Progress in
STEM CELL

DOI: 10.15419/psc.v4i3-4.397

Review

Article History:
Received: 15 November 2017
Accepted: 10 December 2017
Published: 29 December 2017

Keywords:
Cord tissue, Mesenchymal stem cells, Stem cell bank, Umbilical cord tissue

Author for correspondence:
Saharah Nievaleve
e-mail: nievaleve@gmail.com

Concise review: Umbilical cord-derived mesenchymal stem cell bank

Saharah Nievaleve[1]

[1]Stem Cell Center and Regenerative Medicine, India

Mesenchymal stem cells (MSCs) are the most promising stem cells for clinical applications. MSCs are widely used in disease treatment in some different countries. Recently, some MSC banks are developed to cryopreserve MSCs from umbilical cord tissues, adipose tissues, and bone marrow. This review aims to discuss some techniques, some advantages, as well as disadvantages of the umbilical cord, derived mesenchymal stem cell banking (UCMSCB). From 2010 to date, there are more than 10 UCMSCBs established in the world. There are two methods to isolate UCMSCs including tissue culture and single cell culture. Then they are cryopreserved in the liquid nitrogen for a long time. Although UCMSCBs can provide more the choice to store the MSCs from the umbilical cord, allogeneic MSC transplantation with high efficacy in disease treatment suggests that UCMSCBs should change with new approaches to use the cryopreserved samples.

1. Introduction

The first transplantation of cord blood was performed in 1988 [1]. Indeed, this is a rich source of hematopoietic stem cells (HSCs) [2–4]. These cells can be differentiated into some functional blood cells including red blood cells, white blood, and platelets [5,6]. Therefore, they were used to treat some diseases related to blood cell disorders or leukemia, lymphoma, anemia as well as non-malignant hematological disorders [7–9]. These cord blood-derived HSCs transplantation gave the promising results in some diseases [10–12]. These results triggered the establishment of many cord blood banks in the over the world [13–15]. In during time, the cord tissue was not used.

However, about 10 years ago, scientists realized that the umbilical cord is a rich source of mesenchymal stem cells (MSCs) [16]. MSCs from cord tissues also display some advantages properties compared to MSCs from adult sources. Different to HSCs that almost used to treat blood diseases, MSCs can widely be used for various conditions in nearly degenerative diseases or injuries [17–19]. These results suggested some cord blood banks begin the cord tissue banking services. It seems that the first cord tissue banking service was introduced within Asia by a Taiwanese company, HealthBanks Biotech Company Ltd. Then HealthBaby, Cryolife…launched this service. Therefore, Asia is recognized as the region in which cord tissue emerged as a commercial service.

In 2010, the first cord blood bank in the US (Cord Blood Registry) added cord tissue banking as a commercial service at this company. To date, 75% of private US cord blood banks offer cord tissue banking service and about 65% of private international banks providing this service.

This concise review aimed to discuss some achievements and progress of cord tissue banking, and analysis some progress in allogenic MSC transplantation. These analyses explore the demands of umbilical cord tissue banking.

2. Cord tissue and stem cells inside cord tissue

Cord tissues were known as a rich source of stem cells, especially MSCs. Although MSCs can be detected at some different zones in the cord tissues [20–22], the highest concentration of MSCs was discovered at the perivascular space surrounding the three blood vessels [23]. This is the results of a study at the University of Pittsburgh published in 2009 that found that 88% of all MSCs in cord tissues are at perivascular tissue [23]. As in **Figure 1**, although MSCs can exist at all sites in cord tissue, MSCs concentrated at the perivascular tissue, while an only small quantity of MSCs at the membrane of cord tissue.

3. Extraction of cord tissue-derived mesenchymal stem cells

MSCs can be extracted from cord tissues by two different methods, including tissue expansion and single cell culture [24–26]. Generally, cord tissue is cut to small fragments, remove the vascular tissues. Then, they were sometimes washed with PBS or washing buffer before they are dissected into pieces of 1-2 mm2. Finally, these tiny fragments are used to extract MSCs by tissue expansion or used to treat with the enzyme (collagenase) to get the single cells, then for unique cell culture. Both methods are using at various laboratories. Some advantages and disadvantages were compared and described in some previous publications [27,28].

