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Wharton' jelly mesenchymal stromal cell therapy for ischemic brain injury

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Abstract:

Increasing evidence have supported that Wharton's jelly mesenchymal stem cell (WJ-MSCs) have immunomodulatory and protective effects against several diseases including kidney, liver pathologies, and heart injury. Few *in vitro* studies have reported that WJ-MSCs reduced inflammation in hippocampal slices after oxygen–glucose deprivation. We recently reported the neuroprotective effects of human WJ-MSCs (hWJ-MSCs) in rats exposed to a transient right middle cerebral artery occlusion. hWJ-MSCs transplantation significantly reduced brain infarction and microglia activation in the penumbra leading with a significant reduction of neurological deficits. Interestingly, the grafted hWJ-MSCs in the ischemic core were mostly incorporated into IBA1 (+) cells, suggesting that hWJ-MSCs were immunorejected by the host. The immune rejection of hWJ-MSCs was reduced in after cyclosporine A treatment. Moreover, the glia cell line-derived neurotrophic factor expression was significantly increased in the host brain after hWJ-MSCs transplantation. In conclusion, these results suggest that the protective effect of hWJ-MSCs may be due to the secretion of trophic factors rather than to the survival of grafted cells. This paper is a review article. Referred literature in this paper has been listed in the references section. The data sets supporting the conclusions of this article are available online by searching various databases, including PubMed. Some original points in this article come from the laboratory practice in our research center and the authors' experiences.

Keywords:

Cyclosporin, stroke, Wharton's jelly derived-mesenchymal stromal cells, xenotransplantation

Introduction

Stroke is the second leading cause of death worldwide behind heart diseases.^[1] Only a drug is currently available for the treatment of stroke, tPA, but the restricted time window of application and the severe side effects limit its use. Most of alternative pharmacological therapies developed have not been successful. Stem cell therapies are promising strategies for stroke.

Neuroprotective Effects of Umbilical Cord Wharton's Jelly Mesenchymal Stem Cells

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The umbilical cord Wharton's Jelly mesenchymal stem cells (WJ-MSCs) have been shown to secrete both trophic and immunomodulatory proprieties.^[2,3] Indeed, lower levels of interferon- γ receptor 1 and CXCR3 receptors and higher constitutive expression of BDNF compared to bone marrow-MSCs have been reported.^[3] In addition, the secretome of WJ-MSCs can stimulate the endogenous repair mechanisms promoting the neurodifferentiation of neural progenitor cells.^[4,5] Moreover, the protective effects of WJ-MSCs can also be associated to the suppression of apoptosis, reported in an *in vitro* study, and increase of survival and decrease of vascular atrophy in an *ex vivo* hippocampal CA1 region after oxygen–glucose deprivation.^[6,7]

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Despite few *in vivo* studies involving the treatment of brain diseases with WJ-MSCs, a rat stroke model showed that both intracerebral and intravenous transplantation of WJ-MSCs improved neurological functions.^[8] Furthermore, WJ-MSCs-derived dopaminergic neurons improved the rotation behavior in a Parkinson's disease (PD) animal model.^[9] Similarly, in a traumatic brain injury (TBI) model, the intracerebral transplantation of WJ tissue reduced brain edema and increased MAP2 (+) cells in the injured cortex associated with the improvement of neurological function and promotion of cognitive recovery.^[10] Therefore, these results suggest that WJ-MSCs transplantation could be a novel potential strategy for the treatment of neurodegenerative diseases. An advantage of paramount importance in the WJ-MSCs transplantation is that the immunosuppressive medication is not necessary due to their immunomodulatory proprieties as shown in animal models of PD, TBI, epilepsy, spinal cord injury, hypoxic-ischemic encephalopathy, and stroke.^[10-15] However, there is the necessity to find an adequate assessment of the grafted hWJ-MSC survival. In this context, chloromethyl benzamide 1,1'-dioctadecyl-3,3,3'-tetramethylindocarbocyanine perchlorate (CM-Dil)-labeled immunofluorescence has been used to stain the human WJ-MSCs (hWJ-MSCs), but this marker can be transferred among the cells by phagocytosis of dying cells making the survival measurement of grafted hWJ-MSCs inconsistent.^[16,17]

Transplantation of hWJ-MSCs Reduces Ischemic Brain Injury

The neuroprotective effect of hWJ-MSCs transplant has been examined in a rat model of stroke (Wu *et al.*, Cell Transplantation, 2018, in press). In this study, hWJ-MSCs were grafted into the cerebral cortex of experimental rats. Stroke was introduced by a transient (60 min) distal middle cerebral artery occlusion. Transplantation of hWJ-MSCs significantly reduced brain infarction, improved neurological function, and decreased neuroinflammation at 3 and 5 days after stroke surgery. These data suggest that transplantation of hWJ-MSCs reduces ischemic brain injury.

