Vascular endothelium and infectious diseases: Trick and treat

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In the past, infectious diseases caused by viruses, bacteria and parasites were shown to be associated with functional and structural disturbances of the cardiovascular system particularly involving the endothelium. This includes, for example, acute haemorrhagic fevers caused by Ebola and Lassa viruses, inflammatory diseases of the central nervous system via meningococci, staphylococci, pneumococci, or infections of the gut via enterohaemorrhagic Escherichia coli. Chronic degenerative diseases such as atherosclerosis have also been suggested to be associated with infections by human cytomegalic virus or the bacterial pathogen Chlamydia pneumoniae. In contrast to these degenerative disease situations, the development of vascular tumors can be initiated by human immunodeficiency virus (HIV) leading to the Kaposi Sarcoma, or by Bartonella henselae, a bacterium first discovered in 1992, that causes a bacillary angiomatosis. Due to its strategic location within the vascular tree and its accessibility via tissue injury, the vascular endothelium in particular is a central target for pathogen adherence, spread and replication, and numerous bacterial mechanisms to circumvent or knock-down the defense mechanisms of the host have been described (1). Furthermore, inflammatory mediators play a critical role in infectious diseases as well, due to their indirect effects on endothelial cells in a local or systemic manner.

While in the past the molecular analyses of particular pathogens have led to a tremendous growth in our knowledge on bacterial interactions with hosts cells, the respective cause-consequence relations of infections of the endothelium are largely unknown and remain a mystery. The funding of a Priority Program, entitled "Infection of the Endothelium", by the German Research Council (DFG), which began in 2002, reflects the need for vigorous biomedical research in this field. To account for this important topic, "Thrombosis and Haemostasis" has initiated the present theme issue under the title "Vascular Endothelium and Infectious Diseases". A collection of review articles and original contributions has been selected addressing in particular novel molecular aspects, invasion mechanisms, laboratory techniques and therapeutic issues in infectious diseases with particular emphasis on the vascular system.

The first part of the theme issue contains review articles related to virus-endothelium cross-talks and starts with Ebola viruses that cause the most severe haemorrhagic fever in humans and primates and are treated as potential bio-terrorism agents. A recently developed approach, the "reverse genetic system" allows investigation of the biology and pathogenesis of the causative viral agents at the sub-molecular level. Hideki Ebihara and colleagues (2) discuss this system in relation to viral haemorrhagic fever agents for uncovering virulence determinants, host interactions and vaccine development. Lisa Hensley and Thomas Geisbert focus on the role of endothelial cells for the development of coagulation disorders that are characteristic in Ebola virus haemorrhagic fever in non-human primates (3). Hans Dieter Klenk gives an overview about the interactions between the highly pathogenic avian influenza viruses with endothelial cells (4). These viruses not only cause devastating "bird flu" outbreaks in domestic fowl, but occasionally are also the cause of human disease with a high mortality rate. Molecular mechanisms of viral replication in endothelial cells and the background of endothelial tropism are dealt with as well.

In the second part, the central topic of this theme issue is devoted to interactions between bacteria and endothelial cells. Systemic infection by Staphylococcus aureus causes severe diseases such as endocarditis, abscess formation in visceral organs and the central nervous system that might lead to septic thrombophlebitis or general sepsis with still a high mortality rate. Bhanu Sinha and Mathias Herrmann address the quite complicated invasion strategy of S. aureus in endothelial cells and discuss the cellular consequences following bacterial invasion, such as apoptosis (5). The subsequent review by Trian Chavakis and colleagues deals with the role of soluble factors released by S. aureus, coined as "secretable expanded repertoire adhesion molecules" (SERAM) (6), that provide multiple facets of the bacterial box of tricks to escape and/or survive the host defense machinery and to allow vascular tropism of bacteria. Two of these proteins, the "extracellular fibrinogen binding protein" and the "extracellular matrix binding protein", seem to be associated with vascular diseases after S. aureus infections, and have an impact on immunomodulation. Another member of this class, S. aureus fibrinogen binding protein "clumping factor A" may weaken or disrupt the function of the host clotting protein as outlined in the article by Chao-Zong Liu and colleagues (7), thereby enabling the bacterium to gain access to host tissues.

Streptococcus pneumoniae is another pathogen that causes infection of endothelial cells at different vascular locations in the body. Although being part of the human nasopharyngeal flora,
the bacterium has a widely ranging pathogenic potential. Under certain circumstances, humans in particular suffer from infections by *S. pneumoniae* causing pneumonia, arthritis, meningitis, otitis and, in severe cases, bacterial sepsis. By haematogenous spreading *S. pneumoniae* gains access to their primary cellular target, the vascular endothelium. Philippe Dje N’Guessan and coworkers document that infection of endothelial cells by *S. pneumoniae* can cause cellular apoptosis, and the authors present supporting evidence for the underlying signaling pathways (8). The pathogenic invasive potential of *S. pneumoniae* further depends on its ability to degrade extracellular matrix. The original contribution by Simone Bergmann and coworkers provides structural data on the plasminogen-binding motif of *S. pneumoniae* enolase as an essential cofactor in plasmin-mediated degradation of extracellular matrix material and fibrin (9). This discovery might facilitate bacterial spreading through tissues and out of thrombi and may guide the search for new anti-microbial drugs.

Vascular damage in enterohaemorrhagic *E. coli* (EHEC) infections causing a haemorrhagic colitis and the haemolytic uraemic syndrome (HUS) is largely mediated by shiga toxins. However, shiga toxin-negative strains also cause diseases with comparable severity. Martina Bielaszewska and Helge Karch address the contribution of the vascular wall in EHEC infections (10). *Chlamydia pneumoniae* is a facultative intracellular bacterium that is involved in a variety of diseases, partly due to different infection strategies of the bacterium. Mathias Krüll and colleagues summarize the current knowledge about *Chlamydia pneumoniae* infection and discuss this in relation to vascular disease (11), with particular emphasis on the multiple activation pathways of the target cell at the molecular level. Although the contribution of *C. pneumoniae* in atherogenesis is still discussed controversy, Hanna Kälvegren and coworkers provide evidence for the participation of the bacterium in NO-dependent mechanisms and immune-regulation during infections of the CNS (14). The final original contribution in this theme issue stems from Michaela Dehio and colleagues who analyze the transcriptional activation of human umbilical vein endothelial cells by *Bartonella henselae* in a gene array (15). The authors found certain genes that are involved in controlling cell proliferation and innate immune responses. This contribution is an instructive example of how gene arrays might quickly and sufficiently contribute to the identification of target genes that are important in endothelial cell infections.

In conclusion, the present theme issue addresses novel aspects, methods and findings on the role of vascular endothelial cells in infectious diseases. Future studies will without doubt also include the lymphatic endothelium as a target in bacterial and viral infection strategies and may thereby shed light on the detailed molecular mechanisms thereof. Furthermore, a hitherto not addressed aspect is the termination of infectious diseases by (therapeutically) interfering with functional activities of the vascular endothelium. Finally, many of the bacterial weapons utilized to invade the body or to escape defense mechanisms of the host can be trimmed into useful therapeutic strategies for different vascular diseases, once the underlying mechanisms have been deciphered. Here, we can certainly learn from the many bacterial tricks and can introduce new therapeutic modalities to treat.

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