

# Thrombotic microangiopathies as a prime example for translational medicine

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**T**hrombotic microangiopathies (TMA) represent common thrombotic disorders that affect small microvessels but manifest in different organs. In haemolytic uraemic syndrome (HUS) the kidneys are affected, and in thrombotic thrombocytopenic purpura (TTP) the disease establishes at neurological sites. Research in the field of TMA is moving fast towards an understanding of the underlying mechanisms and has seen a dramatic development in this regard over the last decade.

TMA also represent a prime example of translational medicine. This group of disorders has moved from the outskirts of rare, almost neglected diseases to the centre stage in clinical medicine. During the last few years, this field has profited from the close interaction and exchange between basic researchers and clinicians, which has ultimately improved the situation of patients. Furthermore, the lessons learned from these rare disorders have substantially shaped the understanding in the pathogenesis of more common diseases. Very similar genetic causes and related disease mechanisms are observed for the rare, renal disease HUS and for the frequent, retinal disorder age-related macular degeneration (AMD). Thus, research on rare disorders can pave the ground for understanding the disease mechanisms of common disorders, which then allows the use of similar or related diagnostic and therapeutic approaches.

This theme issue of *Thrombosis and Haemostasis* covers central and timely topics which were presented at the 3<sup>rd</sup> **International Workshop on Thrombotic Microangiopathies**, held in Jena in October 2007, and the contributions represent “state of the art” presentations in this field. The articles document how fast results from basic and genetic research can be translated into the clinic leading to an eventual improvement of the situation of patients. Both reliable diagnostic tests and novel therapeutic options are now established.

The article by Skerka et al. (1) describes a novel subform of HUS, termed DEAP HUS (**D**eficient for CFHR1 and CFHR3 and **A**utoantibodies **P**ositive). This form is characterized by the combination of a genetic defect (deficiency of a 84 kbp long chromosomal fragment in the Factor H gene cluster) and the

presence of autoantibodies to the complement regulator Factor H. DEAP-HUS can be directly diagnosed by assaying plasma parameters and autoantibody levels and has a very good prognosis for therapy. The article by Bresin et al. (2) summarizes the promising results of a therapy with the monoclonal antibody rituximab for TTP patients who developed autoantibodies against ADAMTS13, the protease responsible for cleavage of von Willebrand factor (VWF). In addition, during inflammatory conditions the plasma levels of both, VWF and ADAMTS13, vary and the exact protein levels provide a good and reliable marker for prognosis of organ failure, as reported by Claus et al. (3). These data clearly demonstrate that gene products, which are associated with HUS and TTP, play a central role in tissue and cell homeostasis. In addition, the indicated proteins not only represent relevant markers for inflammation but they are also likely associated with other thrombotic disorders.

Although several genetic causes for HUS and TTP have been identified, the initial trigger(s) that lead to a change in tissue homeostasis are still not clearly understood. A wide range of conditions can initiate morphological and cellular changes, as indicated by Gerth et al. (4), who give a detailed report on a case of a pregnancy-associated form of TTP. Additional common triggers for HUS are infections with Shiga toxin-producing *Escherichia coli*. The paper by Müthing et al. (5) reviews the current concepts on the mode of action and the translocation of Shiga toxin across the membrane of the host cell to the cytosol, where this bacterial virulence factor exerts its toxic activity.

Recent evidence further supports the hypothesis that TMA and the renal disease membrano-proliferative glomerulonephritis (MPGN) represent different outcomes of related genetic deficiencies. Consequently, the pathological aspects that are essential for a proper diagnosis particularly from tissue specimen are relevant. Such morphological signatures and changes leading to one of the subforms of the disease are summarized in the article by Benz and Amann (6). The authors present the relevant pathological issues that need to be addressed for proper diagnosis. The current discussion on a reclassification of the various forms of mem-

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brano-proliferative glomerular disorders, which may represent a spectrum of different but related diseases, is presented in the contribution by Licht and Fremeaux-Bacchi (7). These authors summarize the evidence obtained from animal models and from clinical studies, which show that the alternative complement pathway plays an essential role in the pathogenesis of renal damage. Future developments will be highly relevant for understanding the dysfunction of alternative pathway complement activation, which likely is also relevant for other thrombotic diseases as well.

This series of articles provides an in depth overview on current, burning issues in the field of TMA. On the one hand these manuscripts show how results from basic research on disease mechanisms can immediately be translated into the clinic to improve both diagnosis and therapy, and on the other hand, the detailed understanding of the underlying disease mechanisms help to highlight the open issues that need to be addressed in the future.

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