Promoting neurovascular repair after ischemic stroke by targeting pericytes

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BACKGROUND

Ischemic stroke constitute a major cause of death and disability of the adults worldwide. Unfortunately, there is no efficient therapy so far. Ischemic stroke triggers endogenous neurovascular restorative responses within the ischemic tissue as an attempt from the brain to recover. Angiogenesis is one of such compensatory mechanisms, which involves close interactions between brain endothelial cells and pericytes. Pericytes play major roles in regulating the cerebral blood flow, angiogenesis, microvascular stability, and blood-brain barrier. After ischemic stroke, pericytes detach from brain endothelial cells, leading to neurovascular impairment. Therefore, strategies aiming to promote vascular stability by improving pericytic density on the microvasculature have been proposed to constitute a promising therapeutic approach.

OBJECTIVES

Evaluating the therapeutic potential of Vascular Endothelial Growth factor VEGF isoform-B (VEGF-B) in ischemic stroke and deciphering the underlying mechanisms with an emphasis on the pericytes.

OBJECTIVES:
- To investigate the effects of VEGF-B on vascular stability and tissue damage in vivo.
- To dissect the signaling pathway of VEGF-B / VEGFR-1 in pericytes in vivo and in vitro.

RESULTS

1. VEGF-B reduces neurovascular injury after ischemic stroke

2. VEGF-B enhances brain microvasculature density and their coverage by pericytes

3. VEGF-B attenuates structural damage of the microvasculature following VEGF-B administration

4. Association of brain endothelial cells and pericytes increases VEGF-B expression

5. VEGF-B rescues pericyte survival and metabolism upon OGD

6. VEGF-1 is predominantly expressed in brain pericytes and its expression is regulated by hypoxia

7. VEGF-B attenuates pericyte cell loss after OGD

8. VEGF-B promotes restorative angiogenesis

9. VEGF-B enhances the capacity of pericytes exposed to OGD to produce molecules involved in promoting reparative angiogenesis

CONCLUSION

- VEGF-B, promoted the formation of stable microvasculature within the ischemic tissue by specifically enhancing the survival of pericytes and their interaction with brain endothelial cells.
- It induces the expression of soluble factors involved in promoting reparative angiogenesis.
- The effects of VEGF-B are mediated via its specific receptor VEGFR-1 that is predominately expressed in brain pericytes.
- Our study unraveled an unknown role of VEGF-B/VEGFR-1 signalling in regulating the function of pericytes.

SUMMARY: Our findings suggest that strategies aiming to stimulate the endothelial-pericyte crosstalk constitute a promising therapeutic approach to promote neurovascular repair after ischemic stroke.

MATERIALS & METHODS

- Ischemic stroke: Adult C57Bl/6j mice were subjected to transient middle cerebral artery MCA occlusion (MCAo).
- Treatment: Mice were treated with VEGF-B (4 μg/day beginning 24 hours after MCAo onset for 3 successive days; intranasal) and control mice received saline solution.

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