Role of Oxidative and Nitrosative Stress in Dengue Pathogenesis: A Mini-Review

Raimundo Castro-Orozco and Nelson Rafael Alvis-Guzmán

1University of San Buenaventura, University of Cartagena, Cartagena, Colombia
2University of Cartagena, Children’s Hospital Foundation Napoleon Franco Pareja, Cartagena, Colombia

Abstract

Dengue is a mosquito–borne acute viral disease with ubiquitous distribution in tropical and subtropical areas of the world. Dengue virus (DENV) infection is transmitted by the bite of a female Aedes aegypti mosquito (the most important vector) infected with DENV. Clinical presentation of this typical arboviral disease varies along a wide spectrum of clinical symptoms. During the course of DENV infection, some individuals develop severe manifestations related to plasma leakage into tissues caused by increased vascular permeability. The severity of dengue disease may vary considerably according to age, ethnicity, genetic factors, immune status and underlying disease. It may also depend on the co-circulation of DENV serotypes and sequential (secondary) infections with different DENV serotypes. While the exact mechanism of pathogenesis of dengue remains elusive, several lines of evidence demonstrating that DENV infection-derived oxidative stress may trigger the release of proinflammatory cytokines, including TNF-alpha, participating in collective action in dengue disease pathogenesis. In conclusion, we review these findings and discuss about the recent advances that propose a major role of oxidative-nitrosative stress on dengue pathogenesis.

Keywords: Dengue; Dengue virus; Severe dengue; Oxidative stress; Nitrosative stress; Endothelial dysfunction

Introduction

Dengue is a mosquito–borne acute disease with ubiquitous distribution in tropical and subtropical areas of the world. One example of the importance of this viral disease can be seen in the results of a recent multicentric study, which estimates 390 million dengue infections per year (95% credible interval 284-528 million), of which approximately 25% (95% credible interval 67-136 million) manifest clinically (with any severity of disease) [1]. Dengue is caused by Dengue virus (DENV), a single stranded RNA positive-strand virus of the family Flaviviridae. There are four antigenically different serotypes of the virus (DENV-1 to -4) [2,3].

Clinical presentation of this typical arboviral disease varies along a wide spectrum of clinical symptoms. During the course of DENV infection, some individuals develop severe manifestations related to plasma leakage into tissues caused by increased vascular permeability. The severity of dengue disease may vary considerably according to age, ethnicity, genetic factors, immune status and underlying disease. It may also depend on the co-circulation of DENV serotypes and sequential (secondary) infections with different DENV serotypes [4-8]. In this respect, it has been proposed the involvement of DENV infection-derived oxidative stress on the severity of dengue [9].

By definition, oxidative stress is a disturbance in the balance between the production of reactive oxygen species (ROS) and antioxidants defenses in favour of the pro-oxidants [10,11]. A parallel process is nitrosative stress which is defined as an indiscriminate nitrosilation of biological molecules [12]. Under these stress conditions, the activation of several stress-sensitive intracellular signaling pathways have been reported. This activation involves the production of gene products that can lead to cell death and/or pathophysiological conditions [12-15].

Plasma leakage is the most important characteristic and the best indicator of severity in dengue virus infection. The structural basis of altered vascular permeability is more related to endothelial dysfunction that destruction of endothelial cells (ECs) [16-19]. In this regard, Yacoub and coworkers [20] have recently reported association between endothelial dysfunction and dengue severity in children and adults.

Many lines of independent empirical evidence explain the relationship between endothelial dysfunction and oxidative stress [21-31]. Endothelial dysfunction can be defined as the partial or complete loss of balance between vasoconstrictor and vasodilators, growth promoting and inhibiting factors, pro-atherogenic and anti-atherogenic factors, and pro-coagulant and anti-coagulant factors. The earliest manifestation of endothelial dysfunction is impaired endothelium-dependent vasodilatation produced by diminished nitric oxide (NO) bioactivity, mainly due to accelerated NO radical degradation by reactive oxygen species (ROS) [32,33]. Consequently, this free radical and messenger molecule is associated with inflammation and oxidative stress [24,28,30].

Multiple studies have established that oxidative stress as a determinant of vascular homeostasis [34-37], and is involved in the pathogenesis of various infectious diseases, such as chronic hepatitis C [38], Japanese encephalitis [39], leptospirosis [40], respiratory syncytial virus-induced acute lung inflammation [41], malaria [42], chagas cardiomyopathy [43], schistosomiasis [44], sepsis [45], acute herpes simplex virus type 1, measles subacute sclerosing panencephalitis [46], and dengue [47].

For the latter example, Soundravally and coworkers suggest that DENV infection-induced oxidative stress can trigger the release...
of proinflammatory cytokines, including TNF-alpha, participating collectively in pathogenesis of severe dengue [9]. This is consistent with studies indicating that DENV virulent strains have a strong influence on gene expression of a variety of proinflammatory cytokines [48–51].

Nwariaku and coworkers have reported that TNF-mediated junctional dissociation and intercellular gap formation are associated with tyrosine phosphorylation of vascular endothelial cadherin (VE-cadherin) [52]. Interestingly, a growing body of evidence demonstrates increased DENV-infected human ECs permeability in conjunction with a downregulation of VE-cadherin by phosphorylation [52–56].

Additionally, there is evidence that an excess circulating angiopoietin-2 (ang-2) may contribute with endothelial barrier disruption caused by intercellular gap formation and downregulation of VE-cadherin [57]. It is important to note that ang-2 has been associated with transient systemic vascular leak in DENV infection [58,59].

Moreover, Thakur et al., [60] reported elevated levels of vascular endothelial growth factor (VEGF) in adults with severe dengue in comparison with patients with non-severe dengue with and without warning signs. Considering that VEGF induces VE-cadherin tyrosine phosphorylation in ECs [61], it is important note that VEGF induction by NADPH oxidase-derived ROS [62,63], and DENV infection-induced intracellular ROS/RNS production have been reported [64,65]. A related study showed that profile of VEGF upregulated expression was associated with DENV infection in human endothelial cells [66].

These data together provide direct evidence for role of oxidative-nitrosative stress in DENV-induced vascular leakage.

Survey of recent studies suggest important role of oxidative-nitrosative stress in pathogenesis of dengue [67,68]. These evidences shows that oxidative/nitrosative stress may be associated with production of dengue pathogenesis-related protein, increased susceptibility of mice to DENV infection with higher replication, hemorrhage development in experimental animal model, and induction of apoptosis in various human and animal cell lines [67]. Also, changes in plasma levels of reactive nitrogen species (nitric oxide radicals), endogenous antioxidants enzymes, lipid peroxidation and protein oxidation markers has been observed in patients with dengue infection [68].

In this context, we are now executing a study evaluating the potential use of plasma levels of protein carbonyl, lipid hydroperoxides and manganese-dependent superoxide dismutase, as prognostics biomarkers for dengue infection severity in pediatric patients, in order to early identification of patients who risk developing severe dengue, and to focus treatment in these group of patients.

References