The most important note in the umbilical cord tissue-derived MSC extraction is the selection of the cord tissue zone for extraction. Although MSCs can be successfully extracted at all sites in the cord tissues from the perivascular tissues, Wharton's jelly, cord tissue membrane [26], the perivascular tissues are the fatty tissue of MSCs [23]. During cord tissue processing, technicians should keep the perivascular tissues, and only the vascular tissues should be removed.

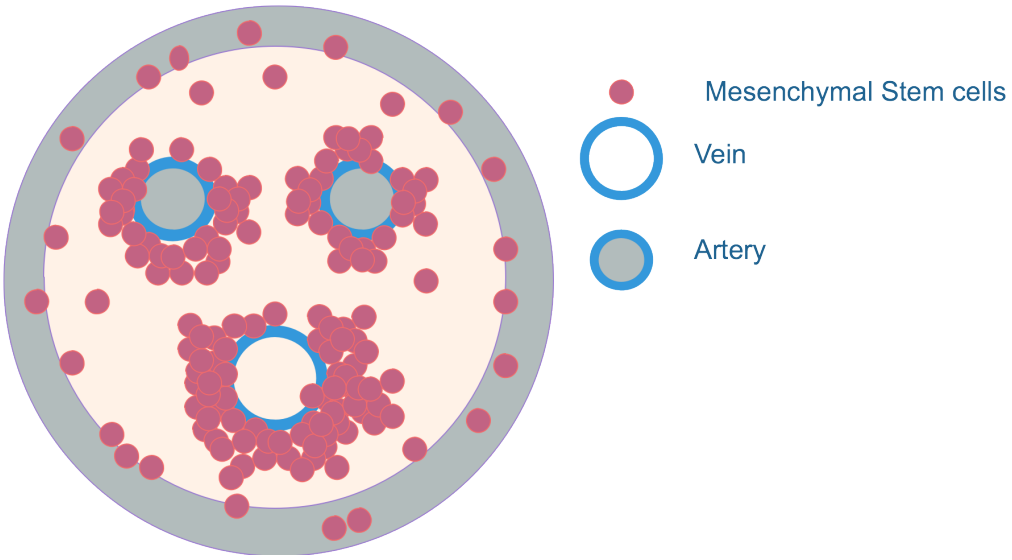

Figure 1. The distribution of mesenchymal stem cells in the cord tissue. MSCs concentrated at perivascular tissues, and their density gradually decreases to the membrane.

4. Cord tissue-derived mesenchymal stem cell transplantation

Cord tissue-derived MSCs become the popular MSCs for both preclinical and clinical application in current years. In animals, they were used to treat the variety of diseases including osteoarthritis, inflammation, diabetes mellitus type 1 and 2…In human, many clinical trials using this kind of stem cells also were performed in some countries included chronic obstructive pulmonary disease (Viet Nam) [29], lupus (China) [30], heart failure (Chile, China) (31, 32) [31,32], thrombocytopenia (China) [33], severe aplastic anemia (China) [34] …Generally, almost preclinical and clinal trials showed that cord tissue-derived MSCs are safe in both allogenic (in human) [29,34] and allogeneic (in animals) [35,36]. These transplantations also significantly improved some symptoms of various diseases.

5. Cord tissue-derived MSC banks

These promising results of cord tissue-derived MSC transplantation triggered a new service in some stem cell banks in the US, Asia. To date, there are two forms of cord tissue-derived MSC banking: (1) banking MSCs extracted and cultured from cord tissue; (2) banking the cord tissues. That means although as known as stem cell banking services, not all stem cell bank would extract the stem cells from cord tissue and do cryopreservation. In this case, the cord tissue will be washed and then cut to tiny fragments before they were mixed in the freezing medium to keep them in the nitrogen liquid. The most advantage of this strategy is the lowest cost for cryopreservation. However, the MSCs are not available for treatments. Indeed, the cryopreserved cord tissues should be thawed and extracted stem cells if clients would like to use their stem cells from the umbilical cord. In a survey, a half of the companies that store minced cord tissues without isolating MSCs before storage.

