Blood to Save Brain

Zvonimir Katusic, MD, Mayo Clinic, Rochester, MN, discussed recent work exploring the therapeutic potential of stimulating angiogenesis via circulating endothelial precursors and endothelial progenitor cells (EPCs).

The ability of EPCs to withstand oxidative stress as a result of a high level of manganese superoxide dismutase (MnSOD) enzymatic activity allows them to perform complex regenerative functions under the conditions of ischemia/reperfusion induced by stroke. Transplantation of early outgrowth EPCs into the lumen of injured arteries has been shown to stimulate regrowth of the endothelium in as little as 4 weeks. EPCs also have been shown to prevent dysfunction of regenerated endothelium by enhancing endothelium-dependent relaxation to acetylcholine. When injected directly into the cisterna magna in animal studies, EPCs stimulated production of the vasoprotective molecules prostacyclin and cAMP. In contrast, injected cells inhibited the production of thromboxane A2 (a molecule that favors platelet aggregation, blood clotting, and vasoconstriction) in the basilar artery. In light of all of these results, it is possible that EPCs may prevent vasospasm after subarachnoid hemorrhage, stimulate formation of collateral vessels, and inhibit thrombosis and restenosis.

S. Thomas Carmichael, MD, David Geffen School of Medicine, University of California, Los Angeles, CA, discussed the integrated responses in neurovasculogenesis after stroke. Although stroke causes cell death, it also leads to the birth and migration of new neurons within the sites of ischemic damage by inducing neurogenesis in the microvasculature adjacent to the infarct (peri-infarct cortex). Waves of newly born immature neurons (neuroblasts) migrate from their origin in the subventricular zone to the peri-infarct cortex and form a tight spatial relationship with the blood vessels. This migration is mediated, in part, by the cytokine erythropoietin.

Within this neurovascular niche, the neuroblasts sprout new connections and closely associate with the remodeling vasculature. Neurogenesis and angiogenesis are causally linked in the reorganizing of the peri-infarct cortex through vascular production of stromal-derived factor 1 (SDF1) and angiopoietin 1 (Ang1), which are trophic factors for migrating neuroblasts and improve behavioral recovery. Dr. Carmichael pointed out the challenges that lay ahead in the field, including the need to understand the environments of neural repair that may lead to novel stroke therapies and how these environments relate to cellular interactions and growth factor signaling in peri-infarct tissue. The role of post-stroke neurogenesis in neurological recovery after stroke remains undefined, and future work will need to define the behavioral effects of post-stroke neurogenesis and the interaction of behavioral or neurorehabilitative "stimulation" and neuronal regeneration, particularly in the aged brain.

In his presentation, Patrick D. Lyden, MD, University of California San Diego and Veterans Affairs Stroke Centers, San Diego, CA, suggested that angiogensis (growth of new blood vessels) may have both favorable and deleterious effects following an acute stroke. As pointed by Dr. Carmichael, angiogenesis signaling after ischemia may create a vascular niche and promote neurogenesis and functional recovery. However, an imbalance in angiogenesis contributes to the pathogenesis of numerous malignant, inflammatory, ischemic, infectious, immune, and wound-healing disorders.

Ischemia-evoked angiogenic signals also have been associated with leaky microvessels and phagocytic macrophages. This association with an increased number of macrophages has been dubbed the "clean up" hypothesis. Following ischemia, microvessel density increases only in the ischemic margin adjacent to areas of pannecrosis, where no neuronal structure can be observed. Increased numbers of macrophages also are observed in this area, suggesting that ischemia-induced microvessels are formed to facilitate macrophage infiltration and removal of necrotic debris. Blocking macrophage infiltration reduces angiogenesis in the microvasculature niche. Dr. Lyden concluded by saying that more effective stroke interventions may be possible through a better understanding of the role of angiogenesis.

The Impact of Medical Legal Issues on Stroke Treatment

Justin Zivin, MD, PhD, University of California, San Diego, CA, presented data demonstrating how legal issues influence the treatment of stroke. Recombinant tissue plasminogen activator (rt-PA) is a well-known FDA-approved thrombolytic treatment. It is estimated that only 4%-8% of acute ischemic stroke patients receive rt-PA, when up to 40%-50% of patients could derive benefit from the drug. In Dr. Zivin's opinion, fear of malpractice lawsuits depresses the use of this drug. The literature and regulatory approvals support the idea that rt-PA is a valid