Introduction

WMI is mainly caused by demyelination of central neuronal cells, which can lead to motor, visual and cognitive disorders. Oligodendrocytes are the only cell type to form myelination. Late oligodendrocyte progenitors at GW24-32 in humans are susceptible to hypoxia-ischemia (HI) or inflammation, therefore resulting in demyelination in periventricular, subcortical and callosal white matters (1). There are some guidelines for WMI treatments, basically supporting or symptomatic treatments. Erythropoietin and hypothermia are also used for treating WMI (2). These treatments can promote neurons regeneration, reduce neuronal loss and axonal injury, but none of them can repair myelin loss. There are growing evidences from clinical and pre-clinical studies that stem/progenitor cells have multiple roles in treating neurological diseases including WMI. Stem cells are undifferentiated cells that include two broad categories: embryonic stem cells (ESCs)/induced pluripotent stem cells (iPSCs) and adult stem cells. ESCs

Therapeutic approach of stem cell transplantation for neonatal white matter injury

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Abstract: The white matter in brain are mainly composed of oligodendrocytes and myelinated axons, and are important for the transmission of neural signals in central nervous system. White matter injury (WMI) is a leading cause of neurocognitive deficits in premature infants as the oligodendrocytes progenitors are easily attacked by hypoxia-ischemia (HI). Various clinical methods are used to treat this disease, while none of them could reverse the sequelae of WMI completely. With the development of stem cell technology, stem cell therapy has attracted huge interest as a novel treatment for WMI. A number of investigations have demonstrated the potential therapeutic effects of stem cell transplantation on WMI. Different types of stem cells have also been used by many researchers to test the therapeutic effect on WMI animal models, such as neural stem cells (NSCs), glial progenitor cells, mesenchymal stem cells (MSCs). In addition, some clinical trials have been conducted. Evidence suggests that transplantation of these stem cells into animals contributes to functional recovery after experimental WMI. The mechanisms of stem cells therapy may include differentiation into neurons and glial cells to replace lost cells, activation of endogenous NSC regeneration, and promotion of the release of neurotrophins. In this review, we summarized effects of different types of stem cells transplantation, the underlying mechanisms, the unsolved problems and concerns before clinical trials and transformation of stem cell therapy for WMI.

Keywords: White matter injury (WMI); stem cell transplant; neonatal

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isolated from the inner cells mass of blastocysts, which have
the capacity of self-renewal and multilineage differentiation.
iPSCs are a type of pluripotent stem cells that can be
obtained by reprogrammed somatic cells and have similar
properties to ESCs (3). Adult stem cells can be obtained
from many tissues, such as brain, adipose and bone marrow.
Depending on their tissue sources, they can be classified as
NSCs, MSCs, hematopoietic stem cells, etc., and they all
have been widely used in clinical and pre-clinical researches.
As early as 1981, NSCs isolated from animal brain tissue
were transplanted for treating neurological diseases,
after that, human fetal brain tissue was used (4). In 1997,
researchers transplanted glia cells which were obtained
from the spinal cord of a normal dog into a neonatal or
adult canine with myelin mutant. They found that the graft
could survive for a long term and form myelin sheath in the
transplantation site (5). After that, many types of cells
such as NSCs, MSCs, and oligodendrocyte progenitor cells
(OPCs) isolated from primary tissue or derived from ESCs/
iPSCs were used for transplantation to treat encephalopathy
of prematurity (6). In recent years, with the development of
stem cell technology, stem cell transplantation has become
a potential therapeutic approach for many neurological
defects including WMI. Different types of stem cells proved
to be therapeutic in WMI. However, the clinical application
of stem cell-based therapy for WMI still faces many
challenges, such as immune rejection and limited effect (7).
This paper reviewed the progresses and the challenges of
stem cell therapy for WMI.

