Vessel wall – where coagulation meets cell biology and immunology

Tomasz J. Guzik1; Jozef Dulak2

1Translational Medicine Laboratory, Department of Internal and Agricultural Medicine, Jagiellonian University School of Medicine, Krakow, Poland; 2Department of Medical Biotechnology, Jagiellonian University, Krakow, Poland

Correspondence to:
Prof. Tomasz Guzik, MD, PhD, MSc
Department of Internal and Agricultural Medicine
Jagiellonian University School of Medicine
J Dietl Hospital,
Ul. Skarbowa 1
31–121 Krakow, Poland
E-mail: t.guzik@uj.edu.pl

or

Prof. Jozef Dulak, PhD, DSc
Department of Medical Biotechnology
Faculty of Biochemistry, Biophysics and Biotechnology
Jagiellonian University
Ul. Gronostajowa 7
30–387 Krakow, Poland
E-mail: jozef.dulak@uj.edu.pl

Received: August 3, 2012
Accepted: August 7, 2012
Prepublished online: August 17, 2012
doi:10.1160/TH12-08-0558

Vascular inflammation, endothelial cell dysfunction and thrombosis are the most important mechanisms for cardiovascular diseases, which constitute major cause of morbidity and mortality (1, 2). These processes, often occurring in distinct vascular beds cause diverse symptoms of vascular pathology. For example, vascular dysfunction of the vessels in the heart manifests as coronary artery disease, while dysfunction of vessels in central nervous system lead to stroke but may also contribute to Parkinson’s disease or dementia. Renal vasculature dysfunction underlies renal insufficiency but also seems to be critical in hypertension. Therefore, vascular pathology remains the common denominator of numerous disease states. Molecular studies of the vessel wall have identified novel drug targets, while translational medicine provides clinical context to these findings. Most of new therapies target vascular inflammation, hypercoagulability and endothelial cell dysfunction. It becomes critical to better understand how these mechanisms interact in the vessel wall. In the current Theme Issue of Thrombosis and Haemostasis, stemming in part from the 6th European Meeting for Vascular Biology and Medicine, held in Krakow, Poland between 21 and 24 September, 2011 (http://emvbm2011.org), numerous aspects of vascular biology are discussed in the context of better identification of molecular mechanisms of atherothrombosis and future clinical usefulness of these findings (Fig. 1).

Fibrinogen and high sensitivity C-reactive protein (hsCRP) are the most important markers, which have been used to clinically link inflammation and thrombosis with cardiovascular risk. These molecules, however, may directly lead to vascular dysfunction and activate coagulation. The central role of fibrinogen as the precursor to fibrin, its ability to cross-link platelets, and its effects on blood viscosity, suggest that fibrinogen is the major risk factor for cardiovascular disease and thrombotic events (3). Fibrinogen, which is produced in the hepatocytes, is also an important acute phase protein, associated with systemic inflammation. Interleukin 6 (IL-6) response element is the critical factor in the regulation of fibrinogen gene expression, which further links thrombosis to inflammation (3). These aspects of the biology and genetics of the regulation of fibrinogen gene expression are comprehensively reviewed by Fish et al. (3). Fibrinogen level in plasma of patients is influenced by environmental and genetic components, with the latter contributing 20 to 50% of the variability (3). Thus, understanding the genetic mechanisms of this variability is critical for future use of fibrinogen as a marker for cardiovascular risk. The three fibrinogen genes, FGA, FGB and FGG, are coordinately expressed in hepatocytes from a compact gene cluster. In the original contribution published in this issue of
Thrombosis and Haemostasis, Fish et al. describe a novel liver enhancer in the human fibrinogen gene cluster, which is located between FGA and FGG genes (4). Given the functional importance of this region, the genetic variation in this new sequence could impact fibrinogen expression levels and, when combined with other risk alleles, could affect cardiovascular risk (4). These observations require now translational studies involving large patient populations.

