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CASE REPORT

Recovery from Bell's palsy after treatment using uncultured umbilical cord-derived mesenchymal stem cells: A case report

Hyunjun Ahn, Won-Ju Jung, Sang Yeon Lee, Kye-Ho Lee

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Abstract

BACKGROUND

Bell's palsy is an idiopathic facial palsy with an unknown cause, and 75% of patients heal spontaneously. However, the other 25% of patients continue experiencing mild or severe disabilities, resulting in a reduced quality of life. Currently, various treatment methods have been developed to treat this disease. However, there is controversy regarding their effectiveness, and new alternative treatments are needed.

CASE SUMMARY

The patient suffered from left-sided facial paralysis due to Bell's palsy for 7 years. The patient received an uncultured umbilical cord-derived mesenchymal stem cell transplant eight times for treatment. After follow-up for 32 mo, the paralysis was cured, and there was no recurrence.

CONCLUSION

Uncultured umbilical cord-derived mesenchymal stem cell transplantation may be a potential treatment for patients with Bell's palsy who do not spontaneously recover.

Key Words: Bell's palsy; Facial palsy; Umbilical cord-mesenchymal stem cells; Allogenic; Case report

Core Tip: The effectiveness of the current treatment methods for Bell's palsy is debated. Therefore, alternative treatments are needed. In this study, we treated a patient with Bell's palsy classified as moderately severe dysfunction using uncultured umbilical cord-derived mesenchymal stem cells. After follow-up for 32 mo, the paralysis was cured, and there was no recurrence. This method could be a new treatment option to replace existing treatments for Bell's palsy.

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INTRODUCTION

Facial paralysis is a disease in which one side of the facial muscles become suddenly or gradually paralyzed. While facial paralysis can be caused by a number of factors, Bell's palsy-defined idiopathic facial paralysis is the cause of 60%-75% of all cases[1], and the cause of Bell's palsy is unknown. Although approximately 75% of the patients will heal spontaneously, it can lead to severe temporary oral insufficiency and potentially cause permanent eye damage because the eyelid on the affected side is unable to close[2,3]. Moderate to severe facial asymmetry persists in approximately 25% of patients with Bell's palsy, often compromising the patient's quality of life[2,3]. This long-term side effect of Bell's palsy can be devastating for patients[2,3].

Although Bell's palsy is considered idiopathic, herpes virus-specific immune response and ischemic or hereditary factors are closely related to its etiology[1,4,5]. In the early stages of the disorder, steroid therapy or antiviral administration has been shown to improve symptoms[6-8]. Nevertheless, in patients with long-term facial muscle dysfunction, symptoms may improve with facial exercises, acupuncture, and occupational and speech therapy[1,9-11]. In severe cases, symptoms can be relieved by nerve decompression and plastic surgery procedures[1,12]. Various treatment methods for patients with insufficient recovery from Bell's palsy have been developed, but the effectiveness of these methods is debated. Despite receiving various treatments, some patients still have symptoms of paralysis. Therefore, alternative treatments for these patients are still needed[1,6,13].

Based on the results of previous studies, mesenchymal stem cell (MSC) transplantation treatment may be effective for treating Bell's palsy. MSCs play an effective role in suppressing the function of the herpes virus and eliminating inflammation[14-16]. In addition, MSCs secrete cytokines that protect and regenerate neuronal cells and have the potential to differentiate into neuronal cells, which aids the regeneration of the damaged lesion site[17,18]. Therefore, we hypothesized that MSCs may be an effective treatment for Bell's palsy in patients with insufficient recovery. In this study, we used uncultured umbilical cord-derived (UC)-MSCs to treat a patient with Bell's palsy who experienced insufficient recovery. The patient had suffered from Bell's palsy for 7 years. We report the treatment of this case using UC-MSCs as evidence that it may be a potential effective treatment of Bell's palsy.

CASE PRESENTATION

Chief complaints

On March 5, 2013, a 49-year-old female, who suffered from Bell's palsy, visited the 97.7 B&H Clinic. The patient had paralysis on the left side of the face.

