The 13th International Conference on Dose-Response Preconditioning: Adaptive Responses in Biology and Medicine; UMass Amherst

Hypoxic Preconditioning Strategy for Stem Cell Transplantation Therapy after Ischemic Stroke

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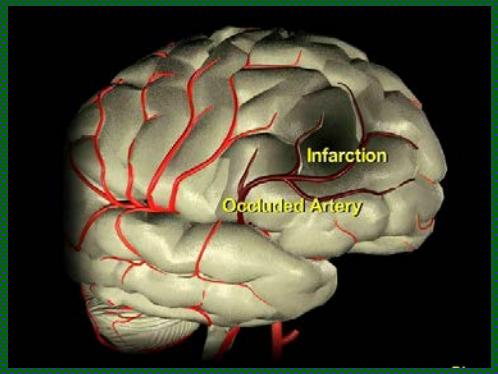
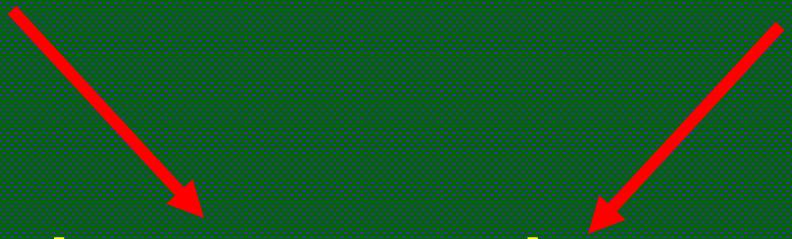
EMORY UNIVERSITY SCHOOL OF MEDICINE



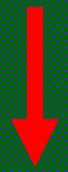
- Stroke is a leading cause of human death;
- 700,000 new cases each year, 4.5 million stroke survivors in the US;
- Failure of clinical trials using neuroprotective drugs
- Regenerative medicine provides a promising hope for the treatment of ischemic stroke and other CNS disorders such as traumatic brain injury.

Regenerative Cell-based Therapy for Brain Repair

- Cell replacement
- Trophic supports



Promoting regenerative mechanisms
(Neurogenesis and Angiogenesis)

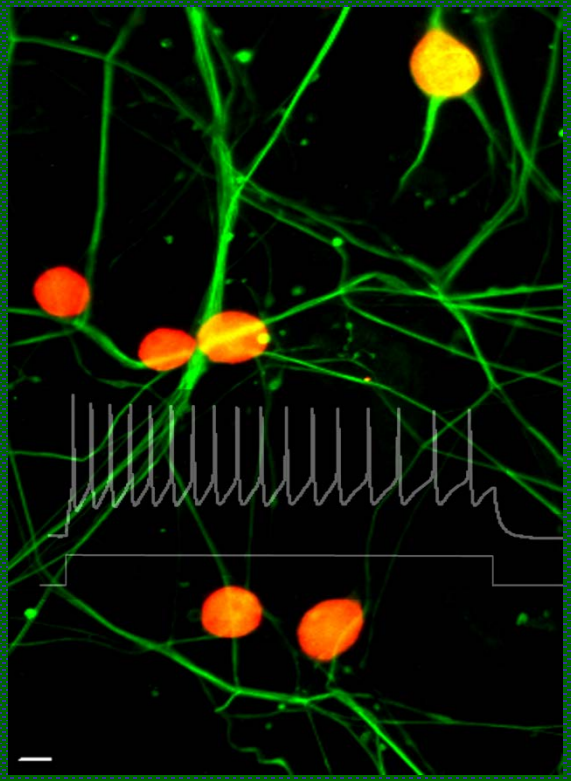


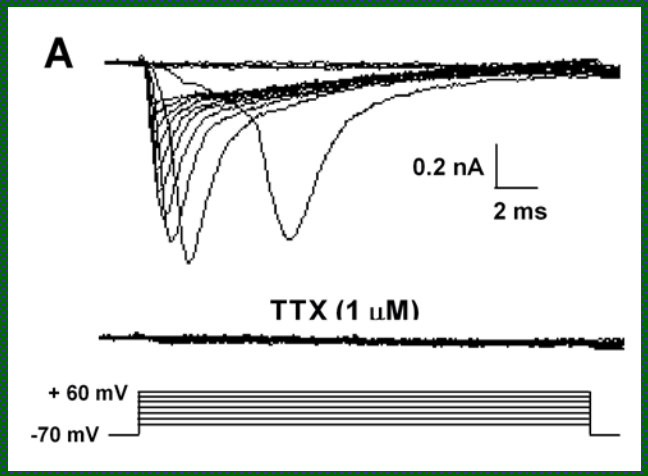
Tissue Repair and Functional Recovery

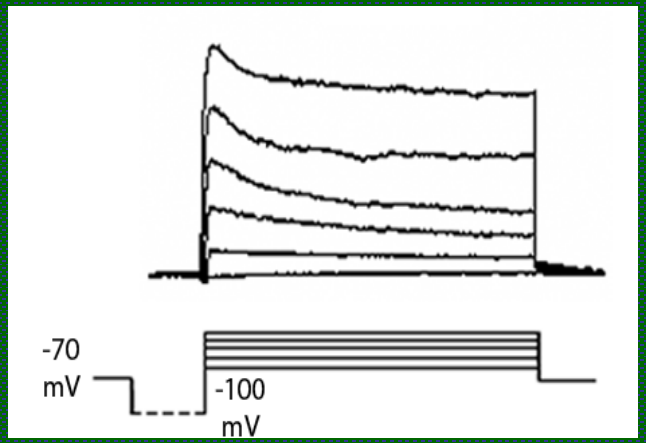
Specific major issues in stem cell transplantation therapy

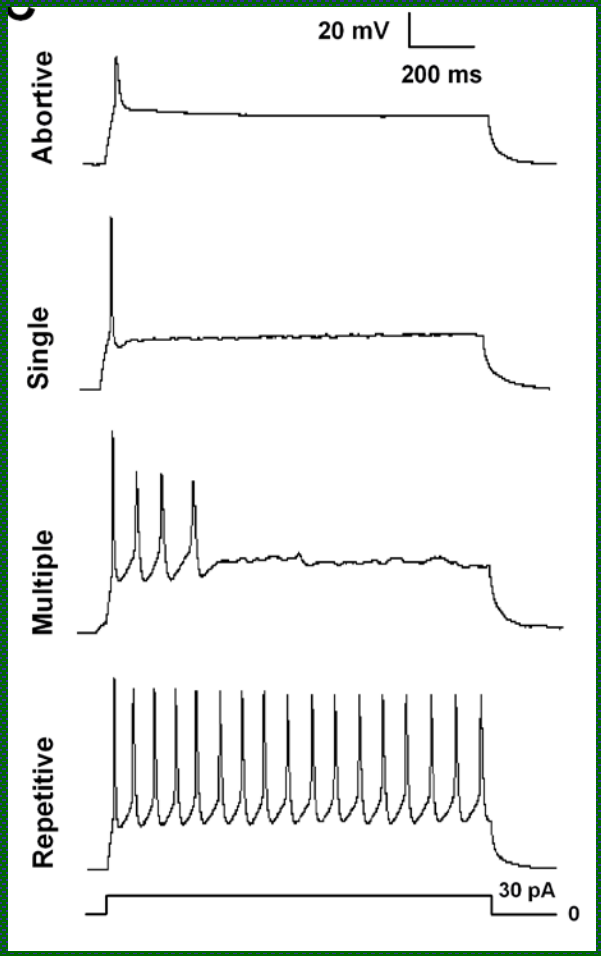
- Cell types and neuronal differentiation: functional neurons and multiple cell types, ethical concerns;
- Survival of transplanted cells in the injurious environment (ischemia, ROS, inflammatory factors, excitotoxicity, apoptotic insults, autophagy and so on);
- Cell delivery and homing to the lesion site;
- Integration/engraftment with host cells/tissues: guided neural network repair;
- Functional recovery;
- …..

