiatkhachorn, Plasma leakage in dengue haemorrhagic fever, Thromb. Haemost. 102 (2009) 1042–1049, https://doi.org/10.1160/TH09-03-0208.
[108] E. Navarro-Sánchez, P. Desprès, L. Cedillo-Barrón, Innate immune responses to dengue vírus, Arch. Med. Res. 36 (2005) 425–435, https://doi.org/10.1016/j.arcmed.2005.04.007.
[109] G.N. Malavige, G.S. Ogg, Pathogenesis of vascular leak in dengue virus infection, Immunology 151 (2017) 261–269, https://doi.org/10.1111/imm.12748.
[110] K.R. Rathi, M.M. Arora, K. Sahai, S. Tripathi, S.P. Singh, D.K. Raman, K.B. Anand, Autopsy findings in fatal dengue haemorrhagic fever - 06 cases, Med. J. Armed Forces India 69 (2013) 254–259, https://doi.org/10.1016/j.mjafi.2012.08.021.
[111] D. Talavera, A.M. Castillo, M.C. Dominguez, A.E. Gutierrez, I. Meza, IL8 release, tight junction and cytoskeleton dynamic reorganization conducive to permeability increase are induced by dengue virus infection of microvascular endothelial monolayers, J. Gen. Virol. 85 (2004) 1801–1813, https://doi.org/10.1099/vir.0.19652-0.
[112] H. Zamudio-Meza, A. Castillo-Alvarez, C. González-Bonilla, I. Meza, Cross-talk between Rac1 and Cdc42 GTPases regulates formation of filopodia required for dengue virus type-2 entry into HMEC-1 cells, J. Gen. Virol. 90 (2009) 2902–2911, https://doi.org/10.1099/vir.0.014159-0.
[113] J.K. Calvert, K.J. Helbig, D. Dimasi, M. Cockshell, M.R. Beard, S.M. Pitson, C.S. Bonder, J.M. Carr, Dengue virus infection of primary endothelial cells induces innate immune responses, changes in endothelial cells function and is restricted by interferon-stimulated responses, J. Interferon Cytokine Res. 35 (2015) 654–665, https://doi.org/10.1089/jir.2014.0195.
[114] S. Singh, M.G. Anupriya, E. Sreekumar, Comparative whole genome analysis of dengue virus serotype-2 strains differing in trans-endothelial cell leakage induction in vitro, Infect. Genet. Evol. J. Mol. Epidemiol. Evol. Genet. Infect. Dis. 52 (2017) 34–43, https://doi.org/10.1016/j.meegid.2017.04.022.
[115] N. Modhiran, D. Watterson, D.A. Muller, A.K. Panetta, D.P. Sester, L. Liu, D.A. Hume, K.J. Stacey, P.R. Young, Dengue virus NS1 protein activates cells via Toll-like receptor 4 and disrupts endothelial cell monolayer integrity, Sci. Transl. Med. 7 (2015) 304ra142, https://doi.org/10.1126/scitranslmed.aaa3863.
[116] H. Puerta-Guardo, D.R. Glasner, E. Harris, Dengue virus NS1 disrupts the endothelial glycocalyx, leading to hyperpermeability, PLoS Pathog. 12 (2016) e1005738, https://doi.org/10.1371/journal.ppat.1005738.
[117] H.R. Chen, C.H. Chao, C.C. Liu, T.S. Ho, H.P. Tsai, G.C. Perng, Y.S. Lin, J.R. Wang, T.M. Yeh, Macrophage migration inhibitory factor is critical for dengue NS1-induced endothelial glycocalyx degradation and hyperpermeability, PLoS Pathog. 14 (2018) e1007033, https://doi.org/10.1371/journal.ppat.1007033.
[118] T. Furuta, L.A. Murao, N.T. Lan, N.T. Huy, V.T. Huong, T.T. Thuy, V.D. Tham, C.T. Nga, T.T. Ha, Y. Ohmoto, M. Kikuchi, K. Morita, M. Yasunami, K. Hirayama, N. Watanabe, Association of VEGF derived from mast cells and proteases in dengue shock syndrome, PLoS Negl. Trop. Dis. 6 (2012) e1505, https://doi.org/10.1371/journal.pntd.0001505.
[119] I. Zachary, Neuropilins: role in signaling, angiogenesis and disease, Chem. Immunol. Allergy 99 (2014) 37–70, https://doi.org/10.1159/000354169.
[120] A. Troupin, D. Shirley, B. Londono-Renteria, A.M. Watson, C. McHale, A. Hall, A. Hartstone-Rose, W.B. Klimstra, G. Gomez, T.M. Colpitts, A role for human skin mast cells in dengue virus infection and systemic spread, J. Immunol. 197 (2016) 4382–4391, https://doi.org/10.4049/jimmunol.1600846.
