

Between microbial attack and defence: The endothelium as a vulnerable player in infectious diseases

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The majority of death-related pathologies worldwide are related directly or indirectly to infectious diseases, and a large variety of invasive mechanisms by which viruses, bacteria and parasites enter our body and also gain access to the vascular system have been identified. Prominent examples are virus-induced haemorrhagic fevers, bacteraemia followed by septic shock syndrome with systemic activation of coagulation and fibrinolytic factors finally leading to organ failure, as well as parasite-provoked vascular and systemic diseases. However, the role of vascular and lymphatic endothelial cells in infectious diseases remained unnoted and was underestimated for a long time. Only within the past decade has the central role of the endothelium in pathogen spreading and infectious diseases been fully appreciated. Its contribution to the body defence machinery is further reflected by the bulk of publications on this topic which have appeared in recent years.

The endothelium as cellular lining of all blood and lymphatic vessels normally provides an effective protective barrier of the underlying tissues against external stressors. Yet, microbes have evolved numerous strategies to specifically target endothelial cells and to overcome the natural body defence systems thereby gaining access to various extracellular and intracellular host sites to start the infection process by virtue of multiple "molecular tricks" (1).

From 2002–2008 the German Research Council (Deutsche Forschungsgemeinschaft, DFG) funded the Priority Program 1130 "Infections of the Endothelium", and a consortium of more than 15 research groups has focussed scientific activities on this exciting and important topic of microbe-host interactions aiming to characterise and decipher mechanisms of invasion, colonisation and infection of endothelial cells by diverse pathogens. Based on the success of the previously published collections of articles and concise reviews in *Thrombosis and Haemostasis* covering this topic in 2005 (volume 94/2) and 2007 (volume 98/3), we felt it was necessary to provide an update of developments in the field by inviting project leaders of the Priority Program and other experts to report on their favourite research themes. Results from this endeavour were presented in August

2009 at the first symposium on "Infections of the Endothelium" in Dresden (Germany) in conjunction with the final meeting of the homonymous Priority Program of the DFG.

The contributions in this issue of *Thrombosis and Haemostasis* address particular invasion mechanisms, pathogen survival strategies, as well as futile host defence reactions. The subsequent developments of diseases reflect the broad spectrum of pathogen-related targeting mechanisms and the as yet hardly manageable situations in infection medicine. In addition, new technologies and analytical methods as well as certain therapeutic issues in infectious diseases with particular emphasis on the vascular system are covered.

Virus entry and vascular pathogenesis

Nipah virus constitutes a recently discovered pathogenic paramyxovirus with high zoonotic potential that causes encephalitis in humans and respiratory tract diseases in animal hosts. Andrea Maisner et al. (2) describe new developments in the endothelial tropism of the virus involving ephrin receptors, generally causing a pronounced vasculitis in the microcirculation followed by necrosis and inflammatory cell infiltration. Whether the identified new mechanism of virus entry and uptake may bear any potential for antiviral therapies is subject to future research.

Arena viruses and new world arena viruses cause emerging human viral haemorrhagic fever, and clinical and experimental studies indicate that the endothelium is critically involved in the pathogenesis. Stefan Kunz (3) summarises the current concept that endothelial cell structure and function is directly or indirectly modulated by certain Arena viruses. This includes expression of cell adhesion molecules, induction of coagulation and release of vasoactive mediators as well as productive viral replication.

Hantaviruses belong to the family of Bunjviridae and cause a haemorrhagic fever with renal syndromes and the "Hantavirus Pulmonary Syndrome" in humans. Erich Mackow and Irina Gavrilovskaya (4) address currently proposed pathogenetic mechan-

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Received: November 9, 2009
Accepted: November 9, 2009

Republished online: November 13, 2009
doi:10.1160/TH09-11-0760

isms leading to insufficient endothelial cell function during Hanta virus infection, whereby loss of barrier function appears to be a hallmark for the pathogenesis particularly in the lung. Pulmonary oedemas are likely to originate from multiple mechanisms, including virus cell tropism, platelet deposition as well as inadequate gas exchange and nutritional insufficiency.

Severe forms of Dengue virus infections cause haemorrhagic fever, which mostly develops after a secondary exposure to Dengue virus. Anon Srikiatkachorn (5) discusses which serotype cross-reactive Dengue-specific T-cells might play a critical role together with angiogenic factors in the development of fever-associated symptoms, such as bleeding and plasma leakage. Further insights into the pathomechanism, involving virus-provoked gene transcription in endothelial cells, may provide a solid basis for the development of prophylactic and therapeutic regimen.