Functional Recovery Does Not Correlate With the Survival of Grafted Cells in Stroke Brain

Microglia can phagocytize CM-Dil-labeled grafted cells at the site of transplantation (Wu *et al.*, Cell Transplantation, 2018, in press), suggesting immunorejection. Interestingly, phagocytosis of grafted hWJ-MSCs is reduced in the animals subjected to cyclosporine. In addition,

we observed an increase of the glia cell line-derived neurotrophic factor (GDNF) expression in the host brain accompanies the hWJ-MSCs transplantation suggesting that the protective role of these cells is not associated to their survival but may be due to the secretion of trophic factors.

hWJ-MSCs and Neuroprotection via Trophic Factor Secretion

Our observations suggest a neuroprotective function of hWJ-MSCs for the treatment of stroke. Notably, we showed that the transplantation of hWJ-MSCs significantly reduced IBA1 immunoreactivity and morphological activation of microglia in the peri-infarct area, but not in the core. In addition, in the core region, microglia displayed an amoeboid morphology indicating inflammatory response. Indeed, the CM-Dil fluorescence was found mainly in microglia in the core region suggesting phagocytosis of grafted cells. Similarly, the localization of MSCs was obtained from GFP-transgenic rats and double-labeled with 5-bromo-2-deoxyuridine (BrdU) and bis benzamide (BBZ) before the transplantation in rats.^[17] The GFP signal was absent after 14 days of transplantation, while BrdU and BBZ markers were detected up to 12 weeks colocalized with host phagocytes, astrocytes, and neurons suggesting the immunorejection of the grafted cells.^[17] In addition, a limited survival of neuronal-primed hMSCs has been reported by positive HuNuc staining detected only within 7 days in the host brain of hemiparkinsonian rats.^[18] Interestingly, we detected an increased CM-Dil fluorescence, accompanied by a reduced phagocytosis of the grafted hWJ-MSCs with CsA treatment. These results support previous studies in which CsA treatment suppressed the endogenous microglia activation in oligodendrocyte progenitor cell transplantation.^[19] Similarly, in an animal model of PD, CsA treatment improved the survival of human xenografts.^[20] Therefore, CsA treatment may suppress immunorejection and increase the survival of hWJ-MSCs in transplants. On the other hand, studies on the neuroprotective effects of human cord blood cell transplantation have demonstrated functional improvements comparable to the results obtained without the CsA treatment in the present work.^[21-23] Interestingly, these findings were associated with upregulation of the neurotrophic factor GDNF and no intravenous injected cell has been detected in the host brain after 3 days of transplantation in a rat model of stroke, even when co-infused with a blood-brain barrier (BBB) permeabilizer.^[24] Therefore, considering that most of the grafted hWJ-MSCs were phagocytized by activated microglia, the improvement of neurological function observed in the absence of CsA treatment could be due to secretion of products able to cross the BBB. In concert with the findings of

Borlongan *et al.*, we also found a significantly increased GDNF expression in the host brain after hWJ-MSCs transplantation.^[24] In addition, the same authors have previously reported a reduction in brain infarction and restored locomotory activity in a stroke animal model following treatment with GDNF protein or herpes simplex virus (HSV) amplicon-based vector encoding GDNF (HSV-GDNF).^[25,26] Similarly, the transplantation of GDNF containing cells, such as fetal kidney cells and reduced cerebral infarction in stroke animals.^[27]

Conclusion

In summary, these results suggest that the transplantation of hWJ-MSCs may be protective for the treatment of stroke, and this beneficial function does not necessarily require the survival of the grafted cells, but their secretion products.

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Conflicts of interest

There are no conflicts of interest.

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