Vascular remodelling processes: Cells, signals and their integration

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The vasculature is one of the most important and complex organs in the mammalian body and the first functional organ to be formed during embryonic development. The initial vascular plexus consists of a homogenous web of endothelial cell tubes and sacs, which later become remodelled into a mature network. Remodelling involves the creation of large and small vessels, the establishment of directional flow, the association with mural cells (pericytes and smooth muscle cells) and the adjustment of vascular density which is essential for the transportation of oxygen and nutrients to and the removal of waste products from the tissues. The maintenance of vessel integrity and the control of vessel physiology and haemodynamics during embryonic development has functional consequences on postnatal and adult life (1).

In general vascular remodelling processes are characterized by structural changes of the vessel wall involving a variety of cellular activities such as proliferation, migration, apoptosis, or restructuring of the extracellular matrix. Together with intercellular activities this may lead to recruitment of stem and progenitor cells, interaction of blood cells with the vascular wall, rearrangement of vascular wall cell topography, resulting in modulation of vascular barrier function and vascular growth into new or existing tissues. Vascular remodelling processes have been recognized in particular to play a role in a variety of disease states, including atherosclerosis, ischemic diseases, systemic and pulmonary hypertension, tumor growth, metabolic syndrome, diabetes mellitus or renal pathologies (2). In this Theme Issue of Thrombosis and Haemostasis, which comprises the second part of a series of review articles and original manuscripts which are based on scientific contributions presented at the Annual Meeting of the Society of Microcirculation and Vascular Biology at the German Heart Center at TU in Munich, October 12-14, 2006, important new findings are highlighted which are related to different aspects of vascular remodelling processes.

It was not until 10 years ago that the importance of endothelial progenitor cells (EPC) for the formation of new blood vessels was appreciated. More recently, progenitor cells have been found in many (adult) organs and have been implicated to contribute to physiological and pathophysiological regenerative processes. In their review, Stellos and Gawaz (3) summarize current findings regarding the recruitment, survival and differentiation of EPC with a specific focus on the role of platelets in these events. Indeed, in addition to their function in haemostasis and thrombus formation, platelets appear to be involved in vascular or tissue regeneration, since at their site of destination they release various growth factors, chemokines and cellular agonists. Platelets are capable of interacting with the vascular wall or with other circulating blood cells including EPC, thereby contributing to their recruitment as well as to their differentiation into mature endothelial cells, macrophages or even foam cells. However, current anti-platelet therapy does not seem to be effective in preventing EPC recruitment and differentiation. Thus, additional insights are required into the nature of specific (non-platelet) mediators which would allow selective recruitment of bone marrow-derived stem and progenitor cells to specific organs, with respective consequences for organ vascularization and regeneration.

In addition to circulating EPC, also vascular wall-resident EPC (VW-EPC) have been identified. Ergün et al. (4) describe the potential role of VW-EPC compared to circulating or bone marrow-derived EPC for new vessel formation in association with different diseases. VW-EPC have been found in large and middle-sized human arteries and veins in several organs in the so called “vasculeogenic zone” which is located between smooth muscle cell and adventitial layers. The authors conclude that the incorporation of pre-existing vessels (e.g. promoted a tumor) could initially lead to the mobilization and recruitment of local VW-EPC as well as tissue-resident EPC for new vessel formation followed by activation of mature endothelial cells and circulating EPC. Similar processes are discussed for VW-ECP in situations of inflammation, ischemia or atherosclerosis, since VW-EPC have the intriguing ability to migrate through the smooth muscle cell layer towards the vascular lumen. Although the exact role of VW-EPC in...
atherosclerosis or tumor vascularization is not deciphered, the authors highlight the double sided role of this newly identified subset of EPC. While easily accessible in ischemic disorders and tissue regeneration, EPC lack a direct access to the vasculature which may protect them from systemic anti-angiogenic tumor therapy.

In her review E. Deindl (5) describes some of the central signalling pathways which may be involved in the regulation of arteriogenesis, a process describing the growth of pre-existing arteriolar anastomoses to form large (coronary) collateral conductance arteries within ischemic tissue. Increasing evidence points to an important role of Rho-GTPases as well as the FGF/MEK/ERK pathway and the SRF/MRTF acting as conjunctive transcription factors connecting both pathways. However, the exact mechanisms how mechanical stress as an important driving force of arteriogenesis is translated into vessel remodelling is still not clear. Whether these signalling systems may become activated in VW-EPC and thus allow these cells to contribute to arteriogenesis would be an interesting new facet to be elucidated in the complex network of signalling pathways related to vessel remodelling.

