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REVIEW ARTICLE

Research progress on the therapeutic effect of olfactory ensheathing cell transplantation on ischemic stroke

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ABSTRACT

Olfactory ensheathing cells (OECs) are a special type of glial cell in the olfactory system, which exhibit neuroprotective, immunomodulatory, and angiogenic effects. Although many studies have focused on the reversal of demyelination and axonal degeneration (during spinal cord injury) by OECs, few reports have focused on the ability of OECs to repair ischemic nerve injury. This article reviews the protective effects of OEC transplantation in ischemic stroke and provides a theoretical basis and new strategy for OEC transplantation in the treatment of ischemic stroke.

1 Introduction

Ischemic stroke is a major cause of death and long-term disability, resulting in a high social and economic burden [1]. There is a strict time window for thrombolysis or mechanical thrombectomy in the acute stage, and patients who fail to receive treatment develop lifelong disabilities [2]. The current methods for treating ischemic stroke are less effective with respect to neurogenesis and functional recovery in the chronic phase, which adversely affects the life and socioeconomic status of patients. Thus, nerve regeneration methods are being developed to promote the repair of damaged neural networks and reduce the risk of disability caused by ischemic stroke [3]. Cell therapy is effective in acute, subacute, and chronic stroke [4] and represents a new therapeutic strategy for the treatment of ischemic stroke. Animal studies have shown that cell therapy may improve neurological dysfunction following stroke and it has been tested in clinical trials with somewhat favorable results [5–8]. However, many issues remain unresolved and require clarification, such as the need to develop techniques that maximally enhance the effects of cell therapy on stroke. These issues relate to defining the

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optimal cell types, cell doses, transplantation routes, and candidate patient types. The specific efficacy of each of these factors also needs to be confirmed. Many studies have demonstrated that neural stem cells (NSCs) [9–11], human umbilical cord blood cells [12–14], bone marrow mononuclear cells [15–17], hematopoietic stem cells, bone marrow/adipose-derived mesenchymal stem cells/stromal cells [18–21], Schwann cells, mesenchymal cells, and other stem cells exhibit tissue remodeling activity in animal models of ischemic stroke injury. However, the survival rate of these cells and their integration into the host tissue after transplantation remain poor. A previous study showed that olfactory ensheathing cells (OECs) have a stronger ability to inhibit glial scar formation and the inflammatory response of astrocytes in spinal cord injury than Schwann cells [22]. They also promoted the growth of nerve axons and established synapses between nerve axons. Several clinical studies [23–27] have also shown that patients with spinal cord injury who received fetal olfactory bulb (OB) or autologous olfactory mucosa (OM) OEC transplantation showed improvement of varying degrees in motor and sensory function. However, it is not clear whether the effects of OEC transplantation can play a role in ischemic stroke and spinal cord injury. This review describes the pathological mechanism of ischemic stroke, the characteristics of OECs, and the role of OEC transplantation in ischemic stroke. It provides a theoretical basis for treating tissue injury after focal cerebral ischemia and the potential of OEC transplantation for the treatment of ischemic stroke.

2 Pathophysiology of ischemic stroke

Stroke is usually caused by a single vascular occlusion that affects downstream processes by deprivation of glucose and oxygen. Although the cerebral artery has a collateral vascular network to compensate, it is usually not sufficient to save the entire ischemic area. Therefore, the closer the ischemic area is to the occluded vessel, the less blood passes through. Inflammation is an important mechanism of secondary nerve injury in ischemic stroke. Astrocytes are widely distributed in the brain, exhibit strong tolerance to hypoxia, and can interact with almost all cells of the neurovascular units. Astrocytes are rapidly activated into reactive astrocytes after ischemic stroke, releasing inflammatory factors and promoting the activation and invasion of other inflammatory cells. This triggers an inflammatory response cascade and aggravates ischemic nerve injury. Inflammatory cascades triggered by cellular ischemic events include primarily impaired cellular energy metabolism, cellular depolarization, excitotoxicity, and blood–brain barrier disruption [22]. Theoretically, the ischemic brain can be divided into two diverse harmed locales, specifically, the ischemic center and the penumbra. The ischemic cascade in the ischemic penumbra advances over time. The events include adenosine triphosphate exhaustion; disturbance of sodium, potassium, and calcium concentrations; increased lactic corrosion; acidosis; increased oxygen free radicals; discharge of excitatory glutamate; and increased intracellular water that may occur from a couple of minutes to hours after a stroke occurs. Inside hours to weeks (subacute phase), neuronal apoptosis, penetration and actuation of inflammatory cells (neutrophils, monocytes, and microglia), angiogenic edema, and elevated intracranial pressure begin to occur. Despite ischemia, the pathological response of the brain appears to be stable after entering the chronic phase, but the irritation and blood–brain boundary spillage, which are not conducive to the recovery of the brain, may continue,

resulting in serious consequences to the body [28]. The injury pathways secondary to ischemic stroke are presented in detail in Fig. 1 [29]. Since the bloodstream within the ischemic center is lower than the level required for cell survival, the cells die, resulting in irreversible damage. In the event the blood flow in the ischemic penumbra decreases and cannot support neurological function, it provides the minimum energy needed to prevent immediate cell death. If the blood flow recovers in time [30], brain cell injury is reversible.