In another strategy, Cryosite developed and patented the technologies to isolate and store the blood vessels of the umbilical cord. The study showed that the number of viable nucleated cells isolated from cord tissue was on average 0.44 million/gram compared to 0.17 million cells per gram from whole cord tissue. In some other companies discovered other techniques to isolate

and expand stem cells from different regions of umbilical cords such as perivascular space, sub-amniotic space... [26].

6. Perspectives and Conclusions

From the 2000s, allogeneic MSC transplantation becomes the popular therapy for almost diseases [18,19]. The successes of allogeneic transplantation opened the new generation of the stem cells based products – the off-the-shelf products of stem cells. Different from hematopoietic stem cells, MSCs display low immunogenicity that they can survive in the allogenic hosts for the long time [37–39]. Moreover, allogeneic stem cells for transplantation also hold other advantages such as easy to control the stem cell quality, be able to scale-up the production that the cost can be significantly decreased... With these characteristics, MSCs were successfully transplanted in both animals and humans in various diseases [18,19].

We would like to discuss the demand of umbilical cord-derived MSCs banking in the context of allogeneic stem cells plays many advantages compared to autologous stem cells. The main, as well as the only target of umbilical cord-derived MSCs banking, is for autologous transplantation for the same patients. However, different to HSCs, allogeneic MSCs also were used to transplant in the patients. And in some reports, the allogenic MSCs gave the better effects on the recipients. It means that the source of autologous umbilical cord-derived MSCs is not essential for the treatments. With the off-the-shelf stem cell technologies, with a sample of the umbilical cord, MSCs can be isolated, generated and used in procedures of some thousands of patients. And by this statement, the cord tissue-derived MSCs banking is genuinely not an essential work.

7. Open Access

8. List of abbreviations

HSCs: Hematopoietic stem cells; **MSCs**: Mesenchymal stem cells; **UC**: Umbilical cord

9. Competing interests

The authors declare they have no competing interests.

References

1. Goldman JM. 1988 Autologous blood stem cell transplantation. *Beitr Infusionsther* **21**, 317–21.
2. Morrison SJ, Scadden DT. 2014 The bone marrow niche for haematopoietic stem cells. *Nature* **505**, 327–334.
3. Crane GM, Jeffery E, Morrison SJ. 2017 Adult haematopoietic stem cell niches. *Nat Rev Immunol* **17**, 573–590.
4. Ng AP, Alexander WS. 2017 Haematopoietic stem cells: past, present and future. *Cell Death Discovery* **3**, 17002.
5. Seita J, Weissman IL. 2010 Hematopoietic Stem Cell: Self-renewal versus Differentiation. *Wiley interdisciplinary reviews. Systems biology and medicine* **2**, 640–653.
6. Eaves CJ. 2015 Hematopoietic stem cells: concepts, definitions, and the new reality. *Blood* **125**, 2605–2613.
7. Mahmoud HK, Elhaddad AM, Fahmy OA, Samra MA, Abdelfattah RM, El-Nahass YH, Fathy GM, Abdelhady MS. 2015 Allogeneic hematopoietic stem cell transplantation for non-malignant hematological disorders. *Journal of Advanced Research* **6**, 449–458.
8. Hsieh MM, Fitzhugh CD, Tisdale JF. 2011 Allogeneic hematopoietic stem cell transplantation for sickle cell disease: the time is now. *Blood* **118**, 1197–1207.

