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Post-Stroke Angiogenesis, Pro: Making the Desert Bloom

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Angiogenesis, in which existing blood vessels give birth to new capillaries, is a widely conserved response to hypoxia, including ischemic hypoxia. Angiogenesis occurs in peri-infarct regions of human brain after stroke, as documented by histological and immunohistochemical studies of postmortem tissue.[1–3] Among many questions that might be asked about angiogenesis and stroke, the most apposite include (1) whether spontaneous post-stroke angiogenesis improves outcome and (2) whether treatment to enhance angiogenesis confers additional benefit. Neither of these questions can be answered definitively, but a case can be made that a likely answer in both cases is yes.

Several studies point to a relationship between angiogenesis and stroke outcome. Krupinski et al.[2] found a correlation between increased microvessel density in affected cerebral hemispheres and duration of survival in 10 patients who died within 92 days after stroke. Slevin et al.[4] reported that among 29 patients with a variety of stroke subtypes studied up to 14 days after onset, those with the highest serum vascular endothelial growth factor (VEGF-A) levels, used as a surrogate for angiogenic activity, showed the greatest improvement in Scandinavian Stroke Scale scores. Navarro-Sobrino et al.[5] studied plasma levels of pro- and anti-angiogenic markers in 109 patients with middle cerebral artery territory strokes treated with thrombolysis. Data collected up to 3 months after stroke showed that ratios of pro-angiogenic (e.g., VEGF-A or platelet-derived growth factor) to anti-angiogenic (e.g., endostatin or thrombospondin-1) factor levels correlated with favorable outcome measured according to the National Institutes of Health Stroke Scale.

The therapeutic potential of induced angiogenesis after stroke must be evaluated based on even less direct evidence. Numerous clinical trials have been conducted involving administration of pro-angiogenic proteins, genes or cells to patients with peripheral or coronary artery disease.[6] Several smaller trials have yielded positive findings and, although the results of larger controlled trials have been less encouraging, they have far from exhausted the range of therapeutic agents, routes of administration, and target diseases to which angiogenesis-based therapy might be applied. In addition, none has addressed cerebrovascular disease.

Disclosures: None

Even conceding that the rodent may be the last refuge of the therapeutic optimist, several preclinical studies have shown beneficial effects of angiogenic factors and cells on outcome from experimental stroke.[7] Some of these studies have also raised concern regarding possible adverse effects, notably increased edema related to the leakiness of new vessels. However, strategies for avoiding such problems, by altering the timing or route of administration, co-administering vessel-stabilizng factors (e.g., angiopoietin-1), or substituting angiogenic factor family members (e.g., placental growth factor), have also been identified.

It is worth noting that treatments for stroke that target angiogenesis may operate through mechanisms other than, or in addition to, providing ischemic brain tissue with oxygen and glucose. For example, salutary effects of angiogenesis may include providing passage for inflammatory cells charged with cleanup of the post-ischemic landscape.[8] In addition, angiogenic factors and cells may promote not only angiogenesis, but also neuroprotection, neurogenesis, and other processes that enhance repair and recovery.[7]

The ultimate role of angiogenesis-based treatment for stroke, if any, cannot be resolved based on current data. However, the state of the art is sufficiently promising, and the therapeutic status quo sufficiently unsatisfactory, that the potential for clinical application of angiogenesis in stroke should not be overlooked.

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