3 Potential mechanism of cell therapy for ischemic stroke

In view of the pathophysiological mechanism of ischemic stroke, the current treatment strategy of cell transplantation is primarily designed to save reversibly damaged cells in the ischemic penumbra or to restore a new neural network through cell transplantation [31]. Cell therapy has multiple effects in animal models of ischemic stroke, such as prolonging the ischemic penumbra (acute phase), inhibiting unnecessary inflammation (subacute phase), and initiating neuroangiogenesis in the chronic phase. This provides an option to expand the treatment window for cerebral infarction stenosis and, at the same time, ameliorates the key components of stroke pathophysiology, which is cell loss caused by ischemia. As outlined in several descriptive reviews [3, 32–34], these mechanisms can be subdivided into two categories: (i) cell differentiation (cell substitution), and (ii) secretion of paracrine factors (bystander effect). Cell substitution can restore lost function by differentiating the transplanted cells into neurons or vascular cells, or through the direct settlement and development of neural progenitor cells (NPCs). An *in vivo* study showed that 2 months after cell transplantation, approximately 50% of the transplanted cells displayed a neuronal phenotype in the ischemic

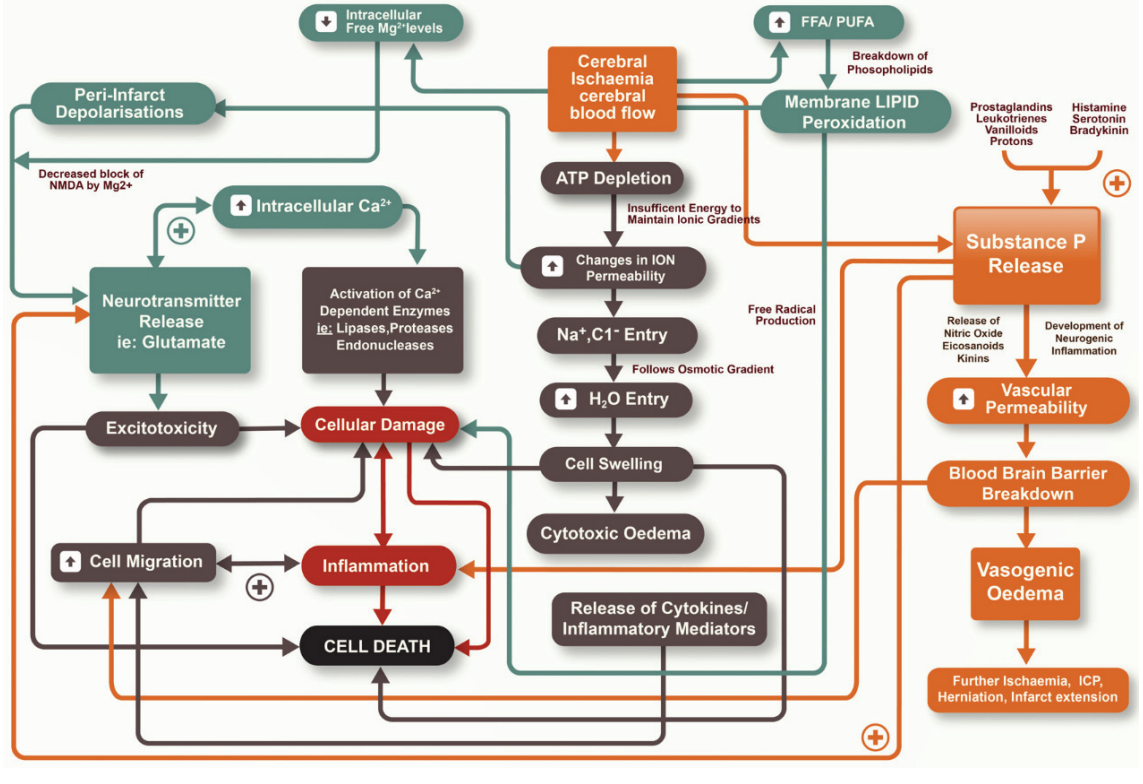

Fig. 1 The injury pathways secondary to ischemic stroke. Reproduced from Ref. [29].

brain [35]. In addition, cell substitution can enhance the expression of neural genes related to the release of nutritional factors. The release of paracrine factors is another potential mechanism of cell transplantation therapy, which occurs primarily through the secretion of a variety of nutritional factors (cytokines, chemokines, exocrine bodies) that contribute to anti-inflammation, immune regulation, and mobilization of endogenous stem cell (NSC)/NPCs [36].