WMI pathology

WMI in preterm infants is mainly caused by perinatal
HI, and could lead to a long-term neurologic disability
or even death. With the development of perinatology,
the survival rate of premature infants increases,
accompanied by the increasing incidence of WMI. In
the rat model of HI, it was found that the mechanism of
white matter damage in premature infants caused by HI
was related to the maturation dependent vulnerability of
oligodendrocytes. White matter maturation in rats/mice
are at postnatal day (PND) 3–5, which corresponds to
24–30 gestational week (GW24-30) in humans. During
this period, oligodendrocytes are at the late progenitor
(O4+/O1−) stage and are highly susceptible to HI (8). Late
oligodendrocyte progenitors are the main apoptosis cells in
the oligodendrocyte lineage when HI occurs. Early OPCs
(NG2+/O4−) and mature oligodendrocytes (MBP+) are
more tolerant to HI. Besides, some late oligodendrocyte
progenitors which survived from HI damage, will go
through an accelerated differentiation process and become
activated oligodendrocytes. However these activated
oligodendrocytes have lost the ability of myelination,
resulting in demyelinating lesions in the white matter (9).
Next, immaturity of the cerebral blood supply in the
deep periventricular regions such as basal ganglia of the
brain, making it vulnerable to cerebral ischemia. When
hemodynamics change, the underdeveloped cerebral
vascular system cannot steady blood flow, thus aggravating
the vulnerability of white matter to HI. In addition, free
radical formation and excitotoxicity of glutamate also
contribute to WMI (9).

NSCs transplant

NSCs are pluripotent stem cells with the potential of
self-renewal and multi-differentiation. It can be obtained
from the fetal/adult brain tissue, ESCs/iPSCs, or direct
reprogrammed by astrocytes (10)/fibroblasts (11). NSCs
are the most commonly used cell type for WMI treatment
because of its potential to differentiate into neurons and
glial cells in vivo and in vitro. In some primitive studies,
mouse primary NSCs were isolated for cell transplantation
to treat WMI. Rumajogee et al. (12) transplanted adult
NSCs isolated from transgenic adult mice expressing
yellow fluorescent protein (YFP) into the corpus callosum
(CC) of HI mice at PND21. Treated mice in this study
demonstrated repair of lesioned structures by histology
and magnetic resonance imaging (MRI), and remyelination
of the CC by endogenous oligodendrocytes. Behaviors
such as cylinder and Cat-Walk tests were qualitatively
improved in transplanted mice. Researchers found
that NSCs derived from human ESCs obtained similar
therapeutic effects (13). Besides, Daadi et al. (14) found
that the axon of transplanted cells can grow into the lesion
site. This suggests that the transplanted NSCs have the
potential of integrating into the host’s neural circuits,
but it requires more electrophysiology evidence. They
also observed that neurogenesis, glial regeneration, and
neurotrophic support related gene expression upregulated
by microarray analysis. These studies have found that
NSCs can improve the outcome of WMI caused by HI
both in structure and function. As for myelination repair,
the mechanism of NSCs transplantation for remyelination
is mainly to promote endogenous myelination, rather than
to directly differentiate into oligodendrocytes to replace
the lost myelin sheath, because these transplanted NSCs are hardly differentiate into oligodendrocytes in a default environment (12). Recently, due to the development of gene editing technology, genetically modified NSCs have been used to improve the therapeutic effect of NSCs. Tian et al. (15) strengthened therapeutic effects of NSCs by overexpressing leukemia inhibitory factor (LIF), which has neuroprotective effect on NSCs. They found that LIF-NSCs could reduce neuron apoptosis in vitro. In vivo, LIF-NSC reduced the infarction area, increased nerve and glia cell regeneration. In the future, gene editing technology and stem cell therapy will be combined to optimize the therapeutic effect of NSCs.

Mesenchymal stem cells (MSCs) transplant

MSCs are pluripotent stem cells that obtained from tissue such as umbilical cord blood (UCB), bone marrow, adipose tissue or placenta. Under certain culture conditions, they can differentiate into many cell types include neurons and glia cells. Studies have confirmed that in the sheep model of WMI, white matter damage caused by HI was reduced after transplantation of UCB-derived MSCs via resisting inflammatory and modulating immune response (16). van Velthoven et al. (17) established the animal model of WMI in PND9 rats, and then transplanted bone marrow derived MSCs into the lateral ventricle of WMI rats. They found that the loss of neurons and oligodendrocytes were significantly reduced, and the motor function of the rats in the transplantation group was improved significantly. In addition, after bone marrow derived MSCs being transplanted for 2 weeks, the proliferated neurons (BrdU / NeuN⁺), oligodendrocytes (BrdU⁺ / Olig2⁺) and astrocyte (BrdU⁺ / S100b⁺) in the HI + MSC-treated animals were increased, while the proliferated microglial cells (BrdU⁺ / Iba1⁻) were decreased compared with HI animals. These studies demonstrated that MSCs in the WMI animal models promoted the regeneration of neural and glial cells, inhibited the inflammatory response. Clinical application of MSCs-based therapy has been developed due to its accessibility and low immunogenicity (18, 19). A recent clinical study reported that, in their phase I study, intraventricular transplantation of allogeneic human UCB-derived MSCs into severe intraventricular haemorrhage (IVH) preterm infants was safe and feasible. Nine premature infants received cell transplants at 11.6±0.9 postnatal days, three received low-dose injections (5×10⁶ cells/kg) and six received high-dose injections (1×10⁷ cells/kg), no serious side effects and dose-limiting toxicities were observed. Cerebrospinal fluid (CSF) biomarkers like vascular endothelial growth factor (VEGF), and brain-derived neurotropic factor (BDNF) exhibited increase in some infants after MSCs intervention compared with baseline values (18). These data support the neuroprotective activity of transplanted MSCs in the treatment of WMI.

