Virulence 4:6, 504–506; August 15, 2013; © 2013 Landes Bioscience

# Special focus
## Endothelial activation/dysfunction

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This *Virulence* special focus highlights the emerging critical role of endothelial activation and dysfunction in the pathogenesis of infectious diseases and associated clinical outcomes. Infectious disease investigators might ask why endothelial biology should be of interest to them. We hope that this special focus will make the research community think otherwise.

The endothelium is comprised of >60 trillion cells lining the surfaces of blood vessels to constitute a total surface area of ~4000 $m^2$, rendering it not only the largest organ in the body but also the organ that links all other organs.[1,2] It represents a massive and essential surveillance organ, equipped with pathogen recognition receptors (PRRs) to recognize pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), that contributes fundamentally to innate immunity and host response.[2] Recent studies highlight the previously under-recognized role of the endothelium as a key innate immune effector cell capable of orchestrating profound pro-inflammatory responses in sepsis and influenza.[2-6] Furthermore, it seems highly likely that endothelial activation/dysfunction will play a central pathogenic role in a number of critical illnesses characterized by systemic inflammation and end-organ dysfunction.[7,8]

Sepsis is a prime example of an infection-related clinical syndrome in which endothelial activation/dysfunction has been recently recognized to play an important mechanistic role in disease pathogenesis. Endothelial activation occurs early in the course of sepsis, and subsequent endothelial dysfunction is now recognized to contribute directly to the morbidity and mortality of sepsis. It has become increasingly clear that impaired microvascular barrier integrity leads to tissue edema, shock, and end-organ dysfunction/injury (e.g., acute respiratory distress syndrome [ARDS] and acute kidney injury [AKI]).[1,7,9] The failure of development and translation of effective treatment strategies of sepsis prompted the Division of Blood Diseases and Resources of the National Heart, Lung and Blood Institute (NHLBI) to convene a workshop involving a multidisciplinary group of experts to address the challenges posed by sepsis and sepsis-induced multi-organ dysfunction/failure in 2010. This group concluded that sepsis represents a syndrome of severe endothelial dysfunction that causes multi-organ failure in response to intravascular or extravascular infection.[10] The participants concluded that sepsis is fundamentally a disease of inflammation-induced endothelial activation/dysfunction and that future sepsis research should focus on the role and regulation of endothelial activation/dysfunction in order to guide development of new therapeutic strategies for treatment of sepsis.

This special focus provides a comprehensive overview of the role and regulation of endothelial activation and dysfunction in the pathogenesis of a number of severe, life-threatening infectious diseases and syndromes, ranging from sepsis to HIV infection. A total of 8 reviews are included in this special focus on endothelial activation/dysfunction in infectious diseases.

The first contribution to this special focus provides an overview of biomarkers of endothelial activation and dysfunction in serious infectious diseases, with an emphasis on their potential diagnostic and/or prognostic utility.[11] Because endothelial activation commonly precedes development of distinct microvascular dysfunction, biomarkers of activated endothelium in serum and/or plasma can often be detected prior to conventionally recognized manifestations of severe disease. Page and Liles discuss the current status of mediators of endothelial cell function (angiopoietins-1 and -2), components of the coagulation pathway (von Willebrand Factor, ADAMTS13, and thrombomodulin), soluble cell-surface adhesion molecules (soluble E-selectin, sICAM-1, and sVCAM-1), and regulators of vascular tone and permeability (VEGF and sFlt-1) as biomarkers in the context of sepsis, *Escherichia coli* O157:H7 infection and hemolytic-uremic syndrome, malaria, and dengue.[11]

The review by Parikh addresses the role of dysregulation of the angiopoietin–Tie-2 axis in the pathogenesis of sepsis and the acute respiratory distress syndrome (ARDS).[12] Regulated changes in microvascular endothelial structure and function play a critical role in inflammation, as a component of the host response to localize infection and eradicate invasive microbial pathogens. This process results in localized microvascular leak that functions to facilitate the recruitment and trafficking of immune effector cells to the site of infection. In sepsis, this "normal", adaptive host response becomes generalized and dysregulated, leading to deleterious complications. ARDS is a major complication of sepsis, associated with a 30–50% mortality, in which pulmonary microvascular leak plays a major mechanistic role. Among the factors that regulate microvascular endothelial function, the angiopoietin-1/2 "system" has received considerable attention from investigators over the past decade. Parikh summarizes the evidence implicating dsyregulation of Tie2, an endothelial tyrosine kinase receptor, and its cognate ligands Ang-1 and -2 in the pathogenesis of sepsis, ARDS, and multiple organ dysfunction syndrome (MODS).[12]

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Submitted: 07/27/2013; Accepted: 07/28/2013
http://dx.doi.org/10.4161/viru.26018

