

Theme Issue Editorial

Cutting edge research for novel therapies of heart and lung diseases

Thomas Braun¹; Klaus T. Preissner²¹Max-Planck-Institute for Heart and Lung Research (WG Kerckhoff-Institute), Bad Nauheim, Germany; ²Department Biochemistry, Medical School, Justus-Liebig-Universität, Giessen, Germany

The contributions collected in this issue of *Thrombosis and Haemostasis* stem from invited lectures of the first international symposium of the excellence cluster “Cardio-Pulmonary System” (ECCPS), held in 2008 in Bad Nauheim, Germany. Founded in 2006, the ECCPS constitutes an outstanding regional biomedical research network and is based on a firmly established and internationally renowned expertise in cardio-pulmonary research of the Universities of Giessen and Frankfurt and the Max-Planck-Institute in Bad Nauheim. The interdisciplinary work of this “research triangle” is focused on basic research as well as the treatment of heart and lung diseases, which in this combination of direct translation of scientific results into new therapeutic concepts appears to be unique on the international level.

Against the background of heart and lung diseases being the leading causes of death and representing the highest socio-economic burden of diseases worldwide, the work of the ECCPS assumes social as well as political importance. With the objective of combining basic research with clinical practice, the ECCPS supports the integration of different research areas from developmental biology to molecular biology and cellular physiology. The following research areas involving various disciplines are addressed in a concerted effort of all ECCPS locations using high calibre technologies *in vitro* and *in vivo*:

(a) Role of stem/progenitor cells in development and repair of the cardiopulmonary system; employment of stem cells for new treatment strategies. (b) Tailoring of anti-and reverse remodeling strategies for restoration of vascular structural and lung functional integrity. (c) Deciphering of key molecular/cellular players in heart and lung vessel generation and alveolar morphogenesis, identification of targets for the induction of angio- and alveogenesis. (d) Decoding pathogenetic pathways involved in lung and heart fibrogenesis, development of new strategies for inhibition and reversal of excessive matrix deposition. (e) Analysis of hypoxia-, ischaemia- and reactive oxygen species-linked pathologies in heart and lung disease; design of specific inter-

vention strategies. (f) Protection and restoration of endo- and epithelial barrier properties in the cardio-pulmonary system, including control of inflammation and maintenance of host defense. (g) Molecular pathogenesis of the vascular abnormalities in metabolic syndrome. (h) Elucidation of the molecular changes underlying aging of the cardio-pulmonary system. (i) Employment of transcriptome-, proteome and *in-vivo* molecular imaging-based signature analysis towards the individualization of therapy in cardio-pulmonary diseases.

Research in these areas is strongly supported by focusing on techniques and technology development, translation of basic science into clinical studies and commercial exploitation and education as well as training fellowships. Among these activities the first international ECCPS symposium was organised in 2008 to foster fruitful exchange between all members of the consortium and outside experts as well as to advance junior researchers and promote collaborative research projects.

Tissue injury, degeneration and repair

The response of tissues to injury has long been believed to depend on the activation of resident fibroblasts that proliferate and express constituents of the extracellular matrix. In their article Keely et al. (1) challenge this classical view. Evidence is presented that circulating fibrocytes (from bone marrow-derived progenitor cells) home and extravasate into sites of tissue injury, differentiate into fibroblasts/myofibroblasts, and contribute to the generation of extracellular matrix during fibroproliferation. Circulating fibrocytes were first described in 1994 as a circulating fibroblast progenitor population producing collagen and expressing the stem cell marker CD34. The phrase “fibrocyte” combines the terms “fibroblast” and “leukocyte” to highlight the unique biological properties of this cell type. The authors review the bone marrow origin of fibrocytes, their differentiation and trafficking, and describe the involvement of fibrocytes in diseases of the lung, heart, and vasculature. Particular emphasis is

Correspondence to:
Klaus T. Preissner, PhD
Institute for Biochemistry
Medical Faculty, Justus Liebig University
Friedrichstr. 24, 35392 Giessen, Germany
Tel.: +49 641 9947 550, Fax: +49 641 9957 509
E-mail: thrombosis@biochemie.med.uni-giessen.de

Prepublished online: March 11, 2009
doi:10.1160/TH09-03-0153

given to the potential role of fibrocytes in physiologic and pathologic remodeling and repair processes. The authors propose that manipulation of fibrocytes might offer an attractive tool to control fibrosis in various disease states.