History of present illness

The patient was diagnosed with Bell's palsy in 2006. At first, the patient experienced only pain on the face, but tremors and paralysis gradually appeared on the left side of her face. As inferred from the patient's comments, at the time of diagnosis, the patient had grade 4 (moderately severe dysfunction) facial paralysis according to the House-Brackmann facial nerve grading system (Table 1)[1]. She was treated with steroids when symptoms first appeared, but the treatment was ineffective. She was further treated with acupuncture, meridian massage, and herbal medicine, but the paralysis remained.

History of past illness

The patient had no specific diseases or disorders.

Personal and family history

The patient's father suffered from a brain hemorrhage. However, the patient had no history of brain

Table 1 House-Brackmann facial nerve grading system

Grade	Description	Characteristics
1	Normal	Normal facial function in all areas
2	Mild dysfunction	Slight weakness noticeable upon close inspection; may have very slight synkinesis
3	Moderate dysfunction	Obvious, but not disfiguring, difference between two sides; noticeable but not severe synkinesis, contracture, or hemifacial spasm; complete eye closure with effort
4	Moderately severe dysfunction	Obvious weakness or disfiguring asymmetry; normal symmetry and tone at rest; incomplete eye closure
5	Severe dysfunction	Barely perceptible motion; asymmetry at rest
6	Total paralysis	No movement

hemorrhage or other related diseases.

Physical examination

At the time of the first visit, the patient participated in a brief question-and-answer session to confirm the history of the present illness and symptoms. The patient had left-side facial paralysis with the following symptoms: muscle tremors, disfiguring asymmetry, and incomplete left eye closure. Based on the House-Brackmann facial nerve grading system, we classified the patient as a grade 4, moderately severe dysfunction (Table 1)[1].

Laboratory examinations

Bell's palsy does not require blood tests for diagnosis or treatment. However, a complete blood count, basic metabolic panel, comprehensive metabolic panel, lipid panel, thyroid panel, and cardiac biomarkers were performed to check the patient's health. Upon examination, everything was normal.

Imaging examinations

Imaging examinations were not performed.

FINAL DIAGNOSIS

The patient was diagnosed, in our clinic, with Bell's palsy with insufficient recovery. In addition, the House-Brackmann facial nerve grading system evaluation through question-and-answer with the patient determined that the patient's symptoms had not improved over the 7 years after the first diagnosis.

TREATMENT

UC procurement

UCs were donated by the Obstetrics and Gynecology Department at Lynn Woman's Hospital (Seoul, South Korea). The donors' mothers consented to the donation of the UCs. The safety of the donated UCs was confirmed through the mothers' medical histories and blood and urine tests.

Isolation and quality evaluation of UC-MSCs

UC-MSCs were isolated from the donated UCs as described previously[17,19,20]. The UC was first disinfected with 70% ethanol and then washed with 1 × phosphate-buffered saline. Then, three vessels and the amniotic membrane of the UC were removed, and the UC was cut into 2-3 cm pieces with surgical scissors. The cut tissues were placed in a 50-mL conical tube containing a mixture solution of collagenase and hyaluronidase, further minced with surgical scissors and ground with a disposable tissue grinder, and incubated in a 37 °C, 50 mL/L CO_2 incubator for 1 h. The mixture solution was filtered (100 μm) and then centrifuged to collect the flow-through containing the purified UC-MSCs. The UC-MSC samples were resuspended in CryoStor® CS10 (Stemcell Technologies, Cambridge, MA, United States), frozen at -80 °C for 1 d, and transferred to a liquid nitrogen tank for storage until clinical application.

The isolated UC-MSCs were suitable for treatment after confirmation of negative microbiological tests and of the expression level of MSC-specific proteins (CD73 ≥ 70%, CD90 ≥ 90%, and CD105 ≥ 90%) (data not shown). The expression level of MSC-specific proteins was measured using CyFlow® Cube 6 (Sysmex, Lincolnshire, IL, United States) and FCS Express 5 software (De Novo Software, Glendale, CA,

United States).

Preparation of injection solution

We prepared a stock 4 mL injection solution consisting of uncultured UC-MSCs and 0.9% sodium chloride, USP with a concentration of 1 × 10^6 cells/mL. Before injection, the prepared 4 mL injection solution was divided into four 1 mL Ultra-Fine™ II Insulin Syringes (BD Biosciences, Franklin Lakes, NJ, United States) containing 1 mL each.

