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Post stroke angiogenesis:

Blood, bloom or brood?

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Angiogenesis, the formation of new capillaries from existing blood vessels, is a naturally occurring phenomenon in adult humans, encompassing a range of normal functions from the physiological maturation of the female reproductive system to wound healing, as well as pathological functions such as aiding unwanted tumor growth. Although ample evidence suggests that angiogenesis occurs in humans and laboratory animals after brain ischemia [1], [2], it has long been debated whether angiogenesis contributes to the recovery of function after stroke and whether it can be harnessed as a therapy to treat stroke. The pro and con opinions of post stroke angiogenesis have been eloquently and pertinently discussed by Dr. David Greenberg, who attests to the benefit of angiogenesis and the potential for clinical application; and by Drs. Joanna Adamczak and Mathias Hoehn, who address the risk of angiogenesis and potential consequences in aggravating stroke progression.

In light of the recent failure of several angiogenesis therapy trials, a critical appraisal of the angiogenic approaches is now overdue [3]. Among the most obvious flaws comes first the overly simplistic selection of angiogenesis therapeutic targets. It is well known that in order to form the correct patterning of a functional blood vessel, multiple angiogenic factors must work together in concert with spatio-temporal precision. However, the majority of angiogenesis therapy regimens only involved the administration of a single angiogenic factor. Second, despite some evidence supporting a positive correlation between pro-angiogenic factor levels and stroke outcome, a potential adverse effect of angiogenesis-based therapy involving VEGF is linked to the generation of immature and unstable vessels that leads to edema and vessel regression over time. To form mature and functional blood vessels, pericytes and vascular smooth muscle cells are required to stabilize capillaries and control vessel conductance, respectively. Co-delivery of PDGF-BB with VEGF was reported to recruit pericytes and enhance vessel maturation. Ang-1 was also shown to reduce VEGF-induced vascular leakage, whereas FGF-9 promoted the recruitment of smooth

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muscle cells and enhanced vasoreactivity. Lastly, considerable effort has been made to improve the delivery technology for angiogenic factors. A polymer-based scaffold system has made it possible to achieve spatial gradients of factors in tissue, whereas electrospun fibers offer controlled release. Together, with the right cocktail of factors, it seems feasible to recreate an angiogenic microenvironment with spatio-temporal precision.

It is apparent that the benefit of angiogenesis is more neurorestorative than neuroprotective in nature, considering the timing of its action. Arteriogenesis, the remodeling of preexisting collateral vessels on the other hand, plays a major role in neuroprotection and has been shown to determine stroke outcome [4, 5]. Although distinct triggering mechanisms are responsible for each vascular remodeling process, similar growth factors and cytokines are likely shared by angiogenesis and the growth of collateral vessels. Emerging evidence suggest that genetics and underlying vascular risk factors might contribute to the variance in native collaterals and the collateral status after stroke, respectively [5–7]. Similar vascular risk factors might also hamper post stroke angiogenesis and consequently, the recovery of function. Thus, a thorough understanding of the pro-angiogenic factors involved in both processes holds the key for developing an effective therapy for stroke.

Focal ischemia-induced angiogenesis appears to be transient and restricted to the border of the infarct. Whether or not the real mission of angiogenesis is to clean up the necrotic brain tissue, it suggests that at least the process is self-contained spatially and temporally. Nonetheless, it does raise another concern that therapeutic neovascularization may increase the risk of cancer if not managed properly. The bright side of this transient improvement in capillary blood flow surrounding an ischemic infarct is that it may promote other regenerative processes and neuroplasticity. While we all contemplate whether it is feasible to develop a safe and effective angiogenesis therapy in the future, for the moment at least we can still rely on the old fashion approach in improving cerebral blood perfusion with physical exercise, which not only “trains the vessel”, but also “gains the brain” [8].

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References

1. Arai K, Jin G, Navaratna D, Lo EH. Brain angiogenesis in developmental and pathological processes: Neurovascular injury and angiogenic recovery after stroke. The FEBS journal. 2009; 276:4644–4652. [PubMed: 19664070]
2. Yanev P, Dijkhuizen RM. In vivo imaging of neurovascular remodeling after stroke. Stroke; a journal of cerebral circulation. 2012; 43:3436–3441.
3. Said SS, Pickering JG, Mequanint K. Advances in growth factor delivery for therapeutic angiogenesis. Journal of vascular research. 2013; 50:35–51. [PubMed: 23154615]
4. Liebeskind DS. Collateral circulation. Stroke; a journal of cerebral circulation. 2003; 34:2279–2284.
5. Liu J, Wang Y, Akamatsu Y, Lee CC, Stetler RA, Lawton MT, et al. Vascular remodeling after ischemic stroke: Mechanisms and therapeutic potentials. Progress in neurobiology. 2014; 115:138–156. [PubMed: 24291532]

6. Sealock R, Zhang H, Lucitti JL, Moore SM, Faber JE. Congenic fine-mapping identifies a major causal locus for variation in the native collateral circulation and ischemic injury in brain and lower extremity. Circulation research. 2014; 114:660–671. [PubMed: 24300334]
7. Akamatsu Y, Nishijima Y, Lee CC, Yang SY, Shi L, An L, et al. Impaired leptomeningeal collateral flow contributes to the poor outcome following experimental stroke in the type-II-diabetic mice. Journal of Neuroscience. 2015; 35:3806–3814. [PubMed: 25740511]
8. Schmidt W, Endres M, Dimeo F, Jungehulsing GJ. Train the vessel, gain the brain: Physical activity and vessel function and the impact on stroke prevention and outcome in cerebrovascular disease. Cerebrovascular diseases. 2013; 35:303–312. [PubMed: 23594423]