**The role of endogenous VEGF in post stroke recovery**

A horizontal section of the human brain shows an acute infarct within the territory of the middle cerebral artery (dotted line). VEGF-A is induced in the ischemic border zone and acts on local neurons and endothelial cells to promote neuroprotection (yellow arrow) and angiogenesis (pink arrow). VEGF-A also stimulates neurogenesis (blue arrow) in the subventricular zone, from which new neurons migrate to the site of ischemia.

**Figure 1.** VEGF effects in acute ischemic stroke.

**Introduction**

A stroke is a cerebrovascular disease resulting from reduction or interruption in cerebral blood flow. Insufficient delivery of oxygen and glucose to support cellular homeostasis causes depletion of ATP stores. This induces multiple processes, also known as the ischemic cascade, that lead to cell death.

**Objectives**

- Explain what a stroke is and how injuries are produced.
- Briefly describe post-stroke regeneration processes.
- Analyze the role of endogenous VEGF in such processes.
- Check out different research work about its possible application in therapeutics.

**VEGF-based therapies**

### Exogenous VEGF administration

**Effects of VEGF administration**

- VEGF administration was associated with an infant size reduction ranging from 34% to 47% and improved clinical outcome.

**Route of administration**

There is great variability between different protocols in terms of the administration route.

**Time of administration**

Post-ischemic (1hr) administration of rhVEGF165 (48 hrs) was associated with angiogenesis enhancement and significantly increases BBB leakage, haemorrhagic transformation and angiogenesis (pink arrow). VEGF-A also stimulates neurogenesis (blue arrow) in the subventricular zone, from which new neurons migrate to the site of ischemia. (Greenberg & Jin, 2013)

**Figure 2.** VEGF stimulates BrdU incorporation into neuroproliferative zones of rat brain in vivo. BrdU was labeled by immunohistochemistry in hippocampus (A) and striatum (B). Note that BrdU incorporation is not confined to neuroproliferative zones, but extends, for example, into the dentate hilus in (B) consistent with the labeling of both neuronal and non-neuronal cells. (Jin et al., 2003)

**Figure 3.** VEGF time of administration and its effects.

(A-B) Evolution of the ischemic lesion after MCA occlusion in a rat treated with 0.9% saline (a) or rhVEGF165 (b). C: 24 h saline treatment with rhVEGF165 enhances cerebral microvessel plasma perfusion in the periphery (2D) compared with the control rat (2C). D-F: Increase CBF was observed in the ischemic lesion during infusion of rhVEGF165 (2 hours); (B) infusion of rhVEGF165 decreases hyperemic areas in the ischemic lesion (30 hours and 52 hour) (D). (Zhang et al., 2000)

**Figure 4.** Dose-dependent effects of VEGF.

(A) Quantitative effects of VEGF on infarct volume after MCAO (mean±SD) compared to saline, middle dose of VEGF significantly reduced infarct volume after MCAO. P = 0.01. (B) Middle and high doses of VEGF significantly increased the number of microvessels in the boundary regions of ischemia compared to stroke rats with saline treatment. (Yang et al., 2003)

**Pre-morbidity status**

- Pre-existing chronic diseases such as diabetes or hypertension can complicate therapeutic angiogenesis, since these diseases directly affect nervous tissue’s blood vessels.

**Combined therapy: stem cells + VEGF**

- Mesenchymal stem cells (MSCs)
  - This therapeutic approach may be used beyond hyper acute phase of stroke.
  - Survival and regenerative capabilities of transplanted MSCs can be enhanced by hypoxic preconditioning of the MSCs.
  - Transplantation of MSCs containing a modified VEGF gene may provide a better autologous cell transplantation therapy for stroke than transplantation of naive MSCs.

**Neural progenitor cells (NPCs)**

- The graft itself is a useful vehicle for GF delivery, promoting the survival of NPCs. Moreover, transplantation of VEGF-expressing NPCs supports angiogenesis in the brain, which may contribute to brain repair.

**Conclusions**

- After the onset of a stroke, hypoxic conditions induce VEGF synthesis, which protects the brain and enhances neurogenesis and angiogenesis.
- But thus endogenous VEGF production is usually insufficient to entirely protect the brain.
- There is multiple evident about the beneficial effects of VEGF administration (alone or combined with stem cells) in post-stroke conditions.
- However, we can not underestimate its potential negative effects, as BBB leakage and edema formation.
- In order to develop specific and efficient therapies, a better understanding of VEGF’s mechanisms of action is required.

**Selected references**