Editor's Perspective

Turning Up the Pressure on Vascular Disease

Vascular cell injury, whether it occurs in the central nervous system or in other locations throughout the body, represents a significant factor for subsequent disability and death in individuals worldwide. In fact, coronary artery disease remains the leading cause of mortality and can be caused by vessel stenosis, atherosclerosis, embolic disease, or thrombosis. Loss of blood flow to critical areas in the vascular system leads to endothelial cell dysfunction and death. Treatments to avert coronary artery disease and maintain adequate blood flow include the use of antiplatelet agents, angiotensin-converting-enzyme inhibitors, statins, β-blockers as well as re-vascularization techniques that include coronary artery bypass grafting and percutaneous coronary intervention. Other new strategies include the induction of angiogenesis such with trophic factors that include vascular endothelial growth factor and fibroblast growth factor, the use of stem cell therapies, and the use of cytokines such as erythropoietin to directly protect cardiomyocytes and endothelial cells.

In the nervous system, approximately 15 million individuals suffer some form of a stroke every year. In addition to cerebral blood vessel occlusion or intra-cerebral hemorrhage as causes of stroke, rupture of intracranial aneurysms with subarachnoid hemorrhage also can lead to ischemic cerebral injury. Intracranial aneurysms can result from genetic origins or be acquired through conditions such as tobacco use, excessive ethanol consumption, and hypertension. Although stroke leads to significant mortality and morbidity, stroke is no longer ranked as the third leading cause of death in the United States. Multiple factors have resulted in the reduction of stroke incidence, now classified as the fourth leading cause of death, that include reduction in tobacco consumption, heightened awareness to seek rapid treatment for stroke, improved care of hypertension, and better management of low-density lipoprotein cholesterol. Treatment with recombinant tissue plasminogen activator in patients suitable for this therapy also has led to a reduction in mortality and morbidity in stroke patients. Several new treatment strategies are under consideration for stroke that also address central nervous system inflammation to include treatment with cytokines and growth factors, progenitor stem cells, metallic ions, and small molecular regulators of hypoxia inducible factor.

Improved management of metabolic disorders such as diabetes also have accounted for the reduction in the incidence of stroke. Yet, diabetes continues to remain a significant factor that leads to vascular cell injury. Diabetes mellitus may affect approximately 170-200 million individuals in the world with millions of additional individuals currently undiagnosed. Complications of diabetes and insulin resistance are associated with oxidant stress that can affect both the cerebrovascular and cardiovascular systems as well as other vessels in the body. Diabetes can lead to platelet dysfunction, acute cerebral or coronary

injury, and dysfunction in the sympathetic nervous system. Elevated glucose in vascular endothelial cells can result in the increase of antioxidants that involve superoxide-dismutase, catalase, and glutathione peroxidase. This may represent a reparative response by the body to attempt to reverse the effects of oxidant stress injury in the vascular system.

Infection and sepsis are additional disorders that can lead to vascular compromise in the body. Coagulation abnormalities occur in sepsis and can lead to diffuse microvascular thrombosis, depleted platelet counts, disseminated intravascular coagulation, and thrombosis in larger vessels. Infection that leads to vascular cell injury may be bacterial, viral, or parasitic in origin. For example, during infection of the parasite *Plasmodium falciparum* that leads to malaria, parasitized red blood cells can adhere to endothelial cells and produce impaired blood flow, mechanical occlusion, and ischemic tissue in the brain as well as in the cardiovascular system. Impaired perfusion and vessel occlusion can even occur in the vasculature of the retina. Vasoconstriction and direct endothelial cell dysfunction also have been reported that may be mediated through impaired nitric oxide bioavailability and modulation of endothelins.