Neuronal Differentiation of Human ES Cells and iPS Cells









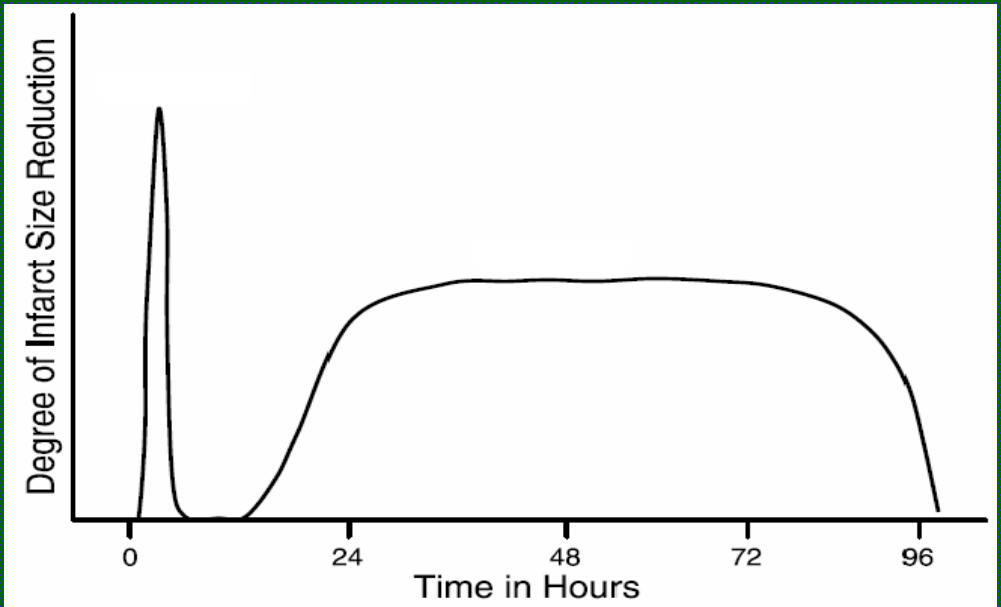
Drury-Stewart et al., 2011;
Song & Yu, 2012

Human neural precursor cells show poor survival following transplantation

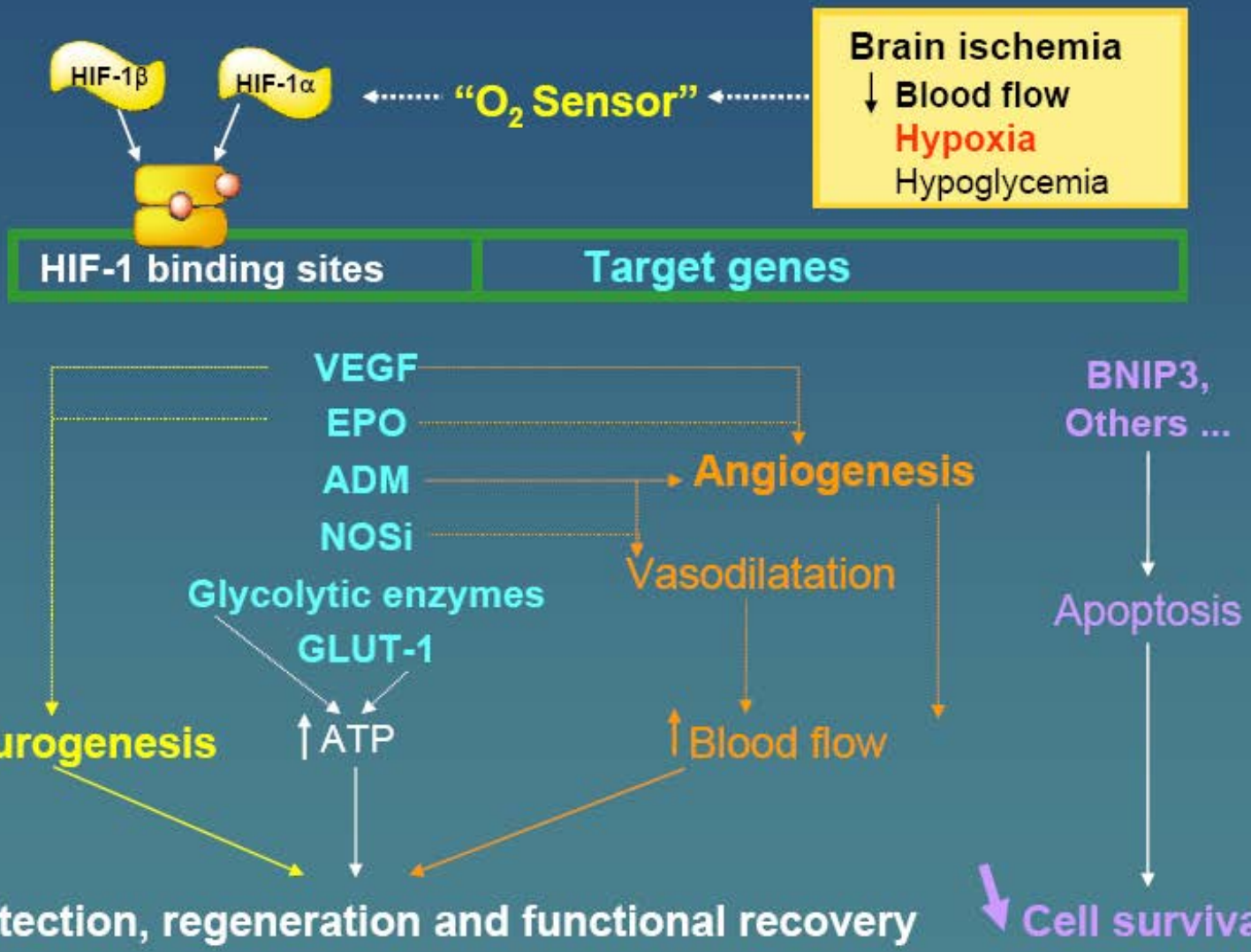
- Daadi et al. 2008. *PLoS ONE*; 3:e1644. (21,200 – 52,800 / 400,000 5.3 – 13.2%)
- Kim et al. 2007. *Neurosci Res*; 58:164-175. (few to innumerable / 500,000 >10 %)
- Yang et al. 2008. *Stem Cells*; 26:55-63 (25,919 ± 4,756 / 200,000 10.6 - 15.3%)
- Roy et al. 2006. *Nat Med*; 12:1259-1268. (136,726 ± 23,515 / 500,000 22.6 – 32%)
- Capowski et al. 2007. *J Neurosci Methods*; 163:338-349. (1,500 / 300,000 0.5%)

New Approach for stem cell therapy:
Hypoxic Preconditioning

- **Exposure to sublethal hypoxia promotes the activation of an endogenous protective phenotype.**
- **Protective effects of hypoxic preconditioning have been shown in virtually all cells and multiple systems, including heart, brain, and many other organs.**



Adaptation to hypoxia: *HIF-1 activation*



Hypoxic preconditioning of transplanted cells

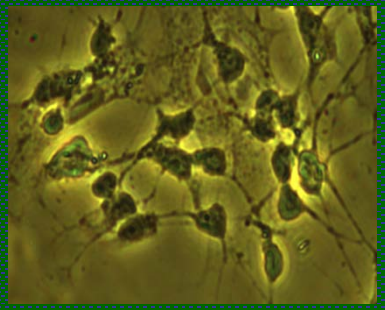
Neuronal differentiation of ES cells or iPS cells

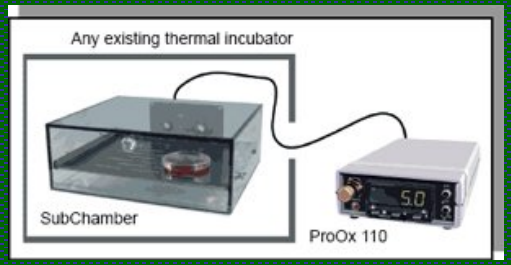
Bone marrow mesenchymal stem cells

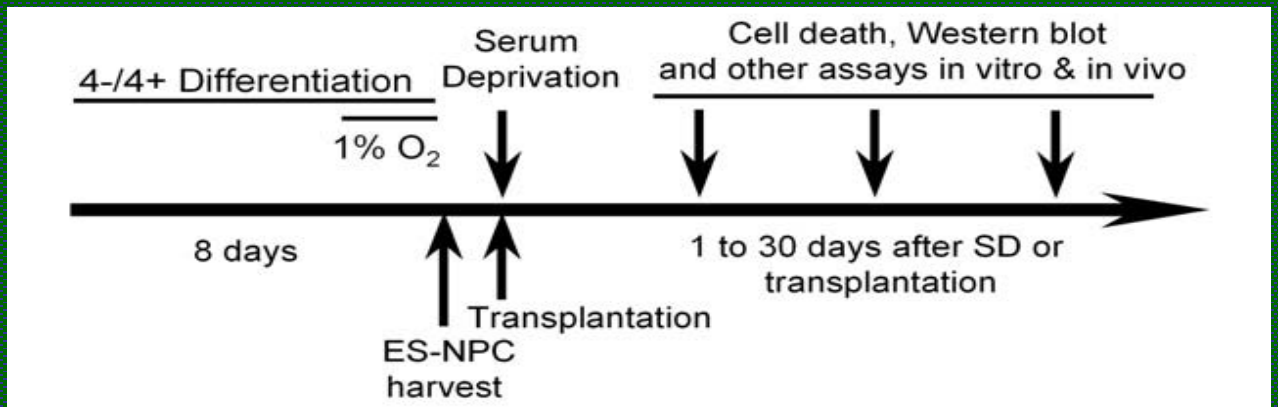
Hypoxic preconditioning with Sublethal low O_2