[121] N.A. Dalrymple, E.R. Mackow, Endothelial cells elicit immune-enhancing responses to dengue virus infection, J. Virol. 86 (2012) 6408–6415, https://doi.org/10.1128/JVI.00213-12.
[122] S. Fernando, A. Wijewickrama, L. Gomes, C.T. Punchihewa, S.D.P. Madusanka, H. Dissanayake, C. Jeewandara, H. Peiris, G.S. Ogg, G.N. Malavige, Patterns and causes of liver involvement in acute dengue infection, BMC Infect. Dis. 16 (2016) 319, https://doi.org/10.1186/s12879-016-1656-2.
[123] A. Kamaladasa, L. Gomes, C. Jeewandara, N.L.A. Shyamali, G.S. Ogg, G.N. Malavige, Lipopolysaccharide acts synergistically with the dengue virus to induce monocyte production of platelet activating factor and other inflammatory mediators, Antivir. Res. 133 (2016) 183–190, https://doi.org/10.1016/j.antiviral.2016.07.016.
[124] S. Inyoo, A. Suttitheptumrong, S.N. Pattanakitsakul, Synergistic effect of TNF-α and dengue virus infection on adhesion molecule reorganization in human endothelial cells, Jpn. J. Infect. Dis. 70 (2017) 186–191, https://doi.org/10.7883/yoken.JJID.2016.123.
[125] P. Avirutnan, P. Malasit, B. Seliger, S. Bhakdi, M. Husmann, Dengue virus infection of human endothelial cells leads to chemokine production, complement activation, and apoptosis, J. Immunol. 154 (1998) 6338–6346.
[126] D. Talavera, A.M. Castillo, M.C. Dominguez, A. Escobar Gutierrez, I. Meza, IL8 release, tight junction and cytoskeleton dynamic reorganization conducive to permeability increase are induced by dengue virus infection of microvascular endothelial monolayers, J. Gen. Virol. 85 (2004) 1801–1813, https://doi.org/10.1099/vir.0.19652-0.
[127] Y.R. Lee, M.T. Liu, H.Y. Lei, C.C. Liu, J.M. Wu, Y.C. Tung, Y.S. Lin, T.M. Yeh, S.H. Chen, H.S. Liu, MCP1, a highly expressed chemokine in dengue haemorrhagic fever/dengue shock syndrome patients, may cause permeability change, possibly through reduced tight junctions of vascular endothelium cells, J. Gen. Virol. 87 (2006) 3623–3630, https://doi.org/10.1099/vir.0.82093-0.
[128] J.F. Kelley, P.H. Kaufusi, V.R. Nerurkar, Dengue hemorrhagic fever-associated immunomediators induced via maturation of dengue virus nonstructural 4B protein in monocytes modulate endothelial cell adhesion molecules and human microvascular endothelial cells permeability, J. Virol. 422 (2012) 326–337, https://doi.org/10.1016/j.virol.2011.10.030.
[129] T.N. Chau, N.T. Quyen, T.T. Thuy, N.M. Tuan, D.M. Hoang, N.T. Dung, I.B. Lien, N.T. Quy, N.T. Hieu, L.T. Hieu, T.T. Hien, N.T. Hung, J. Farrar, C.P. Simmons, Dengue in Vietnamese infants—results of infection-enhancement assays correlate with age-related disease epidemiology, and cellular immune responses correlate with disease severity, J. Infect. Dis. 198 (2008) 516–524, https://doi.org/10.1086/590117.
[130] B.P. Hoh, H. Umi-shakina, Z. Zuraihan, M.Z. Zaiharina, S. Rafidah-hanim, M. Mahiran, N.Y. Khairudin, L.H. Benedict, Z. Masliza, K.C. Christopher, A.B. Sazaly, Common variants of chemokine receptor gene CXCR3 and its ligands CXCL10 and CXCL11 associated with vascular permeability of dengue infection in peninsular Malaysia, Hum. Immunol. 76 (2015) 421–426, https://doi.org/10.1016/j.humimm.2015.03.019.
[131] K.M. Soo, B. Khalid, S.M. Ching, C.L. Tham, R. Basir, H.Y. Chee, Meta-analysis of biomarkers for severe dengue infections, PeerJ 5 (2017) e3589, https://doi.org/10.7717/peerj.3589.
[132] W.A. Muller, Transendothelial migration: unifying principles from the endothelial perspective, Immunol. Rev. 273 (2016) 61–75, https://doi.org/10.1111/imr.12443.
[133] S. Suwarto, R.T. Sasmono, R. Sinto, E. Ibrahim, M. Suryamin, Association of endothelial glycocalyx and tight and adherens junctions with severity of plasma leakage in dengue infection, J. Infect. Dis. 215 (2017) 992–999, https://doi.org/10.1093/infdis/jix041.