A novel signalling system which may have importance for vessel remodelling in many disorders is described by Djordjevic and Görlach (6), namely the vasoactive peptide urotensin II (UII) and its receptor. The authors primarily focus on the role of this peptide hormone in promoting remodelling of the pulmonary vasculature, a major complication of pulmonary hypertension. Being the most potent vasoactive peptide, UII is able to induce proliferation in pulmonary artery smooth muscle cells and possibly also endothelial cells. Indeed, UII has been shown to activate MAP kinases and the release of reactive oxygen species by activation of NADPH oxidases. Furthermore, UII and its receptor contribute to pulmonary hypertension and vascular remodelling as demonstrated in several animal models. Since pharmacological inhibitors of the urotensin receptor system are already available, additional studies should be initiated to further support this exciting new concept.

Adrenomedullin constitutes another vasoactive peptide that has important protective functions towards detioriation of the endothelial barrier function under inflammatory conditions as point out by Temmesfeld-Wollbrück et al. (7). There seems to be good evidence that adrenomedullin (that could be upregulated by UII) increases cAMP levels which leads to a reduction of myosin light chain phosphorylation and stabilization of junctional organization. Although the exact molecular mechanisms of how adrenomedullin exerts its beneficial effects on the vascular wall during acute inflammation awaits further investigations, there is increasing evidence that adrenomedullin may be also important in other situations where vascular remodelling plays a pivotal role such as in myocardial infarction, systemic and pulmonary hypertension or angiogenesis.

Another clinically important aspect of vascular barrier function is addressed by Burggraf et al. in relation to the administration of recombinant plasminogen activator (rt-PA) (8). They investigated how degradation of the basal lamina and thus the vascular integrity can be affected by application of rt-PA, which is successfully used for therapy of stroke patients. They found that exogenous rt-PA increased EMMPRIN, a major inducer of matrix metalloproteinases (MMP) followed by a rise of MMP activity in an experimental stroke model. However, at low to moderate doses of rt-PA the microvascular basal lamina was protected, probably due to upregulation of MMP inhibitors and their blocking activity for MMP-2 and MMP-9. This study further highlights the complex signalling mechanisms affecting vascular integrity that are activated not only by vascular stress factors, but also by some therapeutic regimens employed further emphasizing the need for careful studies that would demonstrate the effects of such therapies on vessel integrity, structure and function.

Endothelial dysfunction, generally defined as a decrease in nitric oxide (NO) availability due to a variety of disturbing conditions, is an important determinant in promoting vascular remodelling processes and has been attributed to the development of atherosclerosis, systemic and pulmonary hypertension or diabetes. Kleinbongard et al. (9) summarize data which indicate that, apart from the endothelium, red blood cells (RBC) contain a functional endothelial-like NO synthase and thus contribute to the availability of NO. It seems that the relative contribution of the endothelium and RBC as sources for NO may vary along the vascular tree. Although the importance of RBC NO may be more prevalent in the microcirculation, investigations determining the impact of the different NO sources in the macro- and microcirculation are still pending. Experimental evidence suggests a counteracting role of RBC NO in platelet aggregation; however, the question of how this NO is released from RBC is still unsolved. Additionally, RBC NO may contribute to the deformability of RBC and may thus play an important role in disorders associated with impaired haemorheologic functions or increased adhesion, both contributors to vascular remodelling.

An interesting approach to evaluate how these different parameters affect vascular function and lead to structural changes in the vessel wall or to cardiovascular disorders in a clinical setting is proposed by J. Waltenberger (10). Based upon the clinical concepts to unmask pathophysiological conditions under specific “stress conditions”, he suggests a cellular stress test to unravel vascular cell function in particular disease settings. Assuming that blood-borne cells are exposed to the same level of “stress” as vascular endothelial cells, it is proposed that patient’s blood cells are not only analyzed by static but also by functional (or dynamic) tests. This concept suggests to integrate the use of cell biological or molecular test systems widely used in the experimental laboratories for measuring chemotaxis, migration or proliferation, but also biochemical analyses on blood-borne cells of patients. The author indicates that monocytes may be particularly valuable for this testing, since they may reflect the endothelial functional state. Although several clinical studies have already been performed, additional investigations are required to validate the diagnostic and prognostic value of such an approach.
References