(0.5-1% O_2 X 8-12 hrs)

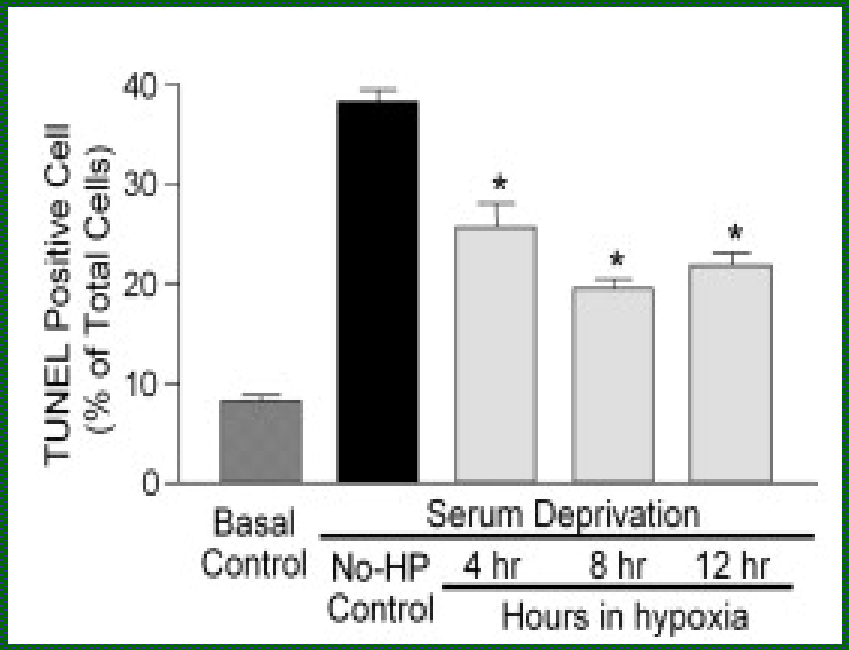
Stem cell transplantation (Systemic and local delivery)

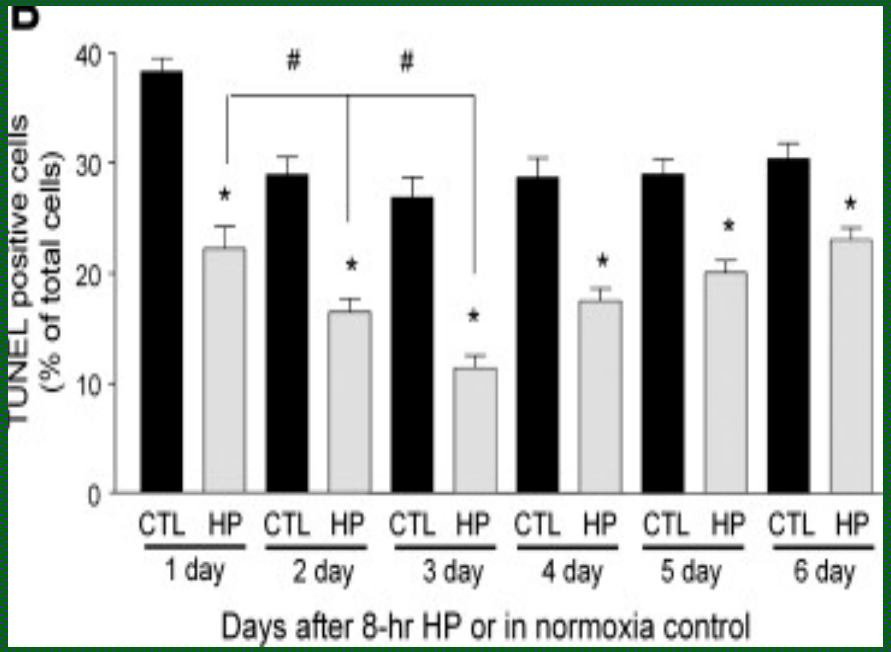






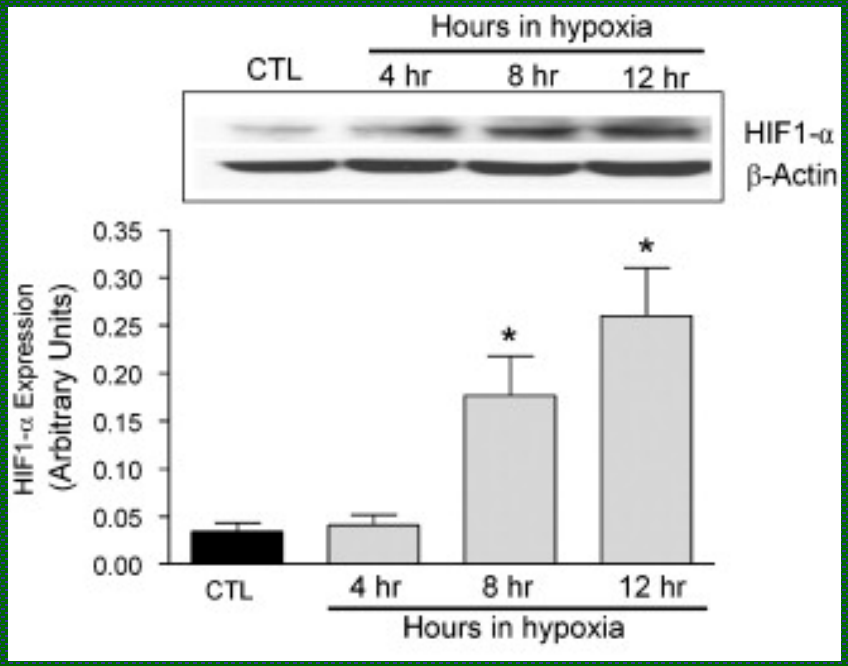
Dose-response Relationship of Hypoxia Exposure and Cytoprotection in vitro