9. Steward CG, Jarisch A. 2005 Haemopoietic stem cell transplantation for genetic disorders. *Archives of Disease in Childhood* **90**, 1259–1263.
10. Granados JM, Benichou G, Kawai T. 2015 Hematopoietic stem cell infusion/transplantation for induction of allograft tolerance. *Curr Opin Organ Transplant* **20**, 49–56.
11. Mantel CR, OĹeary HA, Chitteti BR, Huang X, Cooper S, Hangoc G, Brustovetsky N, Srour EF, Lee MR, Messina-Graham S, Haas DM, Falah N, Kapur R, Pelus LM, Bardeesy N, Fitamant J, Ivan M, Kim KS, Broxmeyer HE. 2015 Enhancing Hematopoietic Stem Cell Transplantation Efficacy by Mitigating Oxygen Shock. *Cell* **161**, 1553–65.
12. Hatzimichael E, Tuthill M. 2010 Hematopoietic stem cell transplantation. *Stem Cells and Cloning : Advances and Applications* **3**, 105–117.
13. Kurtzberg J. 2017 A History of Cord Blood Banking and Transplantation. *Stem Cells Translational Medicine* **6**, 1309–1311.
14. Navarrete C, Contreras M. 2009 Cord blood banking: a historical perspective. *Br J Haematol* **147**, 236–45.
15. Armitage S, Warwick R, Fehily D, Navarrete C, Contreras M. 1999 Cord blood banking in London: the first 1000 collections. *Bone Marrow Transplant* **24**, 139–45.
16. Madlambayan G, Rogers I. 2006 Umbilical cord-derived stem cells for tissue therapy: current and future uses. *Regen Med* **1**, 777–87.
17. Kim N, Cho SG. 2013 Clinical applications of mesenchymal stem cells. *The Korean Journal of Internal Medicine* **28**, 387–402.
18. Squillaro T, Peluso G, Galderisi U. 2016 Clinical Trials With Mesenchymal Stem Cells: An Update. *Cell Transplant* **25**, 829–48.
19. Pham PV. 2016 Clinical application of stem cells: An update 2015. *Biomedical Research and Therapy* **3**, 483–489.
20. Nagamura-Inoue T, He H. 2014 Umbilical cord-derived mesenchymal stem cells: Their advantages and potential clinical utility. *World Journal of Stem Cells* **6**, 195–202.
21. Gokcinar-Yagci B, Ozyuncu O, Celebi-Saltik B. 2016 Isolation, characterisation and comparative analysis of human umbilical cord vein perivascular cells and cord blood mesenchymal stem cells. *Cell Tissue Bank* **17**, 345–52.
22. Arutyunyan I, Elchaninov A, Makarov A, Fatkhudinov T. 2016 Umbilical Cord as Prospective Source for Mesenchymal Stem Cell-Based Therapy. *Stem Cells International* **2016**, 6901286.
23. Schugar RC, Chirieleison SM, Wescoe KE, Schmidt BT, Askew Y, Nance JJ, Evron JM, Peault B, Deasy BM. 2009 High Harvest Yield, High Expansion, and Phenotype Stability of CD146 Mesenchymal Stromal Cells from Whole Primitive Human Umbilical Cord Tissue. *Journal of Biomedicine and Biotechnology* **2009**, 789526.
24. Pham PV, Truong NC, Le PT, Tran TD, Vu NB, Bui KH, Phan NK. 2016 Isolation and proliferation of umbilical cord tissue derived mesenchymal stem cells for clinical applications. *Cell Tissue Bank* **17**, 289–302.
25. Hassan G, Kasem I, Soukkarieh C, Aljamali M. 2017 A Simple Method to Isolate and Expand Human Umbilical Cord Derived Mesenchymal Stem Cells: Using Explant Method and Umbilical Cord Blood Serum. *International Journal of Stem Cells* **10**, 184–192.
26. Mennan C, Wright K, Bhattacharjee A, Balain B, Richardson J, Roberts S. 2013 Isolation and characterisation of mesenchymal stem cells from different regions of the human umbilical cord. *Biomed Res Int* **2013**, 916136.
27. Hua J, Gong J, Meng H, Xu B, Yao L, Qian M, He Z, Zou S, Zhou B, Song Z. 2013 Comparison of different methods for the isolation of mesenchymal stem cells from umbilical cord matrix: proliferation and multilineage differentiation as compared to mesenchymal stem cells from umbilical cord blood and bone marrow. *Cell Biol Int*.
28. Salehinejad P, Alitheen NB, Ali AM, Omar AR, Mohit M, Janzamin E, Samani FS, Torshizi Z, Nematollahi-Mahani SN. 2012 Comparison of different methods for the isolation of mesenchymal stem cells from human umbilical cord Whartonś jelly. *In Vitro Cell Dev Biol Anim* **48**, 75–83.
29. Le PTB, Duong TM, Vu NB, Pham PV. 2016 Umbilical cord derived stem cell (ModulatistTM) transplantation for severe chronic obstructive pulmonary disease: a report of two cases. *Biomedical Research and Therapy* **3**, 902–909.
30. Sun L, Wang D, Liang J, Zhang H, Feng X, Wang H, Hua B, Liu B, Ye S, Hu X, Xu W, Zeng X, Hou Y, Gilkeson GS, Silver RM, Lu L, Shi S. 2010 Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus. *Arthritis Rheum* **62**, 2467–75.

