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Review

Endothelial cells in dengue hemorrhagic fever

Anon Srikiatkhachorn [a,*], James F. Kelley [b,c]

[a] Department of Medicine, University of Massachusetts Medical School, Worcester, MA 01655, USA
[b] Faculty of Tropical Medicine, Department of Microbiology and Immunology, Mahidol University, Bangkok, Thailand
[c] Department of Tropical Medicine, Medical Microbiology and Pharmacology, University of Hawaii, USA

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ABSTRACT

Therapies to prevent or reverse endothelial dysfunction and vascular leak found in dengue hemorrhagic fever (DHF) have not been identified. In this review we summarize dengue viruses and the spectrum of human disease and highlight evidence of endothelial cell dysfunction in DHF based on studies in patients and mouse and tissue culture models. Evidence suggests that both virus antigen and host immune response, can cause endothelial cell dysfunction and weaken endothelial barrier integrity. We suggest possible therapeutic interventions and highlight how therapies targeting altered endothelial function might be evaluated in animal models and in patients with DHF.

Contents

1. Introduction

Infection with dengue virus can lead to a wide spectrum of clinical illness from a nonspecific febrile syndrome to dengue hemorrhagic fever (DHF) which is characterized by increased vascular permeability, hemorrhage and shock (Gubler, 1997; Nimmannitya, 1993). The endothelial barrier is of central interest to those

Abbreviations: CLEC5A, C-type lectin domain family 5 member A; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; DENV, dengue virus; DF, dengue fever; DHF, dengue hemorrhagic fever; ICAM-1, intercellular adhesion molecule-1; IFN, interferon; IL, interleukin; MMP, matrix metaloprotease; NS, nonstructural; S1P, sphingosine-1-phosphatase; SCID, severe combined immunodeficient; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

* Corresponding author.
E-mail address: anon.srikiatkhachorn@umassmed.edu (A. Srikiatkhachorn).

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investigating vascular permeability in dengue infections. The barrier consists of a number of elements such as endothelial cells, smooth muscle cells, an extracellular matrix, basement membrane, cytoskeleton and cell–cell junctions (Dejana et al., 2009; Dvorak, 2010), all of which undergo changes both during normal physiology and likely during a dengue infection. Endothelial cells are a critical element of the barrier and much dengue research has focused on endothelial cells in attempts to pinpoint mechanisms of vascular leakage.

In this article we review current concepts of the role of the endothelium in dengue and efforts to develop interventions to prevent or reverse vascular leak. We focus on the role of endothelial cells in vascular leakage in dengue by assessing findings from human studies, animal, and cell culture models. Other factors involved in DHF such as coagulation, host and virus mediators and the autoimmune phenomena found in DHF are considered. We highlight candidate mediators involved in plasma leakage and discuss possible therapeutic interventions targeting altered endothelial function and how they might be evaluated in animal models and in DHF patients.

2. Dengue virus and clinical disease

2.1. Dengue virus

Dengue is caused by dengue viruses (DENV), a group of four serologically distinct positive strand RNA viruses: DENV1, DENV2, DENV3, and DENV4. Dengue viruses belong to the Flaviviridae family which includes yellow fever virus and Japanese B encephalitis virus. The DENV viral genome is ten kilobases in length and encodes 10 gene products including structural proteins: C (capsid), prM (membrane), and E (envelope); and nonstructural proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 (Gubler et al., 2007; Lindenbach et al., 2007). The E protein plays an important role in viral binding and entry into host cells (Leitmeyer et al., 1999; Modis et al., 2004; Tassaneetrithep et al., 2003). The serologic reactivity to the envelope proteins defines the serotypes of DENV (Gubler et al., 2007).