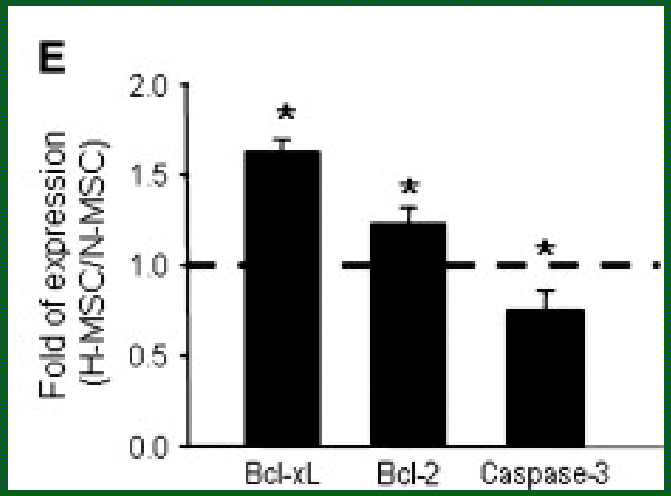




Theus et al., Exp Neurol 2007

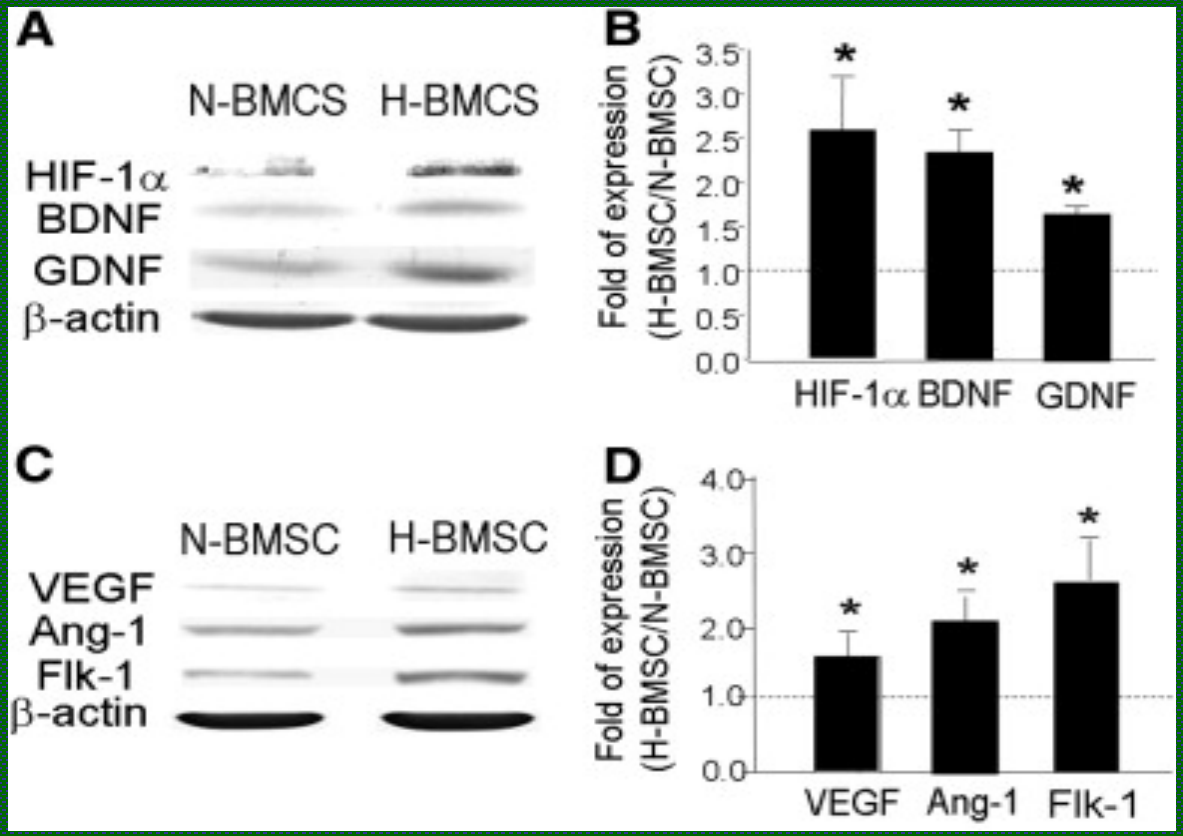
Hypoxic Preconditioning Enhances HIF-1alpha and Surviving Factors in Conditioned Cells





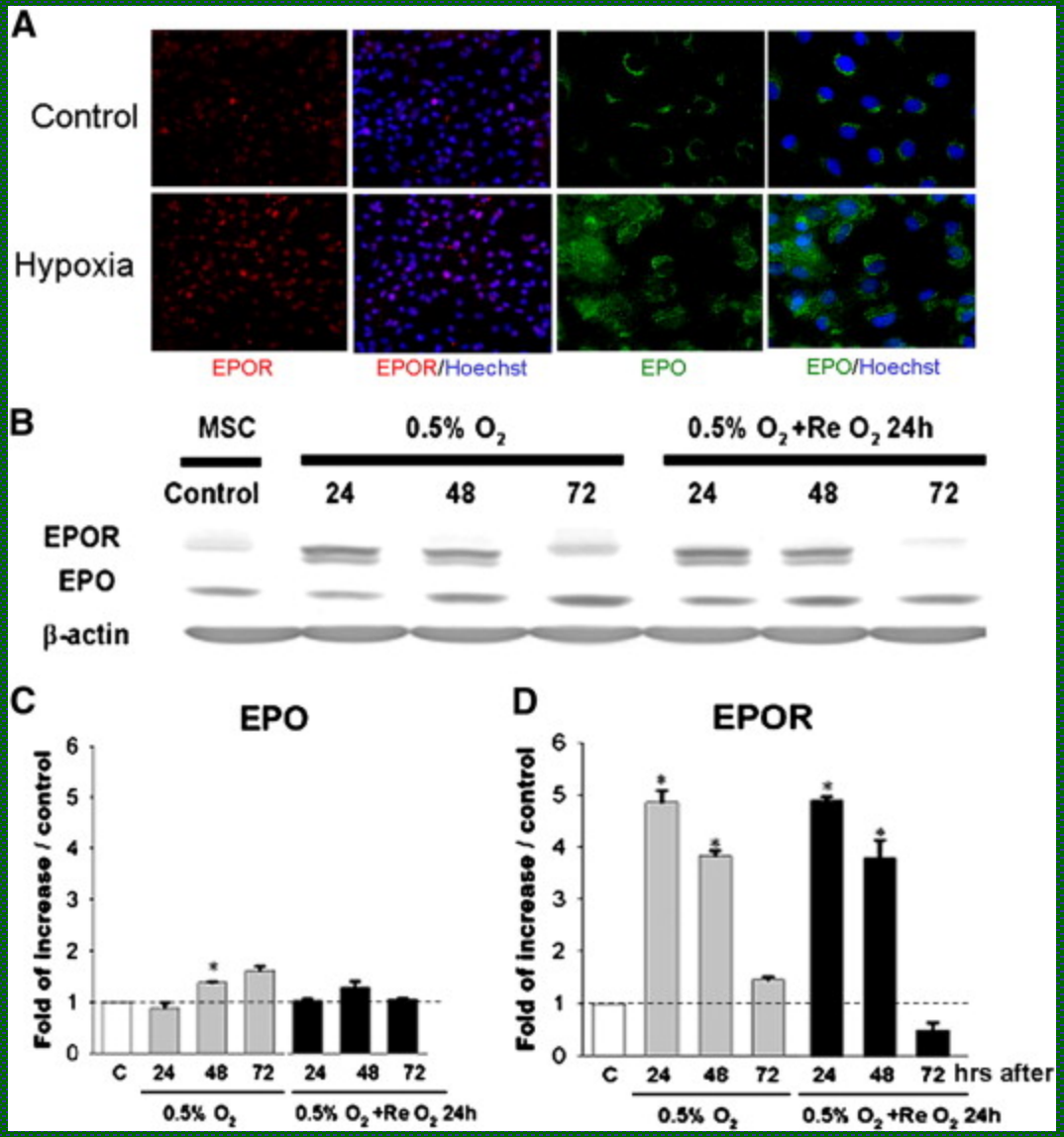
Hu et al.
Am J Physiol Cell Physiol. 2011

Hypoxic Preconditioning Enhances HIF-1alpha and Trophic/Angiogenic Factors in Conditioned Cells

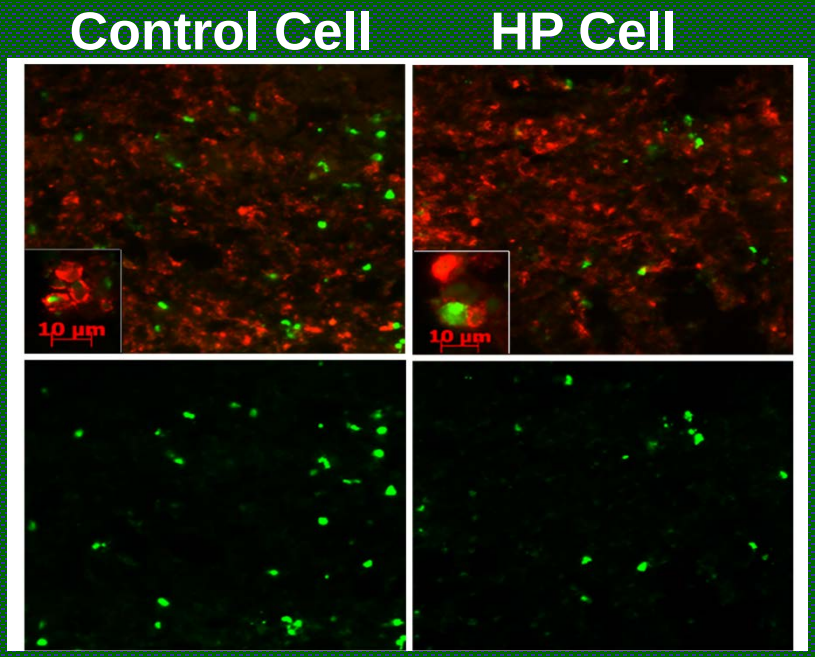


Hu et al.
Am J Physiol Cell Physiol. 2011

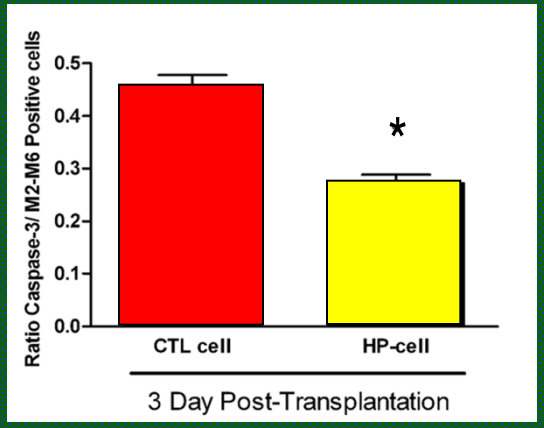
Hypoxic Preconditioning Enhances Erythropoietin and its Receptor in Conditioned Cells