4 Biological characteristics of OECs

OECs are a special type of glial cell that have the properties of both Schwann cells and astrocytes. OECs can accompany olfactory nerve axons from the peripheral nervous system to the central nervous system and combine with the mitral cells of the OB at the skull base [37]. OECs are the only known glial cells that can cross the barrier between the peripheral and central nerves, and have the ability to regenerate at a mature stage. OECs exhibit a faster proliferation rate in culture and have the potential for various applications. In addition to spinal cord injuries, they may be used for the treatment of cerebrovascular and ophthalmological diseases [38]. OECs are considered to be the key to the lifelong regeneration of the primary olfactory nervous system. Therefore, the transplantation of OECs to repair the damaged nervous system has been a focus of research over the past two decades [39–41]. In the natural environment, OECs support and guide the extension from the OM to the target synaptic area of the OB [42]. This promotes nerve regeneration at the anatomical location as well as after transplantation. The mechanism mainly includes direct interaction with surrounding axons and support structures, secretion of neurotrophic and guide factors [43, 44], phagocytosis of axonal fragments, and effective migration and integration with other types of cells, such as astrocytes and microglia [45, 46].

5 The principle of OECs in the treatment of ischemic stroke

Different stages of the ischemic process provide different targets for OEC therapy. Early application of OECs can reduce inflammation, regulate the dynamic environment of anti-toxicity, and reduce injury to the infarcted area. Two or 3 weeks after ischemia, late cell transplantation can regulate the repair process, which is beneficial to angiogenesis and nerve regeneration. As described in many experiments [47–50], vascular endothelial growth factor, brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, and nerve growth factor, secreted by OECs, play an important role in the function of nerves, glia, and endothelial cells [51, 52]. They have significant potential in promoting brain plasticity and functional recovery. In addition, Nazareth et al. showed that OECs exhibit higher phagocytosis and transport activity than Schwann cells and have a stronger inhibitory effect on inflammation [53]. OECs are different from astrocytes and Schwann cells, but they exhibit characteristics of both. OECs are similar to Schwann cells in promoting axon growth, but they are more likely to promote axon growth over long distances than Schwann cells; that is, they are more migratory. As astrocytes, OECs also contribute to neuronal survival and axonal growth. OECs have no myelin, but they can wrap around neurons to form a myelin sheath and support neurite growth after transplantation into the central nervous system. These characteristics enable OECs to have a superior therapeutic effect on nerve repair.

6 OEC transplantation pathway and dose

OEC transplantation is generally performed through intracranial and intravascular methods. Most strategies of intracranial injection are done by intracerebral injection and intraventricular injection [54]. Stereotactic injection makes a difference in transporting OECs directly to the infarcted zone, but requires preciseness to reach the target area [55]. Intracerebroventricular infusion disseminates OECs to a more extensive range in the brain, and the level of inflammatory cytokines increases after dead tissue absorbs OECs to the center of the ischemic range. Thus, the restorative impact depends on the number of cells entering the infarcted region [56]. Strategies for intravascular infusion include intravenous and intra-arterial infusion. OECs injected intravenously have difficultly passing through pneumonic vessels because of their size; thus, few cells reach the target area [57]. Inner carotid supply route infusion can deliver OECs in a short period; however, intra-arterial infusion may lead to peripheral cerebral artery occlusion [58]. Intracranial transplantation may cause mechanical harm, but it can transport cells to the target location more efficiently than other strategies. Intravascular transplantation requires more cells than intracranial transplantation and has a better therapeutic effect on large areas of infarction. In clinical applications, endovascular therapy is easier to perform than intracranial therapy. Nasal injection (IN) is a new method of transplantation, which needs further study [59]. Cells may be transported from the nasal mucosa to the injured area through the blood circulation [60]. As a non-invasive method, IN represents a promising new method of cell transplantation [61, 62]. OEC treatment could be a new strategy for neuroprotection against intense ischemic stroke. Although there have been trials of OECs in the treatment of ischemic stroke, there is still no consensus on the optimal dose for cell therapy. In addition, it is still unknown whether the dose of OECs should be personalized based on the size of the infarction [63].