Measle virus infections are a human disease that is transmitted predominantly by aerosols, whereby viruses need to pass epithelial and endothelial cell layers. Martin Ludlow et al. (6) refer to a possible transmission mechanism by which viruses particles infect immune and epithelial cells via the "signalling lymphocytic activation molecule" (SLAM, CD150). Thus, virus dissemination is accomplished by the same host factor on infected leukocytes as well as on epithelial and endothelial cells, where transfer can occur via adjacent cell junctions.

Endothelial cells appear to be central in the dissemination of human cytomegalovirus because they support productive replication and thus contribute to haematogenous spread as reported by Barbara Adler and Christian Sinzger (7). Endothelial cell entry critically depends on a complex between virus envelope proteins and host cell components, and due to an angiogenic response, the virus may even promote growth of its own habitat. Based on the development of a new animal model, the pathogenetic mechanisms may become deciphered in the near future.

Bacterial interactions leading to extra- and intracellular host responses

The pathogen *Chlamydia pneumonia* has evolved several strategies for infected host cell survival to ensure its own intracellular reproduction. Although strong correlations between bacterial infection and atherogenesis have already been documented that are exemplified by reprogramming the host cell metabolism with the development of proinflammatory and proliferative responses, any underlying mechanistic insights are still pending. Jan M. Kern et al. (8) present new data on bacteria-provoked modification of endothelin-1-related signalling pathways which may provide explanations for the mitogenic and inflammatory responses observed in infected vascular cells. The vascular endothelium is also the main target of arthropod-transmitted *Rickettsiae*, whose life-cycle in host cells is obligatory, and which cause different types of spotted fever and typhus. Gustavo Valbuena and David H. Walker (9) review the current knowledge about *Rickettsiae*-induced diseases with emphasis on the particular role and cellular responses of the endothelium.

Enterohaemorrhagic *Escherichia coli* cause "Haemolytic Uraemic Syndrome" (HUS), associated with thrombotic micro-

angiopathy due to endothelial cell injury within the renal glomeruli. Martina Bielaszewska et al. (10) describe the molecular characterisation of a bacteria-specific vacuolating cytotoxin, a secreted non-serine protease polypeptide that appears to be causative in the development of HUS.

Parasite interactions with the vascular system

In the progress of cerebral malaria the pathogen *Plasmodium falciparum* provokes destruction of red blood cells, leukocytes and platelets, and the disturbed interactions between platelets and endothelial cells may cause additional procoagulant events leading to multifocal capillary obstruction. Dorothee Faille et al. (11) provide evidence for the role of disturbed platelets as effectors of endothelial cell damage in cerebral malaria that might be instructive for deciphering new approaches in disease treatment.

Antimicrobial and immunoregulatory mechanisms

As an immediate response following exposure towards infectious agents derived from bacteria and viruses, endothelial cells recognise the "pathogen-associated molecular patterns" (PAMP) by "pattern recognition receptors" (PRR) and produce inflammatory mediators as well as express diverse cell surface proteins. The signalling properties of PRR, including Toll-like, NOD-like and RIG-I-like receptors, are depicted by Bastian Opitz et al. (12) with regard to their complementary role in innate immunity by inducing multiple gene expression and post-translational modifications to defend e.g. sepsis and vascular diseases. A major defence response in this regard is the production of interferon- γ that gives rise to further downstream signalling events to cope with infection. In addition, Walter Däubener et al. (13) report on the immunoregulatory activities of interferon- γ -dependent effector molecules such as inducible NO-synthase and indoleamine-2,3-dioxygenase in endothelial cells that appear to also play a role in modulating immunological responses related to tumour and transplant biology.

New technologies and systems biology

The complex analysis of the large genomes of herpesviruses, in particular herpesvirus-8 as causative agent of endothelial cell-derived Kaposi's sarcoma, bears a number of challenges and pitfalls that are described in the article by Andreas Konrad et al. (14). The adaptation of host cellular functions during viral replication is reported with regard to the use of systems biology and reverse genetics approaches. Difficulties in the transfer of genetic information and stable expression of transfected genes in primary and other endothelial cell types have been overcome by the use of viral vectors, originally designed for gene therapy. In the final paper by Dirk Lindemann and Hans Schnittler (15), principles and versatile applications of retro- and adenoviral vector systems are presented that allow to safely and efficiently deliver transgenic information into different types of endothelial cells.

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