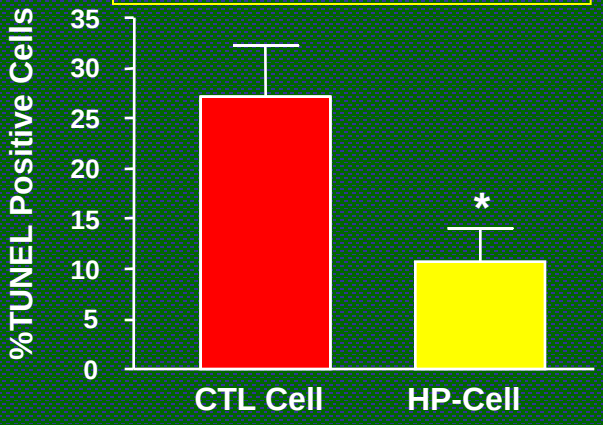
Hypoxic Preconditioning Enhanced Survival of Transplanted Cells in vivo



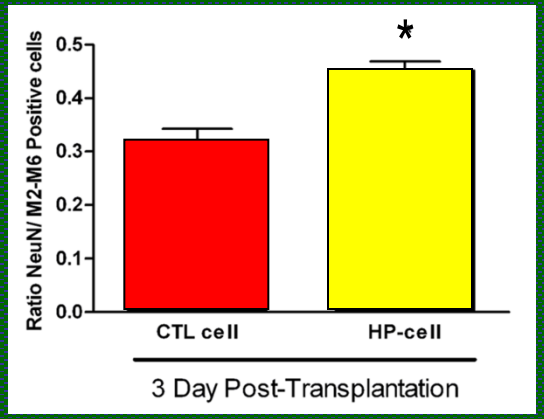
Caspase-3 positive ES cells



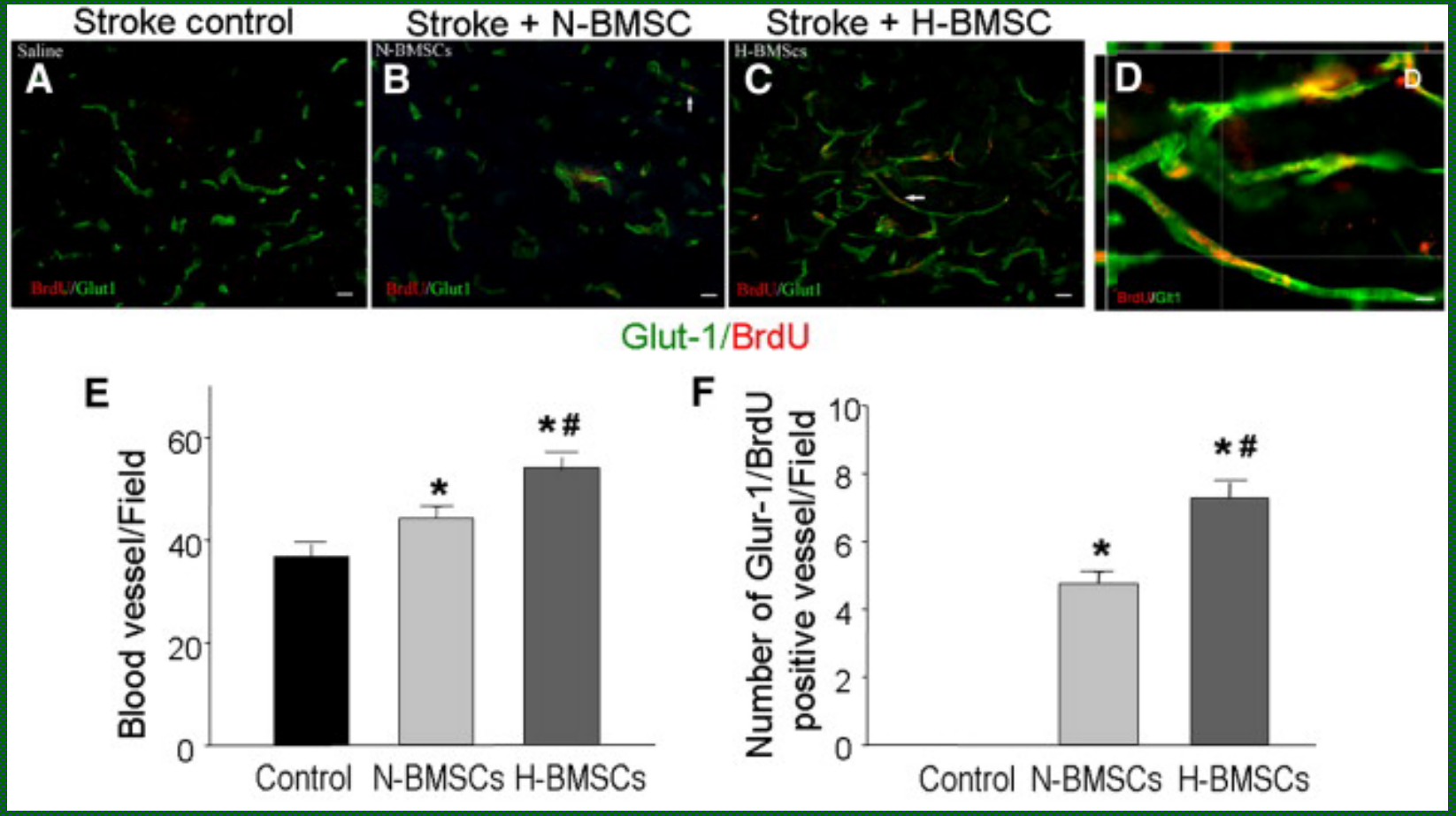
TUNEL Positive ES Cells



ES cells-derived neurons

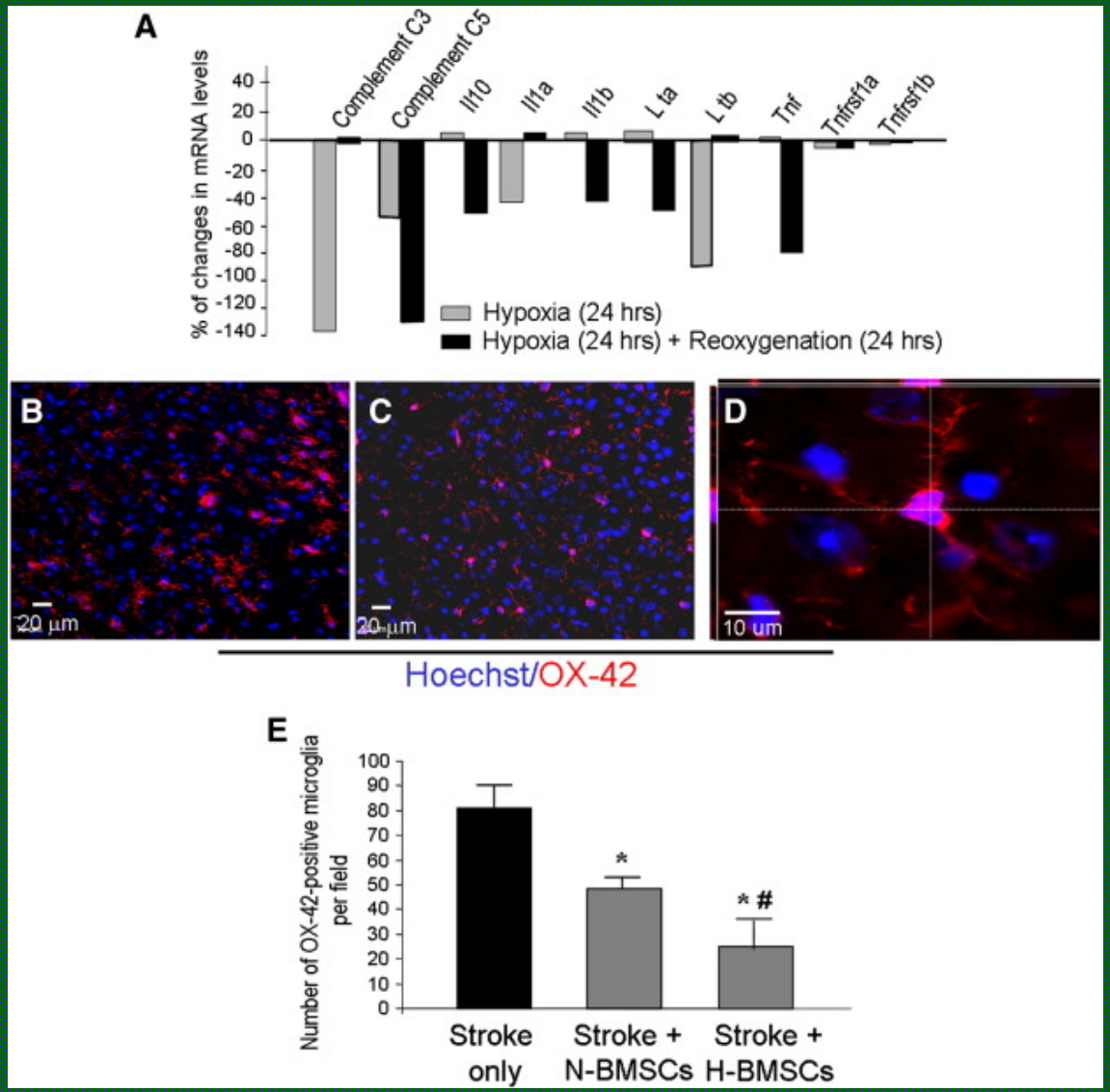


Transplantation of Hypoxic Preconditioned Cells Promotes Angiogenesis in the Ischemic Brain



