Editor's Perspective

Vascular Patency: A Biomarker and Clinical Target Quantified with High Resolution MRI and Novel Cellular Pathways

Kenneth Maiese

Inflammation of the cerebral blood vessels can lead to atherosclerotic disease resulting in limited vascular patency, decreased cerebral blood flow, and build-up of lipids in the vessel wall. In addition, inflammatory cell invasion may trigger endothelial cell dysfunction, release of cytokines, and vascular smooth muscle invasion of the vessel wall intimal layer. With inflammatory cell monocyte recruitment, these cells can differentiate into macrophages to form foam cells from the engulfment of oxidized low-density lipoproteins. Further progression of the atherosclerotic vessel wall is fostered by platelet cells and other circulating micro-particles that can include portions of cell membranes, messenger ribonucleic acids (mRNAs), microRNAs (miRNAs), and membrane outer leaflet structures such as phosphatidylserine residues.

With the onset and growth of atherosclerotic lesions that may occur over multiple years, plaque (composed of multiple entities that include lipids, cholesterol, calcium, etc.) progression and continued pulsatile stress from elevated systemic blood pressure can further narrow and lead to the occlusion of blood vessels. A number of inflammatory mediators can be produced during atherosclerosis that include interleukins, mitogen-activated protein kinases, inducible nitric oxide synthase, metalloproteinases, and tumor necrosis factor-α that can degrade the extracellular matrix, promote oxidative stress, and lead to apoptotic cell death of parenchymal cells such as neurons and astrocytes of the brain. Calcification of the vessel as well as arterial stiffness also can develop. In regards to arterial stiffness, this may be considered an additional complication of atherosclerotic disease. It is hypothesized that extensive arterial pulsations and increased pulsatile pressure that stress already reduced lumens with atherosclerotic disease can lead to cerebral microvasculatory damage and result in remodeling of the microvasculature. Ultimately, a number of clinical risk factors and disorders can ensue that include stroke, loss of cognition, and progressive decline in other systems of the body such as cardiac and renal disease.

Given the cellular onset of atherosclerosis in vessels and the eventual progression to vessel occlusion and severe clinical disease, it becomes critical to develop new strategies for maintaining vascular patency by detecting and following atherosclerotic lesions. In this issue of *Current Neurovascular Research*, a number of studies provide new perspectives for addressing the cellular mechanisms and treatment that impact atherosclerotic disease, altered cerebral vascular flow, and clinical disease. In the work by Li *et al.*, the authors employed high-resolution magnetic resonance imaging (HR-MRI) to assess plaque burden in patients suffering a middle cerebral artery infarction within seven days following stroke onset. Interestingly, the authors demonstrate that plaque burden imaged in the M1 segment of the middle cerebral artery was a positive predictor for cerebral infarction and significantly associated with infarct size, suggesting the HR-MRI may offer both an attractive preventive and prognostic clinical tool for managing cerebrovascular disease. MRI also appears to be important for the classification and identification of stroke risk factors. Chun-Hsien *et al.* used perfusion magnetic resonance imaging (MRI) to differentiate cardio-embolic stroke from large artery atherosclerosis. The authors illustrated that perfusion MRI could be a valuable asset to identify and differentiate cardio-embolic stroke from other ischemic etiologies that lead to cerebral infarction. Vascular patency also appears to be a vital issue with the observed neuroprotection of fingolimod (FTY720), a functional sphingosine-1-phosphate receptor 1 ($S1P_1$) antagonist. Schuhmann *et al.* illustrate that fingolimod (FTY720) can limit experimental stroke in rodents not through expected immune modulation and direct cytoprotection, but through the reduction of microvascular thrombosis, increased vessel patency, and enhanced cerebral blood flow to assist cortical tissue at risk. In the paper by Fang *et al.*, the authors evaluated the role of intracranial collateral blood vessels to predict stroke recurrence in the presence of carotid artery atherosclerotic disease using color velocity imaging quantification ultrasound studies. They found that the presence of intracranial collateral flow estimated by color velocity imaging quantification ultrasound was associated with a lower risk of recurrent stroke and could be a valuable prognostic tool to predict new cerebrovascular disease.

Other cellular mechanisms also may play a role in the function of the vascular architecture of the nervous system and the onset of clinical disease. Jayant and Sharma evaluated the role of a selective agonist of cannabinoid receptor type 2 (CB2) during chronic cerebral hypoperfusion. They describe that agonism of CB2 not only reduced memory loss, markers of oxidative stress, and cholinergic activity loss, but also limited brain edema, suggesting that maintenance of the blood brain barrier and endothelial cell function is vital for cerebral protection. Furthermore, it appears that the serum level of alkaline phosphatase in acute ischemic stroke patients with atrial fibrillation and/or rheumatic heart disease also is closely related to endothelial cell function. Liu *et al.* show that patients with elevated serum levels of alkaline phosphatase were more likely to experience cerebral micro-bleeds that highlights a potential therapeutic target to control cerebral bleeds in stroke patients with atrial fibrillation and/or rheumatic heart disease.

Additional novel targets and clinical strategies are presented in this issue of *Current Neurovascular Research* with our articles investigating pathways of transient receptor potential ankyrin 1 (TRPA1) receptor, transient receptor potential melastatin 8 (TRPM8) receptor, triggering receptor expressed on myeloid cells 2 gene (*TREM2*), 5-hydroxytryptamine (5-HT) receptors, erythropoietin, and the mechanistic target of rapamycin (mTOR). Pan *et al.* show both TRPA1 and TRPM8 receptors may lead to peripheral vasodilatation followed by vasoconstriction that can aggravate oxaliplatin-induced peripheral neuropathy that is amenable to 17β-estradiol treatment. The work brings to light the potential role of abnormal vascular responses in peripheral neuropathy and the control of these vascular networks by TRPA1 and TRPM8 receptors. In a meta-analysis involving 14,510 clinical subjects, Jiang *et al.* show that p.H157Y (rs2234255), a rare coding variant of *TREM2*, is associated with an increased risk of Alzheimer's disease and offer insight for focusing upon *TREM2* as a clinical gene target for neurodegenerative disease and cognitive loss. Xiang *et al.* show in their paper that activation of 5-HT_7 receptors leads to the enhancement of N-methyl-D-aspartate (NMDA) receptor activity, neurotransmission, and synaptic plasticity in the visual cortex that also can have relevance for the treatment of other disorders such as Alzheimer's disease and schizophrenia. In an article that highlights the conundrum of the benefits of increased life expectancy with the detriments of accompanying aging-related disorders, Maiese discusses implementation of novel strategies for cognitive loss, trauma, inflammation, and vascular disease. New avenues of investigation link the growth factor and cytokine erythropoietin with the control of programmed cell death pathways of apoptosis and autophagy through mTOR and its signaling pathways. Overall, the common denominator for multiple diseases in the nervous system may very well rely upon maintaining vascular patency and vascular cell function, a premise that holds the spotlight in this issue of *Current Neurovascular Research*.

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