Fibrinogen is critical for the generation of typical fibrin-rich clots, such as coronary thrombi during acute coronary syndromes or the intraluminal thrombus of aortic abdominal aneurysms (AAA). While fibrinogen and fibrin clot structure are important, cells such as platelets but also erythrocytes and leukocytes play a critical modulatory role in thrombosis (5). Moreover, complex interactions between vascular signalling and immune cells are critical for acute coronary thrombosis leading to myocardial infarction (6). Matusik et al. discuss the role of immune cells in both vessel wall and thrombus in the acute coronary syndromes and in particular myocardial infarction (6). Blood derived cells are equally important in thrombus generation in a more chronic situation – in AAA (5). Martin-Ventura et al. focus on the role of erythrocytes, leukocytes and platelets in the generation of oxidative stress in the intraluminal thrombus (ILT) in atherosclerotic aorta (5). The presence of such thrombus in AAA is associated with adverse clinical prognosis including increased AAA rupture risk (7). The mechanisms through which ILT may affect vessel wall structure and function are discussed. Interestingly, haemolysis of red blood cells releases haemoglobin, which promotes pro-oxidant mechanisms and transfers heme to tissue and low-density lipoproteins (5). Thus red blood cells are not just the bystanders of thrombosis and atherosclerotic plaque formation, but are active participants of this process (8). Leukocytes, along with activated platelets produce superoxide by myeloperoxidase and NADPH oxidase, both enzymes clinically linked to adverse cardiovascular risk (9). Reactive oxygen species cause endothelial dysfunction, activate metalloproteinases, and increase expression of redox sensitive genes such as nuclear factor (NF)-kB, which in turn open the way for vascular inflammation (9).

While there are numerous factors, which may attract immune cells and platelets to the sites of thrombosis, chemokines are the most important players (1, 2). Flierl and Schäfer discuss the role of chemokines in thrombosis, pointing special attention to recently described interactions between fractalkine and its receptor CX3CR1 (10). This interaction has been shown in human atherosclerosis and thrombosis as fractalkine is expressed in the vessel wall by both endothelial cells and vascular smooth muscle cells, while its receptors are expressed on immune cells and platelets (11). While fractalkine is not a very strong platelet agonist, at sites of endothelial dysfunction and atherogenesis, elevated fractalkine concentrations could contribute to aggravation of platelet stimulation (11). This is greatly related to the unique property of this chemokine to exist as a membrane-bound form, apart from classical soluble form (10). Expression of fractalkine on dysfunctional endothelium may initiate platelet binding. Moreover, fractalkine binding to CX3CR1 receptor initiates signalling cascades, which contribute to vascular dysfunction and ultimately, vascular disease. Thus fractalkine may be a marker of unstable, vulnerable atherosclerotic plaque, at risk of rupture (6).

Inflammatory cells, which are present in the dysfunctional vascular wall, and in atherosclerotic plaque, may not only serve as important drug targets for future therapies of cardiovascular disease, but may also be an important indicator of disease process (6). Presence of macrophages and T cells in the shoulder regions of atherosclerotic plaques is a clear indicator of plaque vulnerability, much more valuable than just morphometric parameters of fibrous cap thickness. Therefore novel imaging modalities such as 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET), or myocardial perfusion imaging techniques, like single photon emission computed tomography (SPECT) are able to detect inflamed plaque (8). These techniques are already available clinically, but their cost as well as their accuracy need to be improved before we can widely use them. Similarly, in spite of relatively good understanding of immune and molecular mechanisms of atherosclerosis and acute coronary events, relatively small number of therapies targeting these robust mechanisms of vascular disease is being used. In the present Theme Issue, Wojakowski et al. investigate the effects of genetically modified cell-based therapy using intracoronary infusion of allogenic bone marrow cells (BMC) overexpressing heme oxygenase 1 (HO-1) in the porcine model of myocardial infarction (12). HO-1 is a modulator of inflammation and vascular dysfunction, therefore its use in cell-based therapies of myocardial infarction is really interesting (13). Indeed, delivery of HO-1 overexpressing allogenic BMC enriched for potential endothelial progenitor cells immediately prior to reperfusion improved the LVEF already 30 minutes after reperfusion. Cell therapy reduced infarct size assessed 14 days later and BMC were nicely visualised in the peri-infarct zone (12). Interestingly, this study demonstrated for the first time such an immediate effect of HO-1 overexpressing cells on the prevention of the reperfusion injury. The mechanism of this improvement requires further elucidation, as it was not clearly associated with changes of major pro-inflammatory gene expression (12).

In summary, increasing understanding of the interactions between thrombosis, vascular inflammation and endothelial dysfunction is opening the possibility for novel diagnostic and therapeutic approaches to cardiovascular diseases. However while we look into the molecular biology of inflammation, thrombosis or stem cell biology, we must not forget the vessel wall, which is the stage for all of these processes.

Acknowledgements
This work was supported by the Foundation for Polish Science Welcome/2009/2 grant and the Wellcome Trust International Senior Research Fellowship and the European Molecular Biology Organization (to TFG) and by grants POIG 01.01.02–00–109/09 and 01.01.02.069/09 from the European Union structural funds (to JD).
Conflicts of interest
None declared.

References