31. Bartolucci J, Verdugo FJ, Gonzalez PL, Larrea RE, Abarzua E, Goset C, Rojo P, Palma I, Lamich R, Pedreros PA, Valdivia G, Lopez VM, Nazzal C, Alcayaga-Miranda F, Cuenca J, Brobeck MJ, Patel AN, Figueroa FE, Khoury M. 2017 Safety and Efficacy of the Intravenous Infusion of Umbilical Cord Mesenchymal Stem Cells in Patients With Heart Failure: A Phase 1/2 Randomized Controlled Trial (RIMECARD Trial [Randomized Clinical Trial of Intravenous Infusion Umbilical Cord Mesenchymal Stem Cells on Cardiopathy]). *Circ Res* **121**, 1192–1204.
32. Fang Z, Yin X, Wang J, Tian N, Ao Q, Gu Y, Liu Y. 2016 Functional characterization of human umbilical cord-derived mesenchymal stem cells for treatment of systolic heart failure. *Exp Ther Med* **12**, 3328–3332.
33. Wang X, Yin X, Sun W, Bai J, Shen Y, Ao Q, Gu Y, Liu Y. 2017 Intravenous infusion umbilical cord-derived mesenchymal stem cell in primary immune thrombocytopenia: A two-year follow-up. *Exp Ther Med* **13**, 2255–2258.
34. Si Y, Yang K, Qin M, Zhang C, Du Z, Zhang X, Liu Y, Yue Y, Feng Z. 2014 Efficacy and safety of human umbilical cord derived mesenchymal stem cell therapy in children with severe aplastic anemia following allogeneic hematopoietic stem cell transplantation: a retrospective case series of 37 patients. *Pediatr Hematol Oncol* **31**, 39–49.
35. Zhu H, Xiong Y, Xia Y, Zhang R, Tian D, Wang T, Dai J, Wang L, Yao H, Jiang H, Yang K, Liu E, Shi Y, Fu Z, Gao L, Zou L. 2017 Therapeutic Effects of Human Umbilical Cord-Derived Mesenchymal Stem Cells in Acute Lung Injury Mice. *Scientific Reports* **7**, 39889.
36. Liu CB, Huang H, Sun P, Ma SZ, Liu AH, Xue J, Fu JH, Liang YQ, Liu B, Wu DY, Lu SH, Zhang XZ. 2016 Human Umbilical Cord-Derived Mesenchymal Stromal Cells Improve Left Ventricular Function, Perfusion, and Remodeling in a Porcine Model of Chronic Myocardial Ischemia. *Stem Cells Transl Med* **5**, 1004–13.
37. Schu S, Nosov M, OFlynn L, Shaw G, Treacy O, Barry F, Murphy M, OBrien T, Ritter T. 2012 Immunogenicity of allogeneic mesenchymal stem cells. *J Cell Mol Med* **16**, 2094–103.
38. Berglund AK, Fortier LA, Antczak DF, Schnabel LV. 2017 Immunoprivileged no more: measuring the immunogenicity of allogeneic adult mesenchymal stem cells. *Stem Cell Research & Therapy* **8**, 288.
39. Cho PS, Messina DJ, Hirsh EL, Chi N, Goldman SN, Lo DP, Harris IR, Popma SH, Sachs DH, Huang CA. 2008 Immunogenicity of umbilical cord tissue–derived cells. *Blood* **111**, 430–438.