Treatment

We injected the injection solution evenly over the left-side of the patient's face. Each site was injected with 0.25 mL at a depth of 0.4-0.6 cm (a total of 16 injections were performed). Each injection site is marked with an 'X' in Figure 1.

OUTCOME AND FOLLOW-UP

The patient received a total of eight treatments at 2-mo intervals for 14 mo, and was followed up 18 mo after the end of treatment. The Bell's palsy did not recur during this period.

After UC-MSC transplantation, the patient experienced rapid improvement in the closure of her left eye. Before UC-MSC transplantation, the patient could only close her left eye about 50%. Three months after the first treatment, the patient was able to achieve left eye closure to 70%. This symptom continued to improve, and by 22 mo after the first treatment, the patient was able to completely close her left eye (Figure 1). In addition, before treatment, the patient's left eyebrow was located lower than the right eyebrow. During the follow-up period, the muscles around the eyebrow normalized, and the eyebrows were even (Figure 2).

The patient also experienced relief of asymmetrical lips after UC-MSC transplantation. Before treatment, the patient had difficulty speaking because her lips were slightly tilted to the right. Three months after the first treatment, the patient reported that the muscles around the lips had softened, and her speech became easier. The patient's lips were gradually improved and normalized over 28 mo (Figure 3).

Report of side effects

Immediately after each treatment, the patient showed no specific local facial nor systemic abnormalities as reactions. Also, during the treatment and follow-up period, the patient did not report any experience of abnormalities nor of side effects.

DISCUSSION

The patient had suffered from Bell's palsy for 7 years and remained disabled despite various treatments (including steroid drug therapy, acupuncture, meridian massage, and herbal medicine). The patient lived with facial asymmetry and discomfort due to stiffness in the affected region; these problems caused the patient to have psychological stress due to loss of self-confidence and lack of sleep. Eventually, her quality of life was greatly reduced due to related social avoidance.

Bell's palsy is an idiopathic disease of unknown cause[1]. Researchers have hypothesized that Bell's palsy develops as a result of damage to the facial nerve system due to various factors, including an immune response, inflammation, ischemia, and hereditary factors[1,4,5]. Although 75% of patients with Bell's palsy recover spontaneously, the remaining 25% experience mild or severe disability, which reduces their quality of life[2,3]. To increase the cure rate of Bell's palsy, steroids or antiviral drugs are given in the early course of the disorder, but their effectiveness is debated[6,7,21]. Patients with Bell's palsy who experience insufficient recovery can receive various treatments such as meridian massage, acupuncture, exercise therapy, *etc*. In severe cases, nerve decompression and plastic surgery procedures can be performed[1,9-11]. Even though new treatments have been developed for patients with Bell's palsy experiencing insufficient recovery, they are controversial, and new alternatives are needed. As mentioned in the previous section, the cause of Bell's palsy is not clearly known, but there are several suspected causes, such as a viral infection or damage to the facial neuron by an assortment of proposed factors[1,4,5]. According to various recent studies, MSCs have antiviral, anti-inflammatory, neuronal protective, and regeneration functions[14,16-18]. Based on these findings, we hypothesized that MSC transplantation could treat patients with Bell's palsy experiencing insufficient recovery. Although the cause of Bell's palsy is unknown, transplantation of MSCs has the potential to overcome the presumed causes of Bell's palsy.

Based on these findings, we hypothesized that MSC transplantation could successfully treat patients with Bell's palsy experiencing insufficient recovery.

