PLOS PATHOGENS

PEARLS

Insights into potential causes of vascular hyperpermeability in dengue

Andrew Teo[1,2]*, **Caroline Lin Lin Chua**[3], **Po Ying Chia**[1,4,5], **Tsin Wen Yeo**[1,4,5]*

1 Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore, **2** Department of Medicine, The Doherty Institute, University of Melbourne, Melbourne, Australia, **3** School of Biosciences, Faculty of Health and Medicine Sciences, Taylor's University, Subang Jaya, Malaysia, **4** National Centre for Infectious Diseases, Singapore, Singapore, **5** Department of Infectious Diseases, Tan Tock Seng Hospital, Singapore, Singapore

* andrewcc.teo@ntu.edu.sg (AT); yeotsinwen@ntu.edu.sg (TWY)

Citation: Teo A, Chua CLL, Chia PY, Yeo TW (2021) Insights into potential causes of vascular hyperpermeability in dengue. PLoS Pathog 17(12): e1010065. https://doi.org/10.1371/journal.ppat.1010065

Editor: Wendy Maury, University of Iowa, UNITED STATES

Published: December 9, 2021

Funding: AT is supported by Nanyang Technological University Research Scholarship Block Fellowship of Singapore and Lee Kong Chian School of Medicine, Singapore, Start-up grant. CLLC receives support from Ministry of Education (MOE) Fundamental Research Grant Scheme of Malaysia: ID FRGS/1/2020/SKK0/TAYLOR/02/1. PYC is supported by NMRC Research Training Fellowship (NMRC/Fellowship/0056/2018). TWY is supported by Lee Kong Chian School of Medicine Singapore, Start-up grant. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Dengue is a mosquito-borne disease caused by dengue virus (DENV), where four serotypes can infect humans. Most DENV infections are self-resolving, but in some individuals, severe dengue characterised by a sudden increase in haematocrit, rapid decrease in platelet counts, and vascular leakage is a complication [1,2]. In severe dengue, a major pathogenic mechanism is a transient increase in vascular permeability resulting in severe plasma leakage (herein referred to vascular hyperpermeability) leading to hypotension, circulatory collapse, and organ dysfunction [1]. The precise mechanism in DENV-associated vascular hyperpermeability is unclear, and several hypotheses including antibody-dependent enhancement (ADE) and "cytokine storm" have been proposed. In ADE, suboptimal DENV neutralising antibodies against a heterologous serotype (in secondary infection) promotes DENV uptake into immunological cells, increasing infection and viral replication that can exacerbate the immune response [3]. Similarly, infected monocytes release excessive amounts of proinflammatory cytokines and, if dysregulated, can lead to "cytokine storm" [4]. In this article, we present current understandings on the potential causes of dengue-associated vascular hyperpermeability, which is a consequence of complex interactions between the virus and the host endothelium immune response.

1. Compromised endothelial glycocalyx integrity contributes to vascular hyperpermeability

The endothelial glycocalyx layer (EGL) is a glycosaminoglycan-rich barrier, 0.5 to 5.0 μm thick, which coats the luminal surface of the endothelium, forming a mesh that acts as a macromolecular sieve across cell–cell junctions. This surface matrix is composed of various proteoglycans tethered to the underlying endothelial cell including transmembrane syndecans and glycosaminoglycans such as heparan sulphate (HS), chondroitin sulphate (CS), and hyaluronic acid (HA) (Fig 1A). Together with bound plasma proteins such as albumin, fibrinogen, and orosomucoid, the EGL forms a physiological barrier between the intravascular compartment and the interstitium, and damage and degradation may increase vascular permeability [5,6].

Recent studies suggest that EGL is compromised during dengue. EGL disruption and hyperpermeability was reported in dengue mouse model [7,8], and, using videomicroscopy, the thinning of the sublingual EGL was observed in dengue patients with vascular hyperpermeability [9]. Furthermore, increased blood levels of HA, syndecan-1 and CS in dengue patients were proportional to disease severity, further suggesting that EGL is damaged in