Mesenchymal stem cells and cerebral palsy

Fa-Kung Lee[a], Yu-Lan Lin[b], Peng-Hui Wang[c,d,e,f,*]

[a]Department of Obstetrics and Gynecology, Cathy General Hospital, Taipei, Taiwan, ROC; [b]Department of Nursing, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [c]Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [d]Department of Obstetrics and Gynecology, National Yang-Ming University, Taipei, Taiwan, ROC; [e]Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; [f]Department of Medical Research, China Medical University Hospital, Taichung, Taiwan, ROC

Cerebral palsy (CP), a heterogeneous group of motor impairments resulting from an insult to the developing central nervous system (brain damage), is one of biggest nightmares in modern obstetrics and pediatrics because of its life-long morbidities as well as the most severe motor disability contributing to a heavy economic burden, including high cost of care, loss of income, and tax revenue losses, etc.[1,2] The worldwide prevalence of CP is constant at two to three per 1000 newborns for more than four decades, despite substantial improvements in perinatal medicine.[1] CP can be classified on the basis of four major components: type and severity of the motor abnormalities, anatomical distribution, associated impairments, and timing of the presumed causal event (prenatal, perinatal, or postnatal).[1] The causes of CP remains elusive, and the precipitating factors include prematurity, low birth weight, birth asphyxia, fetal intrauterine inflammation and infection, hypoxic and ischemic events of fetus, genomic abnormalities, and many uncertains.[1,3] There is still absence of agreement in the prediction, prevention, and management of CP. Hypothermia with/without concomitant administration of medication, such as xenon, or barbiturate might be helpful for newborns who are subjected to perinatal asphyxia.[4–6]

The aforementioned strategy may reduce the risk of both mortality and major neurodevelopment disability to 18 months of age (risk ratio [RR] 0.75, 95% CI 0.68–0.83, and risk difference [RD] –0.15, 95% CI –0.20 to –0.010).[4–6] For a single item, it can decrease mortality rate (RR 0.75, 95% CI 0.64–0.88, RD –0.09, 95% CI –0.13 to –0.04) and reduce the risk and severity of neurodevelopmental disability in survivors (RR 0.77, 95% CI 0.63–0.94, and RD –0.13, 95% CI –0.19 to –0.07).[4–6] However, based on the limited number of subjects enrolled in the analysis and presence of conflicted data, the definitely effective strategies are still pending.

Mesenchymal stem (stromal) cells (MSCs), a heterogeneous population of progenitor cell that possesses differentiation ability, in vitro expansion, release of trophic materials, as well as angiogenic, antiapoptotic, and immune-modulatory properties, can be classified into two main origins: embryonic and adult cells.[7–13] MSCs are obtained and isolated from adipose, bone marrow, Wharton's jelly, cervical tissue placenta, skeletal muscle tissue, amniotic fluid, liver tissue, dental pulp, synovial membranes, saphenous veins, lung, dermal tissues, periodontal ligaments, human umbilical cord (hUC), and hUC blood.[7–13] The applications of MSCs in tissue engineering and regenerative medicine have been developed and progressed apparently.[7–13] Therefore, MSCs might present a profound opportunity to revolutionize CP treatment. In the January issue of the *Journal of the Chinese Medical Association* (*JCMA*), Dr. Niu et al.[14] have pioneered to use hUC-MSC in the management of CP via an animal model. They found that CP rats after hUC-MSC transplantation treatment have significantly improved neurobehavioral ability.[14] Further dissection of the brain tissues from these rats showed two proportions of the CD4+ T helper (Th) cells (Th9 and Th22) have been statistically significantly decreased.[14] Evaluation of the levels of proinflammatory cytokines, including nonspecific markers as tumor necrosis factor-α (TNF-α) and interleukin (IL)-6, or specific Th markers, such as Th9-related IL-9 and purine-rich box 1 (also known as proviral integration 1, salmonella pathogenicity island 1, or salmonella pathogenicity island A) as well as Th-22-related IL-22 and aryl hydrocarbon receptor (AHR), the authors found these biomarkers are dramatically increased in CP rats, but these CP rats after hUC-MSC transplantation therapy could statistically significantly decreased.[14] We appreciate the authors' contribution and happy to give comments for this topic.

As shown in our previous editorial comment,[7] hUC-MSCs take the following advantages, including ease to obtain, absence of ethical concerns, and characteristic of convenient and high impact to use, such as lower immunogenicity, faster self-renewal ability, stable doubling time, and higher proliferation potency, although some limitations impede their popular use, such as high cost to maintain, little amount of bioactive substance, and delayed engraftment.[15] Therefore, the authors used the direct method to inject 10 μL of hUC-MSCs (2×10^6 cells/rat) into the left sensorimotor cortex of the rats to confirm their successful delivery of hUC-MSCs into the "lesion."[14] However, it is interesting to find that CP rats working as control did not receive this injection with the same culture medium without hUC-MSCs. It is wondering to know whether pure culture medium or hUC-MSC–conditioned medium does have the similar effect on the improvement of neurobehavioral ability in CP rats. There is some evidence to support this hypothesis. One publication from the March issue of the *JCMA* in 2018, Ho et al.[11] used the combination of the bone marrow–derived MSCs and MSC-conditioned medium (the main key factor as IL-6) in the management of the large uterine defect, and the defect has successfully been repaired by this treatment.[10] Although the authors did not

*Address correspondence: Dr. Peng-Hui Wang, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail addresses: phwang@vghtpe.gov.tw; pongpongwang@gmail.com (P.-H. Wang).

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2020) 83: 323-324.