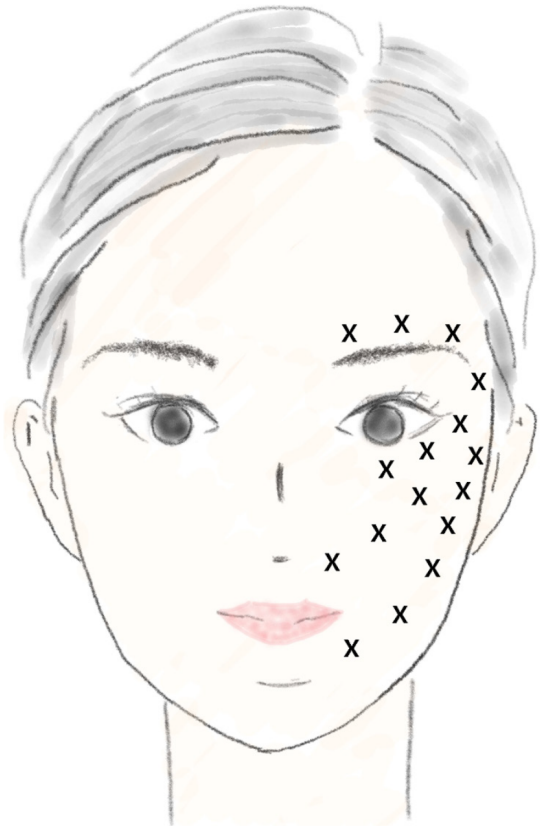

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Figure 1 Injection sites used for the transplantation of uncultured umbilical cord-mesenchymal stem cells. The patient was suffering from left-sided paralysis due to Bell's palsy. X: Injection sites.

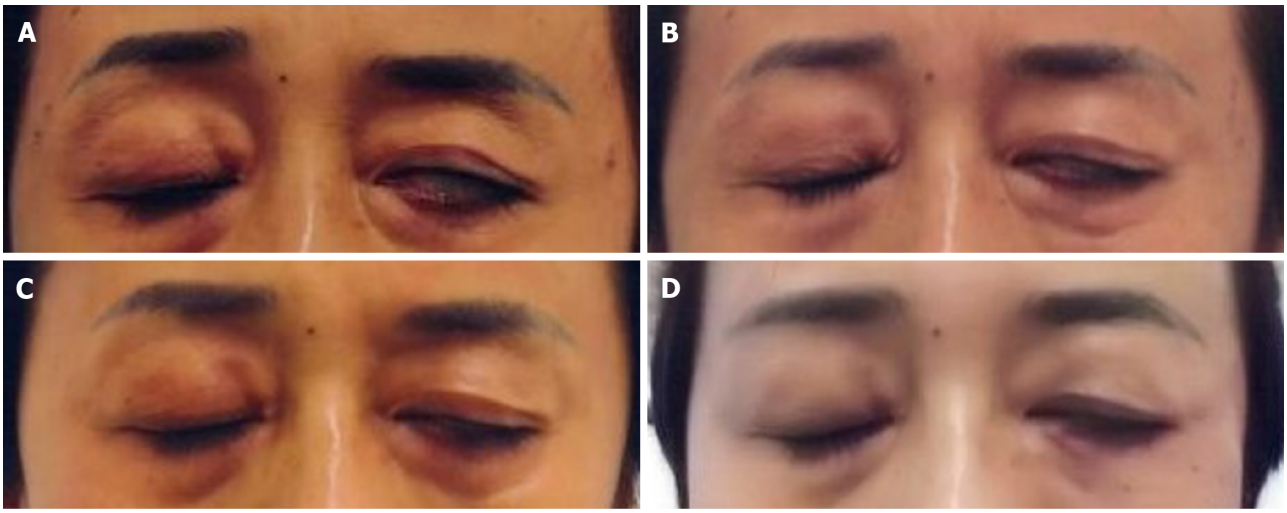

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Figure 2 Left eye closure and eyebrow location during the treatment and follow-up. A: The patient's eye closure and eyebrow location at 3 mo after the first treatment; B: Seven months after the first treatment; C: Twelve months after the first treatment; D: Twenty-two months after first treatment.

Although UC-MSCs are allogeneic cells, they are typically not rejected by the recipient and can be used universally[22]. In general, culturing is performed to obtain the number of MSCs required for treatment, but previous studies have indicated that MSCs undergo changes in their properties during culture, such as loss of their differentiation potential and change in their ability to secrete various cytokines and proteins due to the cell aging that occurs in the culturing period[23-25]. For these reasons, we used uncultured UC-MSCs, which are the youngest and most universally available, for treatment. Three months after the first treatment, the patient reported improvement in the closure of her left eye and stiff muscles around the lips. Over the 32-mo follow-up period, the patient reported that the

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Figure 3 Change in the patient's asymmetrical lips during the treatment and follow-up. A: The patient's asymmetrical lips at 3 mo after the first treatment; B: Ten months after the first treatment; C: Sixteen months after the first treatment; D: Twenty-two months after first treatment; E: Twenty-eight months after first treatment.

symptoms gradually improved and normalized. There was no recurrence of Bell's palsy symptoms during the follow-up.