[134] M.N. Fariz-Safhan, H.P. Tee, G.A. Abu Dzarr, S. Sapari, Y.Y. Lee, Bleeding outcome during a dengue outbreak in 2005 in the East-coast region of Peninsular Malaysia: a prospective study, Trop. Biomed. 31 (2014) 270–280 PMID: 25134895.
[135] S. Honsawek, P. Kongtawelert, P. Pothacharoen, A. Khongphatthanayothin, V. Chongsrisawat, Y. Poovorawan, Increased levels of serum hyaluronan in patients with dengue infection, J. Infect. 54 (2007) 225–229, https://doi.org/10.1016/j.jinf.2006.06.002.
[136] B.A. Wills, E.E. Oragui, N.M. Dung, H.T. Loan, N.V. Chau, J.J. Farrar, M. Levin, Size and charge characteristics of the protein leak in dengue shock syndrome, J. Infect. Dis. 190 (2004) 810–818, https://doi.org/10.1086/422754.
[137] A. Srikiatkhachorn, J.F. Kelley, Endothelial cells in dengue hemorrhagic fever, Antivir. Res. 109 (2014) 160–170, https://doi.org/10.1016/j.antiviral.2014.07.005.
[138] N.J. Marchette, S.B. Halstead, D.R. Nash, A.C. Stenhouse, Recovery of dengue viruses from tissues of experimentally infected rhesus monkeys, Appl. Microbiol. 24 (1972) 328–333 PMCID: PMC376519.
[139] S.H. Waterman, T.P. Monath, Fluorescent antibody techniques applied to the identification of dengue virus in infected tissue, Acta Virol. 26 (1982) 376–381 PMID: 6128906.
[140] M.P. Miagostovich, R.G. Ramos, A.F. Nicol, R.M. Nogueira, T. Cuzzi-Maya, A.V. Oliveira, R.S. Marchevsky, R.P. Mesquita, H.G. Schatzmayr, Retrospective study on dengue fatal cases, Clin. Neuropathol. 16 (1997) 204–208 PMID: 9266146.
[141] T.F. Póvoa, A.M. Alves, C.A. Oliveira, G.J. Nuovo, V.L. Chagas, M.V. Paes, The pathology of severe dengue in multiple organs of human fatal cases: histopathology, ultrastructure and virus replication, PLoS One 15 (2014) e83386, https://doi.org/10.1371/journal.pone.0083386.
[142] T.F. Póvoa, E.R.A. Oliveira, C.A. Basílio-de-Oliveira, G.J. Nuovo, V.L.A. Chagas, N.G. Salomão, E.M. Mota, M.V. Paes, Peripheral organs of dengue fatal cases present strong pro-inflammatory response with participation of IFN-Gamma-, TNF-Alpha and RANTES-producing cells, PLoS One 11 (2016) 1–19, https://doi.org/10.1371/journal.pone.0168973.
[143] L.M. De-Oliveira-Pinto, C.F. Marinho, T.F. Povoa, E.L. de Azeredo, L.A. de Souza, L.D. Barbosa, A.R. Motta-Castro, A.M. Alves, C.A. Ávila, L.J. de Souza, R.V. da Cunha, P.V. Damasco, M.V. Paes, C.F. Kubelka, Regulation of inflammatory chemokine receptors on blood T cells associated to the circulating versus liver chemokines in dengue fever, PLoS One 7 (2012) e38527, https://doi.org/10.1371/journal.pone.0038527.
[144] D. Weiskopf, D.J. Bangs, J. Sidney, R.V. Kolla, A.D. De Silva, A.M. de Silva, S. Crotty, B. Peters, A. Sette, Dengue virus infection elicits highly polarized CX3CR1 + cytotoxic CD4 + T cells associated with protective immunity, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) E4256–E4263, https://doi.org/10.1073/pnas.1505956112.
[145] R. Guabiraba, E.R. Marques, B. Ryffel, C.T. Fagundes, G. Danielle, M.M. Teixeira, Role of the chemokine receptors CCR1, CCR2 and CCR4 in the pathogenesis of experimental dengue infection in mice, PLoS One 5 (2010) e15680, https://doi.org/10.1371/journal.pone.0015680.
[146] I. Peng-Peng, L. Fang, Resistance to dengue virus infection in mice is potentiated by CXCL10 and is independent of CXCL10-mediated leukocyte recruitment, J. Immunol. 10 (2010) 5705–5714, https://doi.org/10.4049/jimmunol.0903484.
[147] M. Hsieh, S. Lai, J. Chen, Y. Lin, B.A. Wu-hsieh, C. Gerard, A. Luster, F. Liao, Both CXCR3 and CXCL10/IFN-inducible protein 10 are required for resistance to primary infection by dengue virus, J. Immunol. 177 (2006) 1855–1863, https://doi.org/10.4049/jimmunol.177.3.1855.