Received January 1, 2020; accepted January 1, 2020.

doi: 10.1097/JCMA.0000000000000263.

use the MSC-conditioned medium alone as controls, the authors still concluded that bone marrow–derived MSC transplantation can facilitate the wound healing process in the uterine defects, and this repair can be further accelerated by IL-6.[10] Because IL-6 is the main component of MSC-conditioned medium, it is believed that only MSC-conditioned medium might have the similar effect, although the authors did not qualify or quantify their effect.[16]

Second, conditioned medium might contain many molecules, which might be the key components of the effective therapy. For example, MSCs-derived exosomes are one of the most promising magic bullets, which have the capacity to transfer or deliver bioactive molecules, such as deoxyribonucleic acid (DNA), protein, messenger ribonucleic acid (mRNA), micro-RNA (miRNA or miR), lipid, and organelles, from their originating cell to the recipient cells, leading to genetic information exchanges, host cell reprogramming, and cellular communication.[7,8,15] All support that conditioned medium might have similar effects, although it still needs further confirmation.

Third, to face the change of inflammatory or proinflammatory biomarkers in any experiment should be with caution. The change of these biomarkers should be based on the time course because all need tightly orchestral guide and direction. For example, overproduction of inflammatory mediators, such as TNF-α, IL-6 as well as, may not accelerate the recovery from injury, and by contrast, it may deteriorate the homeostasis of the body, resulting in more harmful effects on injured body.[17,18] Although Niu et al.[14] evaluated the expression of proinflammatory markers to support their findings, but the "precise time point" is important. We found that the authors have performed the brain section at 1 and 4 weeks after hUC-MSC transplantation; however, the data are not fully provided. We do not know the dynamic change of these proinflammatory biomarkers. In addition, we do not know how many hUC-MSCs are still present in the rat's brain after 4 weeks of injection of hUC-MSCs.

ACKNOWLEDGMENTS

This article was supported by grants from the Ministry of Science and Technology, Executive Yuan, Taiwan (MOST 106-2314-B-075-061-MY3), and Taipei Veterans General Hospital (V108C-085 and V109C-108). The authors appreciate the financial support by the Female Cancer Foundation, Taipei, Taiwan.

REFERENCES

1. Moreno-De-Luca A, Ledbetter DH, Martin CL. Genetic insights into the causes and classification of the cerebral palsies. *Lancet Neurol* 2012;**11**:283–92.
2. Eggenberger S, Boucard C, Schoeberlein A, Guzman R, Limacher A, Surbek D, et al. Stem cell treatment and cerebral palsy: systemic review and meta-analysis. *World J Stem Cells* 2019;**11**:891–903.
3. Wu SH, Li RS, Hwu YM. Live birth after perimortem cesarean delivery in a 36-year-old out-of-hospital cardiac arrest nulliparous woman. *Taiwan J Obstet Gynecol* 2019;**58**:43–5.
4. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2013;**1**:CD003311.
5. Young L, Berg M, Soll R. Prophylactic barbiturate use for the prevention of morbidity and mortality following perinatal asphyxia. *Cochrane Database Syst Rev* 2016;**5**:CD001240.
6. Rüegger CM, Davis PG, Cheong JL. Xenon as an adjuvant to therapeutic hypothermia in near-term and term newborns with hypoxic-ischaemic encephalopathy. *Cochrane Database Syst Rev* 2018;**8**:CD012753.
7. Li YT, Lee FK, Wang PH. Mesenchymal stem cells derived-magic bullets for burns. *J Chin Med Assoc* 2020;**83**: 215–6.
8. Liu JS, Du J, Cheng X, Zhang XZ, Li Y, Chen XL. Exosomal mir-451 from human umbilical cord mesenchymal stem cells attenuates burn-induced acute lung injury. *J Chin Med Assoc* 2019;**82**:895–901.
9. Feng CJ, Lin CH, Tsai CH, Yang IC, Ma H. Adipose-derived stem cells-induced burn wound healing and regeneration of skin appendages in a novel skin island rat model. *J Chin Med Assoc* 2019;**82**:635–42.
10. Chen GY, Chang CP, Wang PH. Burn wound and therapeutic challenge. *J Chin Med Assoc* 2019;**82**:748–9.
11. Ho CH, Lan CW, Liao CY, Hung SC, Li HY, Sung YJ. Mesenchymal stem cells and their conditioned medium can enhance the repair of uterine defects in a rat model. *J Chin Med Assoc* 2018;**81**:268–76.
12. Huang CS, Lin HC, Lu KH, Wu WW, Yang YC, Yang YP, et al. Generation of high quality of hepatocyte-like cells from induced pluripotent stem cells with parp1 but lacking c-myc. *J Chin Med Assoc* 2018;**81**:871–7.
13. Tsai HW, Wang PH, Tsui KH. Mesenchymal stem cell in wound healing and regeneration. *J Chin Med Assoc* 2018;**81**:223–4.
14. Niu X, Xu X, Luo Z, Wu, Tang J. The expression of th9 and th22 cells in rats with cerebral palsy after huc-MSC transplantation. *J Chin Med Assoc* 2020;**83**:60–6.
15. Yaghoubi Y, Movassaghpour A, Zamani M, Talebi M, Mehdizadeh A, Yousefi M. Human umbilical cord mesenchymal stem cells derived-exosomes in diseases treatment. *Life Sci* 2019;**233**:116733.
16. Wang PH. Outstanding research paper awards of the Journal of the Chinese Medical Association in 2018. *J Chin Med Assoc* 2019;**82**:885–6.
17. Wang PH, Huang BS, Horng HC, Yeh CC, Chen YJ. Wound healing. *J Chin Med Assoc* 2018;**81**:94–101.
18. Horng HC, Chang WH, Yeh CC, Huang BS, Chang CP, Chen YJ, et al. Estrogen effects on wound healing. *Int J Mol Sci* 2017;**18**:E2325.