A limitation of this report is the lack of pre-treatment images due to the refusal of the patient to have "before" images taken. However, 3 mo after treatment the patient consented to have images taken due to the improvement of symptoms. Although this is a case report of only 1 patient, we showed that uncultured UC-MSCs were effective in treating Bell's palsy. A well-controlled and large-scale clinical study is required to provide further evidence that uncultured UC-MSC transplantation is an effective treatment for Bell's palsy.

CONCLUSION

In this case study, a patient suffering from Bell's palsy for 7 years was treated with uncultured UC-MSC transplantation. Although this is a case report of 1 patient, we expect that a randomized controlled trial will provide evidence that using uncultured UC-MSC transplantation to treat patients with Bell's palsy with insufficient recovery is an effective new treatment.

FOOTNOTES

Author contributions: Ahn H, Jung WJ, Lee SY and Lee KH designed the report; Ahn H and Jung WJ collected the patient's clinical data; Ahn H and Jung WJ analyzed the data; Ahn H and Lee SY wrote the manuscript; Lee KH provided professional advice and revised the manuscript; all authors issued final approval for the version to be submitted.

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REFERENCES

1 **Singh A**, Deshmukh P. Bell's Palsy: A Review. *Cureus* 2022; **14**: e30186 [PMID: 36397921 DOI: 10.7759/cureus.30186]
2 **Prud'hon S**, Kubis N. [Bell's palsy]. *Rev Med Interne* 2019; **40**: 28-37 [PMID: 29610004 DOI: 10.1016/j.revmed.2018.03.011]
3 **Zhang W**, Xu L, Luo T, Wu F, Zhao B, Li X. The etiology of Bell's palsy: a review. *J Neurol* 2020; **267**: 1896-1905 [PMID: 30923934 DOI: 10.1007/s00415-019-09282-4]
4 **Zandian A**, Osiro S, Hudson R, Ali IM, Matusz P, Tubbs SR, Loukas M. The neurologist's dilemma: a comprehensive clinical review of Bell's palsy, with emphasis on current management trends. *Med Sci Monit* 2014; **20**: 83-90 [PMID: 24441932 DOI: 10.12659/MSM.889876]
5 **Eviston TJ**, Croxson GR, Kennedy PG, Hadlock T, Krishnan AV. Bell's palsy: aetiology, clinical features and multidisciplinary care. *J Neurol Neurosurg Psychiatry* 2015; **86**: 1356-1361 [PMID: 25857657 DOI: 10.1136/jnnp-2014-309563]
6 **Salinas RA**, Alvarez G, Daly F, Ferreira J. Corticosteroids for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev* 2010; CD001942 [PMID: 20238317 DOI: 10.1002/14651858.CD001942.pub4]
7 **Cao J**, Zhang X, Wang Z. Effectiveness comparisons of antiviral treatments for Bell palsy: a systematic review and network meta-analysis. *J Neurol* 2022; **269**: 1353-1367 [PMID: 33674936 DOI: 10.1007/s00415-021-10487-9]
8 **Gagyor I**, Madhok VB, Daly F, Sullivan F. Antiviral treatment for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev* 2019; **9**: CD001869 [PMID: 31486071 DOI: 10.1002/14651858.CD001869.pub9]
9 **Chen N**, Zhou M, He L, Zhou D, Li N. Acupuncture for Bell's palsy. *Cochrane Database Syst Rev* 2010; **2010**: CD002914 [PMID: 20687071 DOI: 10.1002/14651858.CD002914.pub5]
10 **Law D**, McDonough S, Bleakley C, Baxter GD, Tumilty S. Laser acupuncture for treating musculoskeletal pain: a systematic review with meta-analysis. *J Acupunct Meridian Stud* 2015; **8**: 2-16 [PMID: 25660439 DOI: 10.1016/j.jams.2014.06.015]
11 **Teixeira LJ**, Soares BG, Vieira VP, Prado GF. Physical therapy for Bell s palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev* 2008; CD006283 [PMID: 18646144 DOI: 10.1002/14651858.CD006283.pub2]
12 **Wang Z**, Chai Y, Chen Z, Wu H, Wang Z. Endoscopic transcanal facial nerve decompression in Bell's palsy: A pilot study. *Am J Otolaryngol* 2022; **43**: 103167 [PMID: 34371460 DOI: 10.1016/j.amjoto.2021.103167]
13 **Murthy JM**, Saxena AB. Bell's palsy: Treatment guidelines. *Ann Indian Acad Neurol* 2011; **14**: S70-S72 [PMID: 21847333 DOI: 10.4103/0972-2327.83092]
14 **Klimova RR**, Demidova NA, Masalova OV, Kushch AA. Preventive Vaccination with Mesenchymal Stem Cells Protects Mice from Lethal Infection Caused by Herpes Simplex Virus 1. *Mol Biol* 2021; **55**: 413-423 [PMID: 34931092 DOI: 10.1134/S0026893321020242]
15 **Bernardo ME**, Fibbe WE. Mesenchymal stromal cells: sensors and switchers of inflammation. *Cell Stem Cell* 2013; **13**: 392-402 [PMID: 24094322 DOI: 10.1016/j.stem.2013.09.006]
16 **Prockop DJ**, Oh JY. Mesenchymal stem/stromal cells (MSCs): role as guardians of inflammation. *Mol Ther* 2012; **20**: 14-20 [PMID: 22008910 DOI: 10.1038/mt.2011.211]
17 **Ahn H**, Lee SY, Jung WJ, Lee KH. Treatment of acute ischemic stroke by minimally manipulated umbilical cord-derived mesenchymal stem cells transplantation: A case report. *World J Stem Cells* 2021; **13**: 1151-1159 [PMID: 34567432 DOI: 10.4252/wjsc.v13.i8.1151]
18 **Doeppner TR**, Herz J, Görgens A, Schlechter J, Ludwig AK, Radtke S, de Miroschedji K, Horn PA, Giebel B, Hermann DM. Extracellular Vesicles Improve Post-Stroke Neuroregeneration and Prevent Postischemic Immunosuppression. *Stem Cells Transl Med* 2015; **4**: 1131-1143 [PMID: 26339036 DOI: 10.5966/sctm.2015-0078]
19 **Ahn H**, Lee SY, Jung WJ, Lee KH. Treatment of syringomyelia using uncultured umbilical cord mesenchymal stem cells: A case report and review of literature. *World J Stem Cells* 2022; **14**: 303-309 [PMID: 35662863 DOI: 10.4252/wjsc.v14.i4.303]
20 **Ahn H**, Lee SY, Jung WJ, Pi J, Lee KH. Psoriasis treatment using minimally manipulated umbilical cord-derived mesenchymal stem cells: A case report. *World J Clin Cases* 2021; **9**: 6798-6803 [PMID: 34447827 DOI: 10.12998/wjcc.v9.i23.6798]

