Repair of spinal cord injury by hypoxia-inducible factor-1a-expressing neural stem cells

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Abstract
Neural stem cell (NSC) transplantation is an effective method of giving a supplement of cells lost and promoting functional recovery after spinal cord injury (SCI). Nonetheless, owing to hostile environments at the injury site, such as ischaemic hypoxia conditions and inflammatory cytokines, poor cell survival and uncontrolled differentiation are consistent problems encountered following NSC transplantation in ischaemic neural tissue. Hypoxia-inducible factor-1a (HIF-1α) provides profound protection to NSCs against negative factors at the injury site. On the other hand, HIF-1 can induce NSCs to differentiate into neurons. We predict that transplanted NSCs modified by an HIF-1α gene would have a better efficacy for promoting neural regeneration and functional reconstruction.

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Introduction
Spinal cord injury (SCI) is a kind of disabling condition of the central nervous system that leads to a heavy burden on family and society. Cellular therapy provides a method of giving a supplement of cells lost in the injury and promoting functional recovery after SCI. The rationales for this approach can be summarised as follows: (a) to promote the functional reconstruction of neuronal circuits, (b) to exhibit trophic effects and (c) to simulate the remyelination of axons [1]. However, owing to a hostile environment at the injury site, such as ischaemic hypoxia conditions and inflammatory cytokines, poor cell survival and uncontrolled differentiation are consistent problems encountered following...
neural stem cell (NSC) transplantation in ischaemic neural tissue [2–5].

Hypothesis/idea

In order to improve the survival of transplanted NSCs, enhance angiogenesis in the injured site and promote differentiation of neurons, we proposed a conjecture: to introduce the hypoxia-inducible factor-1α (HIF-1α) expression system into the NSCs so as to establish a controlled HIF-1α-expressing stable NSC line. Accordingly, transplantation with HIF-1α-expressing NSCs can effectively solve the above-mentioned problems.

Evaluation of the hypothesis/idea

HIF-1α is a transcriptional regulator of oxygen homeostasis and a key factor for generating the adaptive responses through upregulation of various target genes involved in erythropoiesis, angiogenesis, vascular tone maintenance, mitochondrial function, cell survival following ischaemic/hypoxic injury as well as glucose metabolism and transport. The regulation of the HIF-1α activity depends mostly upon the alpha subunit. The triggered expression of HIF-1α provides profound protection against focal cerebral ischaemia [6–8]. The HIF-1α downregulated the genes responsible for protection in ischaemic hypoxia injury, such as erythropoietin (EPO), vascular endothelial growth factor (VEGF), vascular tone, glycolytic enzymes and so on [9–17]. Potentially intrinsic mechanisms: (a) promote endothelial cell proliferation and blood vessel formation, (b) have a direct protective effect on nerve tissue [18,19], (c) tolerate against excitotoxicity of nerve cell [20] and (d) reduce tissue oedema and inflammatory reaction by the activation of superoxide dismutase and glutathione peroxidase [21,22].

Conditionally inactivating the hypoxia-responsive transcription factor HIF-1α in murine can reduce NSC survival and proliferation rate [23]. Upregulation of HIF-1α can promote NSC proliferation on the one hand and induce NSCs to differentiate into neurons on the other [24,25]. HIF-1α seems to be a transcription factor that is relevant to the development and survival of neurons that are involved in HIF-1α signalling pathway activation and result in a downstream of a variety of target gene upregulation. Furthermore, stem cell factor (SCF), a downstream target gene of HIF-1α, can promote neuronal differentiation and inhibit astroglial differentiation at the early stage of NSC differentiation [26]. Some studies also showed that VEGF plays a guiding role in axon growth [27,28]. Meanwhile, the level of VEGF has an effect on the migration of nerve cells [29].

Discussion/conclusion

Compared with traditional NSC transplantation, the advantages of NSCs that are modified by HIF-1α gene transplantation are as follows: (a) the cell survival rate of the transplanted NSCs is higher in the negative environment at the injury site, (b) local expression of HIF-1α increases angiogenesis after injury and improves cell ability of anti-apoptosis in damaged tissue and (c) the HIF-1α-expressing cells can be self-induced to differentiate into neurons without extra help. In general, transplanted HIF-1α-expressing NSCs will bring a promising therapy method for people afflicted with SCI.

Overview box

First Question: What do we already know about the subject?

Hypoxia-inducible factor-1 (HIF-1) is a transcriptional regulator of oxygen homeostasis and a key factor in the generation of the adaptive responses through upregulation of various target genes involved in erythropoiesis, angiogenesis, vascular tone maintenance, mitochondrial function, cell survival following ischaemic/hypoxic injury as well as glucose metabolism and transport. In addition, upregulation of HIF-1α can promote neural stem cell (NSC) proliferation on the one hand and induce NSCs to differentiate into neurons on the other.

Second Question: What does your proposed theory add to the current knowledge available, and what benefits does it have?

Compared with traditional NSC transplantation, the advantages of NSCs that are modified by HIF-1α gene transplantation are as follows: (a) the cell survival rate of the transplanted NSCs is higher in the negative environment at the injury site, (b) local expression of HIF-1α increases angiogenesis after injury and improves cell ability of anti-apoptosis in damaged tissue and (c) the HIF-1α-expressing cells can be self-induced to differentiate into neurons without extra help.

Third Question: Among numerous available studies, what special further study is proposed for testing the idea?

How does one construct a recombinant defective retroviral vector carrying the HIF-1α gene and stable virus-producing packaging NSCs, and then treat spinal cord injury in a secure way?

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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References