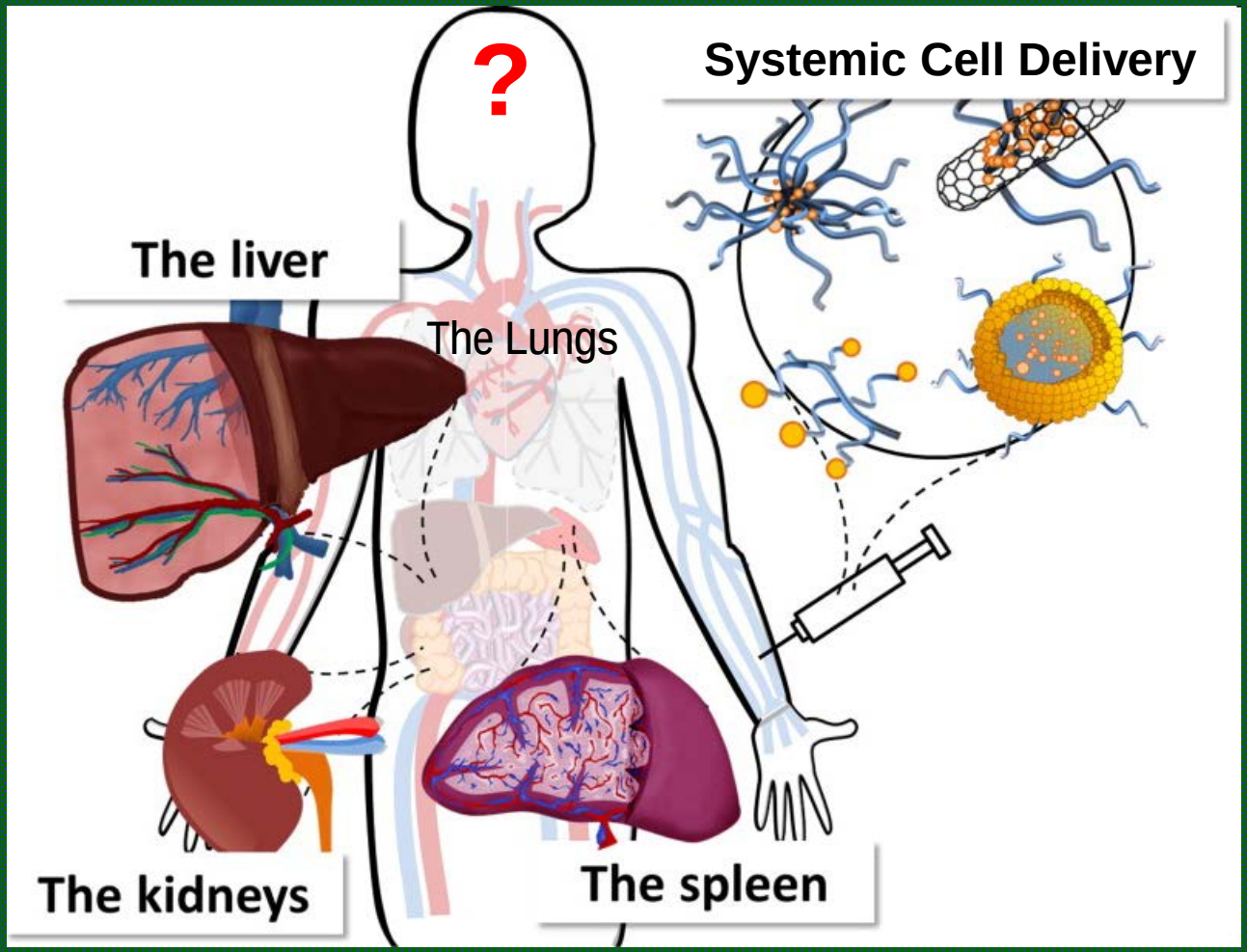
Hu et al.
Am J Physiol Cell Physiol. 2011

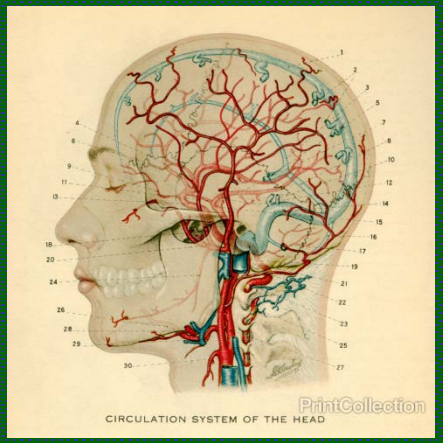
Transplantation of Hypoxic Preconditioned Cells Suppresses Inflammatory Activities in the Ischemic Brain



Wei et al., Neurobiol Dis, 2012

Low Homing Rate of Transplanted Cell to the Brain after Systemic Cell Delivery

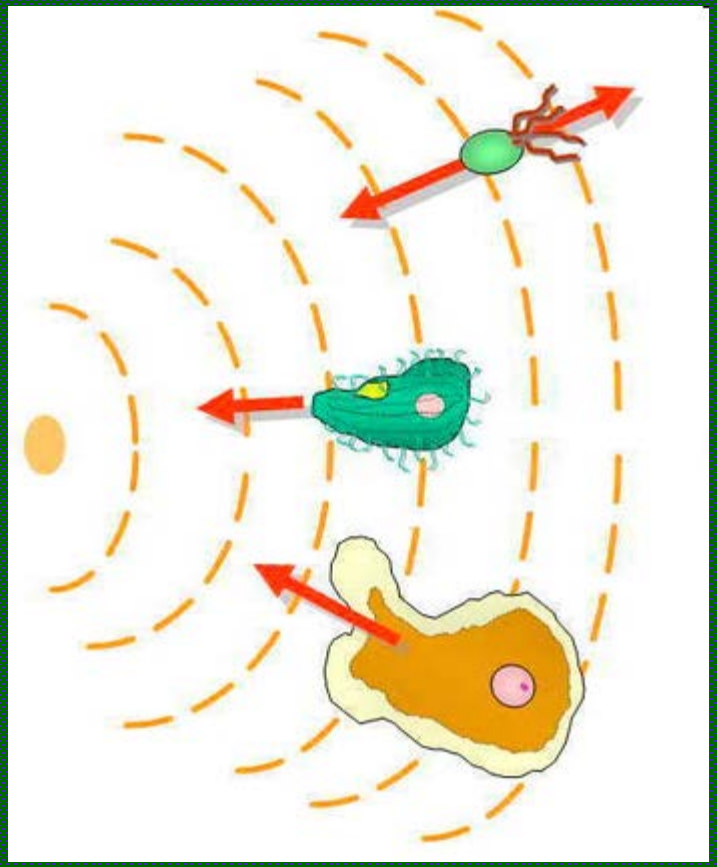




<1% of cells can reach to the ischemic brain

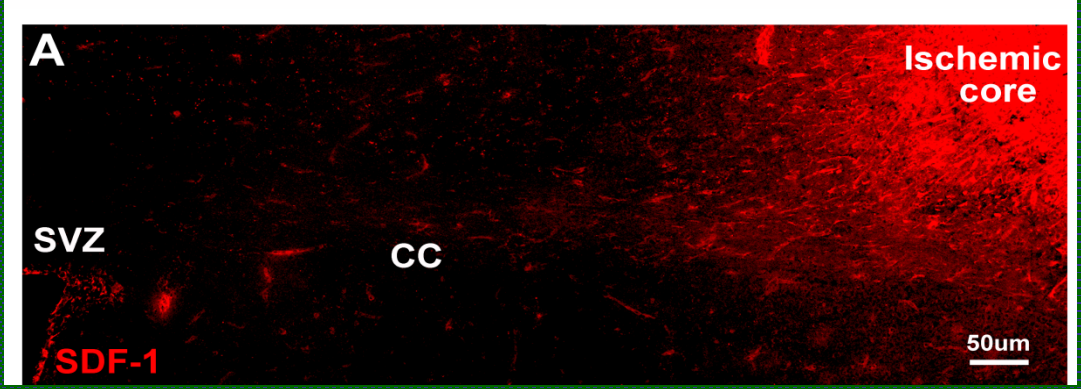
Directional Migration Guided by Chemoattractants