The article by Hecquet and Malik (2) summarises recent findings on the role of “transient receptor potential/melastatin-2” (TRPM2) in vascular endothelial dysfunctions. TRPM2 is a voltage-independent, calcium-permeable non-selective cation channel that confers susceptibility to cell death through the activation of caspases and poly-ADP-ribose polymerase. The channel acts as an endogenous redox sensor for mediating oxidative stress/ROS-induced Ca^{2+} entry and the subsequent specific Ca^{2+} -dependent cellular reactions such as endothelial hyper-permeability and apoptosis. It seems likely that TRPM2 integrates various signals since oxidant-induced activation of TRPM2 is modulated by protein kinase C α and phospho-tyrosine phosphates L1. The authors postulate that manipulation of TRPM2 function in the endothelium might become a useful therapeutic strategy for the treatment of endothelial barrier dysfunction and vascular inflammation.

Cardio-degenerative and -protective processes

While different therapies for acute coronary artery occlusion include timely myocardial reperfusion using either primary percutaneous coronary intervention (PCI) or thrombolytic therapy, the full benefits of myocardial reperfusion are not realised, since the actual process of reperfusing ischaemic myocardium can independently induce cell death (ischaemia-reperfusion injury). Experimental studies demonstrated that “ischaemic post-conditioning” as a phased form of myocardial reperfusion represents an innovative treatment strategy for limiting lethal injury and further reducing myocardial infarct size for those patients undergoing primary PCI. Two articles by Hausenloy (3) and Garcia-Dorado et al. (4) elude to the molecular mechanisms underlying reperfusion injury and ischaemic post-conditioning with particular emphasis on the activation of different receptor systems and intracellular signaling pathways, including the reperfusion injury salvage kinase and the cyclic GMP pathway, respectively, that appear to converge on the mitochondria, especially involving the mitochondrial permeability transition pore. Furthermore, hypercontraction, cytoskeletal fragility, and gap junction-mediated propagation of cell death, as well as alterations in non-cardiomyocyte cells contribute to the disease situation. The identification of the underlying molecular mechanisms can open up the possibility of discovering new pharmacological targets for cardioprotection in the context of interventional procedures such as ischaemic post-conditioning. In particular, cyclic GMP favorably modulates these mechanisms, mainly through protein kinase G-mediated actions, and stimulation of cGMP synthesis during initial reperfusion by means of natriuretic peptides has been found protective in different animal models and in patients.

Based on the classical findings that antibodies directed against G-protein coupled receptors (GPCR) can act as allosteric receptor agonists or antagonists, respectively, and are associated with e.g. “Graves disease” (thyroid gland) or “Myasthenia gravis” as prototype for antagonistic autoimmune actions in neuromuscular junctions, Dragun et al. (5) report in their review on

such modulators of various cardiovascular and renal pathologies. In particular, recent developments are presented, regarding the antibody-mediated targeting of the α -adrenergic and β -adrenergic receptors as well as the angiotensin II type-1 receptor. While auto-antibodies against both adrenergic receptor types in patients were associated with severe cases of hypertension or cardiomyopathies, respectively, the occurrence of auto-antibodies against the angiotensin II type-1 receptor was apparent in pre-eclamptic patients. It is not clear, however, whether auto-antibodies against GPCR represent a primary mechanism inducing target cell damage or may arise secondary to the pre-existing tissue injury or viral infection. Interestingly enough, evidence for molecular mimicry is provided for generation of such disease-related auto-antibodies, since the involvement of *Trypanosoma cruzi* infection or the presence of Parvovirus B19-specific antibodies has been implicated in cardiomyopathies or in pre-eclamptic women, respectively. Although animal models provided proof for the proposed causal pathogenetic relations between generation and function of these auto-antibodies in disease, further studies with well defined patient cohorts and the analysis of valid biomarkers are required to expand our current knowledge of associative relationships and clinical observational studies.