7 Research on OEC transplantation in ischemic stroke

There are few studies describing the effect of OEC transplantation on ischemic stroke. In this review, the literature related to several trials involving OEC transplantation in the treatment of ischemic stroke was obtained from PubMed, CNKI, Wanfang Data, and VIP Chinese journal databases, whereas the search language was unlimited. The keywords searched in the Chinese database were “olfactory ensheathing cell”, “ischemic stroke”, and “cerebral infarction”. The keywords for the PubMed database were “olfactory ensheathing cell”, “ischemic stroke”, and “OECs”. The searches were limited to “Title” and “Abstract”. Five papers were identified, including one clinical trial and four basic research studies. The dosage, pathway, and source of OECs used in each trial were slightly different as shown in Table 1. However, through a comprehensive analysis of the experiments, we found that OEC transplantation is feasible and effective in the treatment of ischemic brain injury. Wang et al. found that after cerebral ischemia–reperfusion, the score of neurological deficit in the OEC transplantation group was significantly lower than that in the control group [64]. The pathological changes of the injured brain tissue were significantly alleviated, and the level of nerve cell degeneration and necrosis was significantly decreased, whereas interstitial edema was alleviated. A large number of glial fibrillary acidic protein and neurotrophin receptor p75-positive cells were observed in the infarcted hemisphere in the cell transplantation

Table 1 Published trials using OECs for ischemic stroke.

Reference	Subject	OECs source	Dose (cells)	Transplant timing	Route
[64]	Patients	OECs in an aborted fetus	5.0×10^6	12 months or more after ischemia	IN
[22]	Rat	OECs in newborn SD rats	3.0×10^5	14 days after ischemia–reperfusion	IC
[65]	Rat	Human nasal polyps OECs	1.0×10^5	1 day after ischemia (no reperfusion)	IC
[66]	Rat	Transgenic rats OECs	5.0×10^5	Ischemia–reperfusion	IC
[67]	Patients	Fetal OECs	1.0×10^5	Sequelae of stroke or chronic phase	IC

IN, nasal injection; IC, intracerebral.

group. It was further verified that OECs can improve the pathophysiological outcome of the ischemic penumbra. Augestad et al. used a middle cerebral artery occlusion (MCAO) model to induce transient focal cerebral ischemia in adult rats and found that OECs implanted into the basal ganglia could promote tissue remodeling [22]. Shyu et al. found that human olfactory ensheathing cells/olfactory nerve fibroblasts (hOECs/ONF) specifically secreted nutritional factors, including stromal cell-derived factor-1α [65]. The behavioral indices of neurological impairment in stroke rats implanted with hOEC/ONF were significantly better than those in the control group. They demonstrated that OESs induced nerve regeneration and improved neurological dysfunction caused by hypoxic and ischemic stress. In another study, OECs promoted the repair of white matter after transplantation in MCAO rats [66]. Immediately after reperfusion, the transplantation of OECs around the infarction reduced the infarct volume, increased the survival rate, and improved the neurological defect. Immunohistochemical analysis showed that this may be caused by myelin regeneration and axon regeneration. The only clinical trial included in our search showed that the neurological function of patients receiving OEC transplantation improved, including improved speech, muscle strength, muscle tension, balance, pain, and breathing [67]. The Barthel index and clinical neurological deficit scores were increased for most patients. However, because of the small number of samples included in this trial, the results of the study need to be further verified in additional clinical studies. The above results, though preliminary, indicate that a new strategy based on OEC transplantation for the treatment of ischemic stroke can be used at different times following ischemic stroke, which has certain benefits, although the safety profile has not yet been established.

8 Perspect

Although the neuroprotective effect of OECs on ischemic stroke has been preliminarily confirmed, the specific protective mechanism remains unclear. Many new strategies have been proposed, including the use of cell transplantation to support the internal repair and recovery mechanisms, single drug administration and combined transplantation, or combined transplantation of several cell types of cells and other substances. However, these effects need to be verified by well-designed large-scale trials. It is necessary to clarify the mechanism of action in cells following transplantation to better select the optimal treatment time window for cell transplantation, the best route for cells to enter the brain, and more suitable cell types and sources. This will enable patients to benefit from treatment, monitor cell therapy by imaging technology, and identify the best way to control cell proliferation, survival, migration, and

differentiation in the pathological environment [68, 69]. To optimize functional recovery, neurorestorative therapy may require comprehensive application [70–72]. Although there are few studies on OECs for the treatment of ischemic stroke and the related studies have some limitations, the results indicate that OEC therapy brings hope for patients with acute stroke or chronic stroke sequelae. Therefore, it is anticipated that it becomes a new treatment option.

Conflict of interests

All contributing authors have no conflict of interests to declare.

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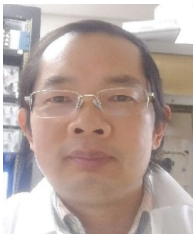

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