Oligodendrocyte precursor cells (OPCs) transplant

OPCs are widespread in central nervous system, most of them differentiate into oligodendrocytes and a few into astrocytes. Oligodendrocytes loss or dysfunction will cause demyelination, which is the main pathological feature of WMI. Myelin regeneration is mediated by OPCs, thus they are considered as seed cells for treating demyelinating diseases including WMI. OPCs can be obtained from fetal brain tissue or derived from ESCs/iPSCs, NSCs, or transdifferentiated from somatic cells like fibroblast (20-22). In early stem cell studies, mouse primary OPCs were isolated and transplanted into WMI mouse/rat brain. Experimental data suggested that rat primary OPCs can survive and migrate in the host brain and promote the secretion of neurotrophic factor (23). Proliferated NSCs (BrdU⁺ /Nestin⁻) increased in treated animals and these animals showed relived behavior deficits compared to sham operated controls (24). These studies suggest that the transplantation of OPCs have neuroprotective effects and can promote endogenous nerve regeneration. More important, it served as a source for myelin repair has been repeatedly reported. Porambo et al. (25) reported that intra-callosal injection of glia progenitor cells derived from embryonic spinal cord 17 days after HI in PND5 mice was associated with increased MBP density in cell treated WMI mice despite limited cell survival. Human ESCs derived OPCs were not applied in that time because of oligodendrocytes differentiation from human ESCs were not possible in the past. Transplantation of human primary NSCs derived OPCs seems like more feasible (26). Wu et al. (26) transplanted OPCs which were isolated from human aborted embryo into the forebrain of HI rats. They found that the myelinated axons were increased significantly in lesion site 90 days after transplantation. These results also showed long term survival of transplanted human OPCs in WMI rats. As the technical difficulties of human ESCs differentiation have been overcome, preclinical studies on human oligodendrocytes transplantation have
also been carried out. Kim and his colleagues showed that neurobehavioral performance were improved when human NSCs derived OPCs being transplanted for 3 days in HI animal models. Transplanted cells migrated to the injury site, differentiated into mature oligodendrocytes, expressing MBP and wrapped the neuronal cells to form new myelin sheaths (27).

Discussion

WMI is primarily caused by perinatal hypoxia and ischemia. Full-term infants and premature infants have different patterns of injuries when exposed to HI owing to late oligodendrocyte progenitors’ selectively vulnerable. Preterm infants are characterized by periventricular leukomalacia while the gray matter is predominantly injured in full-term infants (9). At present, the therapeutic methods of WMI in premature infants are mainly symptomatic support and mild hypothermia, while the effect of these treatments is limited in some severe cases. Cell transplantation is a promising treatment for these cases. The therapeutic mechanisms of cell transplant include replacing the lost cells, secreting neurotrophic factors, modulating inflammatory process, promoting endogenous neurogenesis, stimulating angiogenesis, and so on. However, the determined mechanisms are not fully revealed. Understanding the mechanism of stem cell therapy will be much more conducive to the future utilization. MSCs transplantation for WMI has been demonstrated to be safe in clinical trials (18). Gene editing in combination with stem cell therapy is also under pre-clinical researches (15). Although OPCs can specifically supplement the lost oligodendrocytes, its clinical application has not yet been developed due to the difficulty of obtaining OPCs. With the development of cell differentiation technology, OPC differentiated from ESCs/iPSCs will be wildly used in the treatment of WMI.

Conclusions

Preclinical studies have confirmed the safety and feasibility of different cell types for transplantation. NSCs and MSCs transplantation therapy has entered clinical trial processes, whereas OPCs transplant has not been used in clinical studies yet owing to its differentiation difficulties (18). In addition, more experimental data is needed so that we can choose the optimal cell type, transplant dose and transplant site to enhance the treatment effects and avoid immune rejection.

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Footnote

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