Inflammation and fibrosis

A crucial event in host defense mechanisms in innate immunity is the multi-step process of leukocyte recruitment to sites of infection/inflammation, involving trans-endothelial migration of mobile cells by a well-orchestrated process of adhesive cell-cell interactions. These adhesive contacts are classically mediated by selectins, integrins and their ligands on the endothelium that mediate rolling, firm adhesion and diapedesis of leukocytes in a spatiotemporal manner. Cellular signalling mechanisms are operative to control both heterotypic cell-cell contact and leukocyte chemotaxis, whereby certain adapter proteins that interact with endothelial adhesion molecules are pivotal in receptor clustering, cytoskeletal dynamics and recruitment of regulatory intracellular enzymes. In their review, van Buul and Hordijk (6) in this regard promote filamin and cactin as essential molecular adapters, which are not only required for establishment of the cell-to-cell adhesion machinery but also for the proper coordination with various downstream signalling pathways. Yet, the molecular mechanisms governing flexibility and variability of adapter protein interactions together with their intracellular binding partners that determine the making and breaking of cellular contacts are hardly understood.

The final contribution in this series aims to decipher the role of fibrinolytic proteases, inhibitors and their receptors in the pathogenesis of chronic kidney disease, a major sequelae in nephropathic patients. Their kidney function progressively deteriorates due to inflammatory and fibrotic processes that damage nephrons. In his review, Eddy (7) presents experimental evidence from animal models and patients that plasminogen activator inhibitor-1 (PAI-1) serves a potent fibrosis-promoting function not only due to its protease-inhibiting activity, but probably also based on its interference with cell adhesive functions, as indicated for interstitial lung disease as well (8). Unlike in



Participants of the ECCPS Congress 2008 in Bad Nauheim, Germany.

lung fibrosis, neither urokinase deficiency in mice nor administration of the protease did alter experimental renal fibrosis (9), indicative of a cell-specific role of this protease and/or its receptor. The pro-fibrotic role of PAI-1 is further provoked by its cell proliferative functions in association with e.g. the low-density li-

poprotein receptor-associated protein-1. Thus, molecular pathways activated by serine proteases and their inhibitor, PAI-1, may provide promising targets for future anti-fibrotic therapeutic agents not only in kidney and lung diseases.

References

1. Keeley EC, Mehrad B, Strieter RM. The role of circulating mesenchymal progenitor cells (fibrocytes) in the pathogenesis of fibrotic disorders. *Thromb Haemost* 2009; 101: 613-618.
2. Hecquet CM, Malik AB. Role of H2O2-activated TRPM2 calcium channel in oxidant-induced endothelial injury. *Thromb Haemost* 2009; 101: 619-625.
3. Hausenloy DJ. Signalling pathways in ischaemic postconditioning. *Thromb Haemost* 2009; 101: 626-634.
4. Garcia-Dorado D, Agulló L, Sartorio CL, Ruiz-Meana M. Myocardial protection against reperfusion injury: The cGMP pathway. *Thromb Haemost* 2009; 101: 635-642.
5. Dragun D, Philippe A, Catar R, Hegner B. Autoimmune mediated G-protein receptor activation in cardiovascular and renal pathologies. *Thromb Haemost* 2009; 101: 643-648.
6. van Buul JD, Hordijk PL. Endothelial adapter proteins in leukocyte transmigration. *Thromb Haemost* 2009; 101: 649-655.
7. Eddy AA. Fibrinolytic serine proteases, inhibitors and receptors in renal fibrosis. *Thromb Haemost* 2009; 101: 656-664.
8. Wygrecka M, Jablonska E, Guenther A, Preissner KT, Markart P. Current view on alveolar coagulation and fibrinolysis in acute inflammatory and chronic interstitial lung diseases. *Thromb Haemost*. 2008; 99: 494-501.
9. Ruppert C, Markart P, Schmidt R, Grimminger F, Seeger W, Lehr CM, Günther A. Chemical crosslinking of urokinase to pulmonary surfactant protein B for targeting alveolar fibrin. *Thromb Haemost* 2003; 89: 53-64.