SDF-1

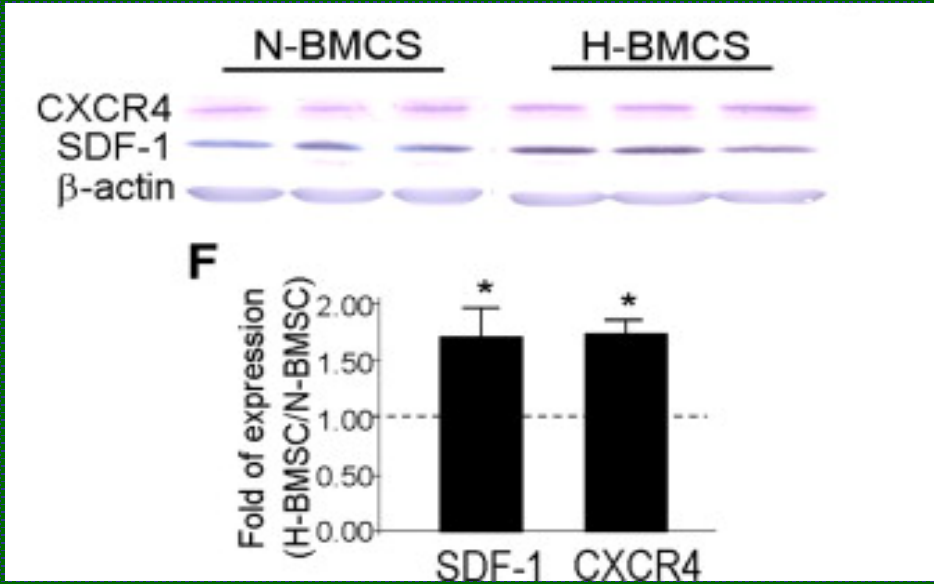


CXCR4: SDF-1 receptor

Hypoxic Preconditioning Enhanced Migration Factors

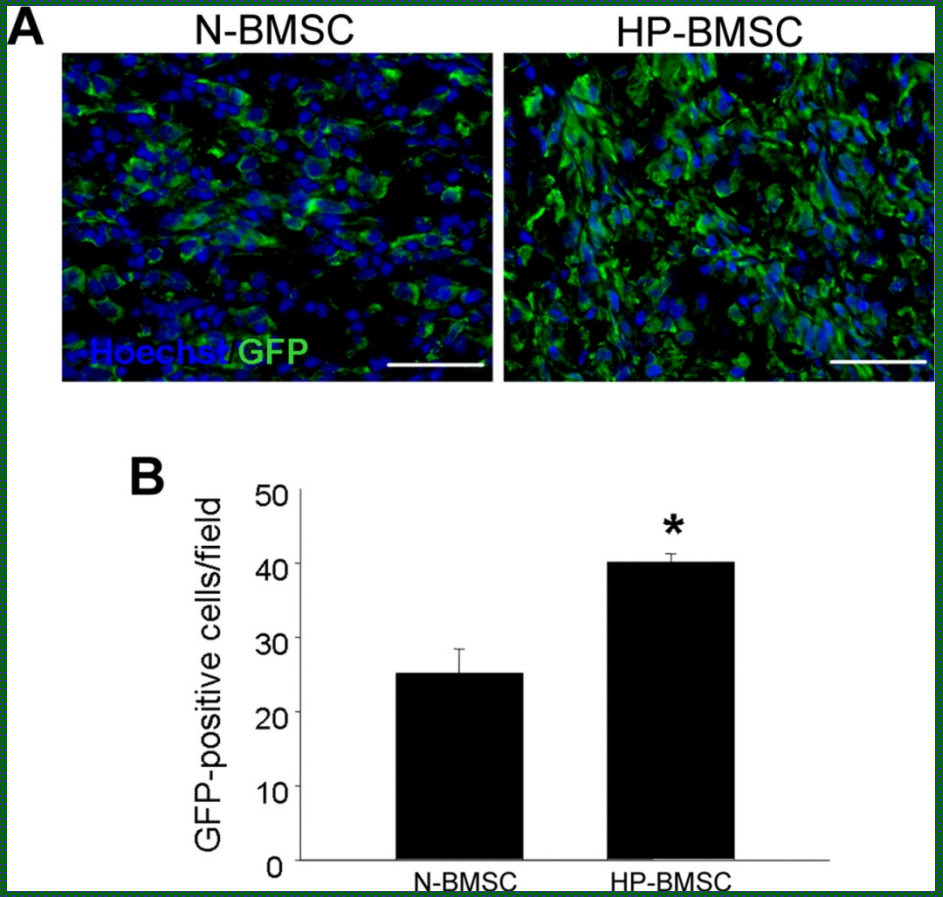


SDF-1



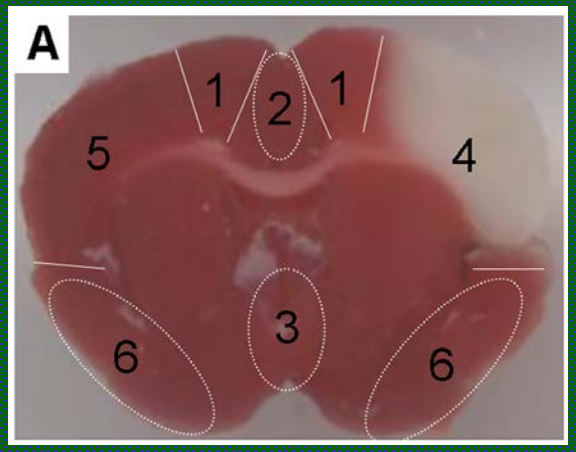
Hu et al. Am J Physiol., 2011
Wei et al., Cell Transp., 2013

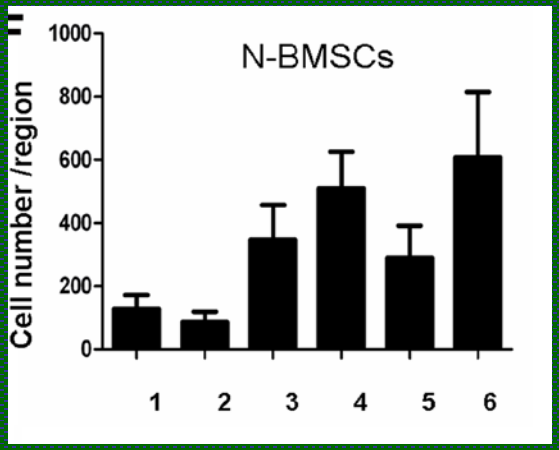
Hypoxic Preconditioning Increased Homing of Transplanted BMSCs

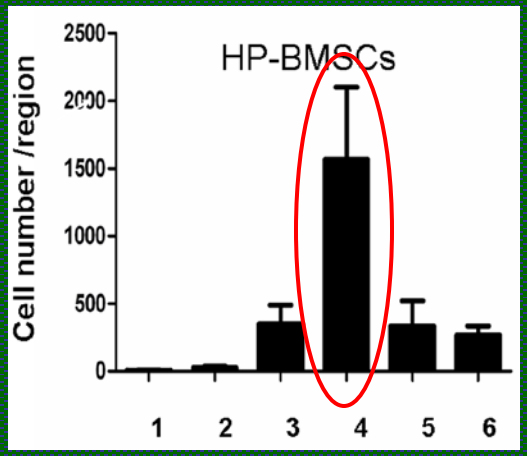


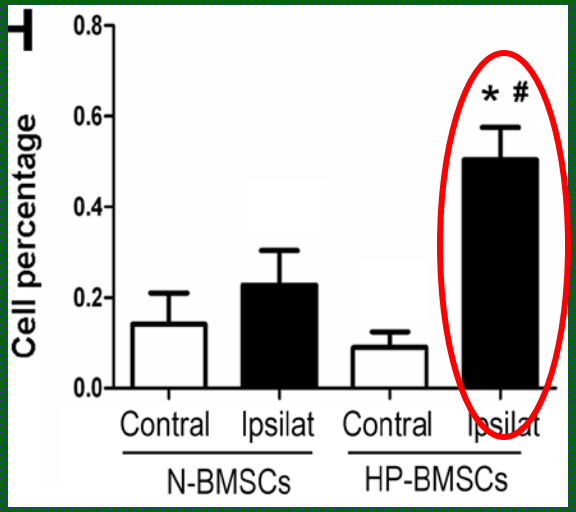
Hu et al.
Am J Physiol Cell Physiol. 2011