In this issue of *Current Neurovascular Research*, new work targets several novel mechanisms for the treatment of vascular disease in the body that can significantly impact blood vessel and vascular endothelial function. In the paper by Lin *et al.*, the authors examined a mechanism for the development of sporadic aneurysms in the Chinese Han population as a result of *endoglin*, a gene that is involved in vascular development and angiogenesis. *Endoglin*, as a potential biomarker, would be of great interest to follow and potentially prevent intracranial aneurysm rupture, since most individuals have no symptoms until intracranial aneurysms become symptomatic. The investigators illustrate in the population examined that the *endoglin* D366H variant (rs1800956) may be clinically relevant since it has an increased association with intracranial aneurysms and may contribute to the sporadic risk in the development and progression of intracranial aneurysms. Takagi *et al.* consider factors that can lead to intracranial hemorrhage during excessive alcohol consumption. In a model of ethanol-induced endothelial damage, they identify metalloproteinase 9 (MMP-9) as a key mediator of cell injury and show that tight junction disruption and loss of transendothelial electrical resistance was a result of MMP-9 activation in the setting of oxidative stress. Endothelial damage during ethanol-induced damage could be blocked by cilostazol, a phosphodiesterase III inhibitor, through cellular pathways that require protein kinase A and decrease MMP-9 activity.

In regards to the use of stem cells for regenerative strategies following vascular injury, Banik *et al.* identify an enriched population of CD45, CD34 and CD117 stem cells in human umbilical cord. The authors advocate that this cell population is a viable primitive stem cell source that may possess high regenerative properties for the development of future vascular repair strategies. The work of Martončíkova *et al.* is an interesting companion to the Banik study. Martončíkova *et al.* show in the rostral migratory stream in a rat model that blood vessels may form a scaffold for the migration of neuronal precursors in the brain, illustrating the vital role of the vascular system in the brain during development and potentially during repair processes

following injury. Carvalho *et al.* focus upon the pathways that contibute to vascular injury during Type 2 diabetes and examine the antioxidant defenses as future therapeutic targets that exist in brain vessels and synaptosomes in animal models of experimental diabetes. They identify several cellular pathways of oxidative imbalance and show that manganese superoxide dismutase activity and vitamin E levels increase with a concomitant decrease in aconitase and glutathione reductase activities, glutathione (GSH)/glutathione disulfide (GSSG) ratio, and GSH and malondialdehyde levels in brain vessels and synaptosomes. Interestingly, an age-dependent increase in hydrogen peroxide levels in both diabetic synaptosomes and vessels was also noted. In their meta-analysis, Panato *et al.* identify biomarkers markers of bacterial and aseptic meningitis, disorders that can directly lead to vascular cell dysfunction and injury. They show that tumor necrosis factor-α and interleukin-1β are accurate markers to differentiate between bacterial and aseptic meningits with significant elevation of these markers in bacterial meningitis but lower levels of these markers in aspetic meningitis.

In our review articles for this issue of *Current Neurovascular Research*, Maiese presents Wnt1 inducible signaling pathway protein 1 (WISP1) as an emerging novel target for a number of therapeutic strategies especially those relevant for vascular and cardiovascular restoration. WISP1 is a target of the *wingless* pathway Wnt1 that fosters neuronal and vascular development. WISP1 promotes vascular smooth muscle proliferation that may be important for tissue repair during injury. The reparative properties of WISP1 may be driven by the ability of WISP1 to influence stem cell proliferation, migration, and differentiation. Nabavi *et al.* examine the antioxidant properties of resveratrol, a natural polyphenolic antioxidant, during stroke. They describe the therapeutic potential of this agent for stroke that modulates several pathways including sirtuins, superoxide dismutase 2, glutathione peroxidase, and nuclear factor-erythroid 2-related factor-2 as well as anti-inflammatory mediators.

In this issue of *Current Neurovascular Research,* new insights into vascular disease and endothelial cell survival are brought forward for the exciting development of new clinical entities. Of course, as with any new developments, we must continue to acquire further understanding of the relevant biology critical for the initiation of new therapeutic strategies and clinical care of vascular disease to avoid unwanted outcomes such as unchecked vascular proliferation. In any event, elegant and focused studies on the problem at hand are always warranted as we “turn up the pressure on vascular disease”.

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