A number of molecules have been reported to interact with DENV and serve as receptors for viral attachment and entry (Mukhopadhyay et al., 2005). Among these, the best characterized are C-type lectins including DC-SIGN (CD209) and CLEC5A expressed on dendritic cells and macrophages respectively (Chen et al., 2008; Tassaneetrithep et al., 2003). The primary role of DC-SIGN is likely viral attachment since internalization occurs in cells expressing DC-SIGN that lacks internalization sequence (Lozach et al., 2005). Therefore, additional molecules not yet specified are involved in virus internalization. Interaction between viral particles and CLEC5A has been shown to induce production of proinflammatory cytokines which may play a role in dengue pathogenesis (Chen et al., 2008). Although DENV can infect many cell types in vitro including epithelial cells, endothelial cells, hepatocytes, muscle cells, dendritic cells, monocytes and mast cells, the roles of these cells in dengue pathogenesis and the cellular receptors involved in infection are not known (Arevalo et al., 2009; Basu et al., 2011; Brown et al., 2011; Huang et al., 2000; Paes et al., 2009; Salgado et al., 2010).

2.2. Clinical disease

Dengue is transmitted by bites of infected mosquitoes: *Aedes aegypti*, and less commonly *Aedes albopictus* (Gubler et al., 2007). In endemic areas, primary DENV infections occur early in life and are usually mild and often undiagnosed. Primary infections in older children and adults can result in dengue fever (DF). Dengue virus infections were once thought to cause a non-fatal illness before several severe dengue hemorrhagic fever (DHF) outbreaks that occurred in the 1950–1960s changed this perception (Fresh et al., 1969). Dengue hemorrhagic fever is characterized by fever, thrombocytopenia, hemorrhagic tendency, and plasma leakage (World Health Organization, 1997). Plasma leakage is the clinical feature that distinguishes DHF from DF and is the most important risk factor for severity.

Individuals can be infected more than once with different serotypes of DENV due to the lack of long lasting cross-protective immunity. Epidemiological evidence strongly indicates that a secondary infection poses a higher risk for DHF in comparison to a primary infection. Although the majority of cases with a secondary infection develop DF, which are usually self-limited without requiring significant intervention, a minority of cases develops plasma leakage which occurs around the time of defervescence, resulting in accumulation of fluid in the chest and abdominal cavities (Pramuljo and Harun, 1991; Srikiatkhachorn et al., 2007b). Severe plasma leakage may lead to circulatory insufficiency and death. Increased vascular permeability in other vascular beds such as the kidneys has been suggested on the basis of increased urine protein levels in DHF compared to DF. However, the severity of proteinuria in DHF is mild and not the primary cause of fluid accumulation in the serosal cavities. Hemorrhagic manifestations, ranging from minor skin hemorrhage to mucosal (nose, gum) and gastrointestinal bleeding, are common in both DF and DHF but are more severe in DHF (Nimmannitya, 1993; World Health Organization, 1997).

Although the DF/DHF clinical classification has been in use since the 1960s and has been instrumental in the development of a clinical treatment algorithm that significantly improved case mortality, the 1997 World Health Organization (WHO) guideline defining DF and DHF (World Health Organization, 1997) has been under criticism for its applicability, validity, and ability to identify severe dengue (Bandyopadhyay et al., 2006; Deen et al., 2006). In 2009 the WHO issued a new clinical classification scheme (World Health Organization, 2009) based on information from a multicenter study conducted in Asia and Central and South Americas (Alexander et al., 2011). In this new scheme dengue is classified into dengue and severe dengue. The definitions of severe dengue are: (1) dengue with plasma leakage leading to shock or respiratory distress, (2) severe hemorrhage, and (3) organ failure. This review will be based on the 1997 DF/DHF classification since most studies have until recently utilized this classification scheme.

3. Dengue virus and the endothelial barrier

Since the cardinal manifestations of DHF, namely plasma leakage and hemorrhagic tendency, are suggestive of changes in vascular functions, the roles of the endothelium in the pathogenesis of dengue have long been investigated. Although other cells and structures including perivascular smooth muscle cells, the extracellular matrix and basement membrane, and the glycocalyx participate in the regulation of vascular permeability, the roles of these cells and structures in permeability regulation in dengue have not been intensively investigated. As such, most of the evidence reviewed in this article will be largely related to the roles of endothelial cells. In the following sections we highlight evidence of DENV infection of endothelial cells and subsequent effects of viral antigens and host mediators on endothelial cells in human infections, and in animal and in vitro cell culture models.

3.1. Studies of human infections

Based on human autopsy studies, cells of the immune system including monocytes, tissue macrophages, and lymphocytes have