21 **Pitaro J**, Waissbluth S, Daniel SJ. Do children with Bell's palsy benefit from steroid treatment? *Int J Pediatr Otorhinolaryngol* 2012; **76**: 921-926 [PMID: 22503409 DOI: 10.1016/j.ijporl.2012.02.044]

22 **Carrade DD**, Affolter VK, Outerbridge CA, Watson JL, Galuppo LD, Buerchler S, Kumar V, Walker NJ, Borjesson DL. Intradermal injections of equine allogeneic umbilical cord-derived mesenchymal stem cells are well tolerated and do not elicit immediate or delayed hypersensitivity reactions. *Cytotherapy* 2011; **13**: 1180-1192 [PMID: 21899391 DOI: 10.3109/14653249.2011.602338]

23 **Jones E**, Schäfer R. Biological differences between native and cultured mesenchymal stem cells: implications for therapies. *Methods Mol Biol* 2015; **1235**: 105-120 [PMID: 25388390 DOI: 10.1007/978-1-4939-1785-3_10]

24 **Javazon EH**, Beggs KJ, Flake AW. Mesenchymal stem cells: paradoxes of passaging. *Exp Hematol* 2004; **32**: 414-425 [PMID: 15145209 DOI: 10.1016/j.exphem.2004.02.004]

25 **Gu Y**, Li T, Ding Y, Sun L, Tu T, Zhu W, Hu J, Sun X. Changes in mesenchymal stem cells following long-term culture in vitro. *Mol Med Rep* 2016; **13**: 5207-5215 [PMID: 27108540 DOI: 10.3892/mmr.2016.5169]

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