Hypoxic Pre-conditioning Promotes Cell Migration to Ischemic Region



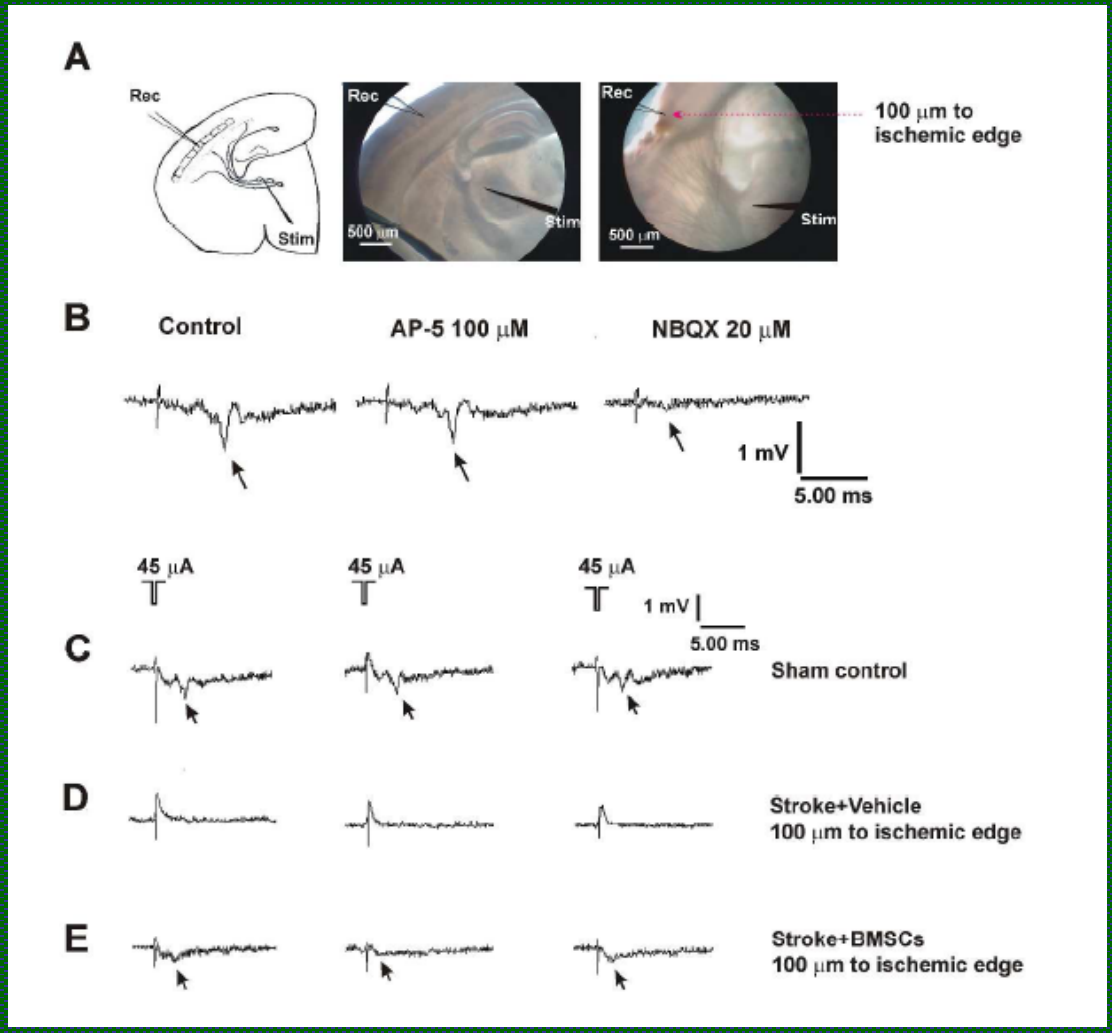






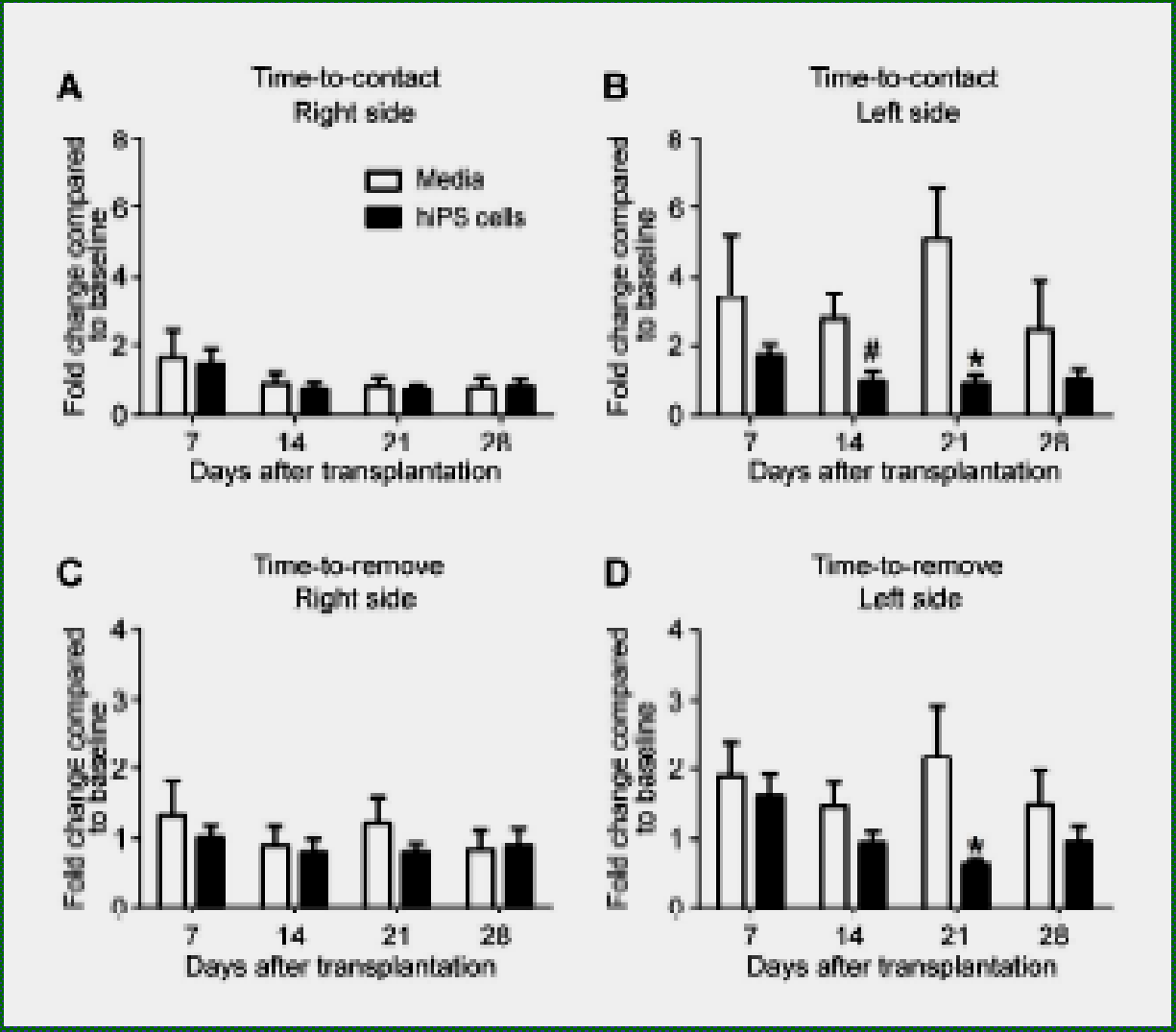
Wei et al., Cell Transplantation 2012

Repair of Thalamo-cortical Connections



Functional Recovery after Stroke and Transplantation of iPS-derived Neural Progenitors

Sticky Dot Test



SUMMARY

- **Hypoxic preconditioning is an effective pre-treatment for increased tolerance of stem cells and neural progenitor cells both in vitro and after transplantation into the ischemic brain.**
- **The increased expression of angiogenic factors in preconditioned cells can promote angiogenesis in the ischemic brain.**
- **Hypoxic preconditioning increases the expression of migration factors such as SDF-1 and its receptor CXCR4, thus enhancing cell homing to the ischemic region.**
- **Improved cell survival, differentiation and homing to the ischemic region will benefit clinical applications of cell transplantation therapy.**

Acknowledgment

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