Loss of the endothelium barrier integrity and vascular leakage are recognized as cardinal features of infection by hemorrhagic fever viruses. These pathological effects can be caused directly by viral infection and damage of the vascular endothelium or indirectly by inflammation-induced activation of the endothelium. Spiropoulou and Srikiatkhachorn provide an overview of our current knowledge of the role and regulation of endothelial activation and dysfunction in dengue hemorrhagic fever and hantavirus pulmonary syndrome.[13] Both viruses cause changes in vascular permeability without damaging the endothelium. The authors contend that "understanding the dynamics between viral infection and the dysregulation of the endothelial cell barrier will help us to define potential therapeutic targets for reducing disease severity".[13]

Epidemic and pandemic influenza continue to be important global health threats. Although exaggerated, dysregulated pro-inflammatory host responses (i.e., "cytokine storm") are thought to play key pathogenic roles in the development of severe influenza, Armstrong et al. review recent intriguing evidence implicating endothelial activation, loss of barrier function, and consequent microvascular leak as contributing factors in the pathogenesis of severe influenza.[14] The authors summarize the evidence in support of endothelial activation/dysfunction as a central pathological feature preceding the onset of overt severe influenza. This review also examines the effect of influenza on platelet–endothelial interactions.[14]

Malaria remains a major cause of global morbidity and mortality, especially in individuals who develop cerebral malaria, a condition characterized by sequestration of *Plasmodium falciparum*-infected red blood cells in the brain microcirculation. As discussed by Hawkes et al., accumulating evidence suggests that endothelial activation and dysfunction may contribute mechanistically to the development of cerebral malaria.[15] Based on observations that the clinical presentation of cerebral malaria differs between children and adults, Hawkes et al. hypothesize that postnatal developmental changes, occurring in both endothelial physiological responses response and the neurovascular unit, are responsible for differences in the presentation of cerebral malaria in children and adults.[15]

Shiga toxin-producing *Escherichia coli* infection, with the associated risk of hemolytic-uremic syndrome (HUS), continues be a significant global health problem. Shiga toxin (Stx) is recognized to play a key role in the microangiopathic events underlying the development of HUS. Petruzziello-Pellegrini et al. summarize recent developments in our understanding of the mechanisms of Stx-mediated endothelial dysfunction, including Stx-mediated gene regulation in the absence of protein synthesis inhibition, and discuss new insights into the role of complement activation in HUS.[16] They also review accumulating evidence for detectable serum biomarkers of endothelial activation prior to the onset of frank HUS. The authors conclude that "further investigation of newer therapeutic targets and potential prognostic markers is essential to assess their utility in mitigating disease and/or predicting outcomes and will provide an improved overall understanding of HUS pathogenesis".[16]

In the post-HAART era, non-AIDS defining diseases are recognized as major causes of morbidity and mortality in HIV-infected individuals. In particular, it is increasingly recognized that HIV infection is associated with vascular dysfunction and adverse cardiovascular outcomes. Graham et al. performed a systematic review of the current evidence regarding the clinical utility of endothelial activation and coagulation biomarkers for the prognosis of HIV-infected patients.[17] This review found that "published studies support an association between P-selectin and venous thromboembolism in HIV-infected patients, an association between tissue-type plasminogen activator and death, and associations between D-dimer and several clinical outcomes, including venous thromboembolism, cardiovascular disease, and all-cause mortality".[17] These results indicate that endothelial activation/dysfunction is likely to play a currently underappreciated mechanistic role in HIV-related morbidity and mortality in the post-HAART era. As discussed by Graham et al., large-scale prospective studies are clearly warranted to determine the utility of endothelial activation and coagulation biomarkers for risk stratification and prediction of adverse outcomes in HIV-infected individuals.

To conclude this special focus, Darwish and Liles discuss a number of emerging therapeutic strategies to prevent or limit infection-related microvascular endothelial activation and permeability in an effort to decrease end-organ injury/dysfunction and improve clinical outcome.[18] Specifically, VEGFR2/Src antagonists, sphingosine-1-phosphate agonists, fibrinopeptide $B\beta_{15-42}$, slit2N, secinH3, angiopoietin-1/tie-2 agonists, angiopoietin-2 antagonists, statins, atrial natriuretic peptide, and mesenchymal stromal (stem) cells are discussed in terms of their translational potential for treatment of serious clinical infectious diseases.

We hope that the scientific community will find this special focus interesting, informative and timely. Clearly, endothelial activation and dysfunction play important mechanistic roles in a number of infectious diseases currently associated with high morbidity and/or mortality. Further translational investigation into the role and regulation of endothelial activation/dysfunction in the pathogenesis of infectious diseases has the potential to transform the field and lead to innovative therapeutic strategies to improve patient outcomes.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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