Editorial

Translational Research in Thrombosis and Haemostasis

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Disorders of the haemostatic system have an impact on essentially every clinical discipline and display an increasing prevalence with demographic, environmental and life style changes in populations worldwide. While the introduction of target-specific direct oral anticoagulants has markedly altered clinical practice in antithrombotic therapy over the last decade, similar major transformations can be expected from the introduction of new haemostatic agents in haemophilia care. However, many basic questions remain on how to accurately diagnose haemostatic impairments and antithrombotic efficacy for improved individualized therapies in acute and chronic thromboembolic diseases.

The Center for Thrombosis and Hemostasis (CTH) in Mainz was founded with substantial funding from the Federal Ministry for Education and Technology (BMBF) some 10 years ago to create a dedicated translational research environment suitable to train the next generation of researchers. The opportunity for defining timely current and future directions of research in our field brought together basic researchers and physician-scientists who built up and developed a novel translational research structure at a German university medical centre. The research spectrum assembled at the CTH ranges from basic research on fundamental mechanisms of thrombosis initiation and cross-disciplinary relevance of the haemostatic system to translational proof-of-principle studies in animal models and in relevant patient cohorts, on to large epidemiological trials and guideline-relevant clinical research. The selected reviews in this theme issue were written by junior investigators and physician-scientists at the CTH. The current contributions reflect not only the success in supporting career development,[1] but also identify areas of research with open questions and challenges in the field for the years to come.

A key objective at the CTH is the structural and thematic integration of basic, translational and clinical research. New research directions in the prevention, diagnosis[2] and treatment of thromboembolic diseases are one of the prototypic areas for cross-fertilization between basic and clinical scientists. Barco and Konstantinides[3] discuss evolving concepts of risk-adapted management of acute thromboembolic diseases as one example where improvements in diagnosis and therapeutic management will ultimately allow for tailored therapies. Despite this progress, the impact of risk-stratified anticoagulant intervention on the chronic complications of acute thromboembolic events remains largely unexplored. Complementing the clinical research, Bochenek and Schäfer[4] review experimental progress to better define the role of the endothelium in initiating thrombosis and the pivotal transition from acute to chronic thrombosis. Clinical biomarker discovery in the on-going FOCUS study[3] combined with early translational research has the potential to break new ground in these currently difficult to predict late-stage complications of thromboembolic diseases, including chronic thromboembolic pulmonary hypertension.

Acute and chronic thromboembolic events are fine-tuned by platelet signalling responses.[5] Jurk and Walter[6] describe the advances in platelet proteomics that allow the molecular definition of molecular targets for activating and inhibitory signals in platelets. Such unbiased approaches identifying novel targets in platelet signalling networks will yield crucial new information relevant for the diagnosis of not only thrombophilia but also hereditary and acquired bleeding disorders. The challenges and opportunities to integrate platelet research in large epidemiological studies are discussed by Panova-Noeva et al.[7] Progress made so far indicates that large-scale biodatabases integrating clinical, molecular and genomic information can be linked to platelet function analysis for understanding disease processes and risk assessment in vascular, metabolic and thrombotic disorders.

Other cornerstones of the CTH research focus are the intimate links between thrombotic processes, inflammation, and immunity[8] that may involve neuroendocrine cross-talks.[9] While immuno-thrombosis is central to innate immunity and thrombotic events frequently cause inflammation, the concept is evolving that signalling of the extrinsic coagulation pathway through protease-activated receptors (PARs) connects coagulation with the immune system in a variety of chronic diseases from cancer to atherosclerosis and obesity.[10]

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Madhusudhan and Ruf[11] discuss the link of PARs and insulin signalling in the context of metabolic diseases. Specifically, the authors review the lessons learned from animal models. It is also clear that obesity is a complex disease that not only depends on inflammation and genetic risk modifiers but also on other environmental factors contributing to major cardiovascular complications in the context of excess nutrient uptake. Reinhardt[12] describes the emerging pathways by which the microbiome influences immune homeostasis in the gut and causes prothrombotic alterations in the vascular and haemostatic system. These initial insights uncovered additional thrombosis risk factors that will require evaluation in future clinical translational studies.

In the absence of overt thrombosis, thrombotic circuits induce vascular inflammation.[13] Karbach et al[14] discuss the connections between the coagulation system and atherosclerosis, atherothrombosis and inflammation. Moreover, the authors provide a review on how multicellular interactions in the haemostatic system and cytokine networks are linked to vascular inflammation and hypertension. Lackner and Müller-Calleja[15] discuss the cellular events by which antiphospholipid antibodies cause inflammation and review the preclinical evidence that relates antigen specificity to diseases processes. This dissection of the clinical spectrum of antiphospholipid antibody reactivities and the uncovered pathways through which these antibodies trigger thrombosis suggests that the antiphospholipid syndrome is another example of a thrombo-inflammatory disease.

The complex interactions of the haemostatic system in cardiovascular diseases, acute and chronic inflammation, and cancer will increasingly require integrated approaches in translational research in our field. Broader applications of oral anticoagulants in cancer patients, the effects of new bypassing agents on the functions of coagulation and platelets beyond haemostasis and the management of complex bleeding disorders in intensive care settings illustrate important areas for future integrated research in translational centres.

Conflict of Interest
None.

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