anatomy
www.anatomy.org.tr
An International Journal of Experimental and Clinical Anatomy

Review

www.anatomy.org.tr
Received: July 16, 2015; Accepted: August 1, 2015
doi:10.2399/ana.15.014

Anatomy of stem cells

Feyzan Özdal Kurt[1], Işıl Aydemir[2], Mahmud Özkut[2], Enis Cezayirli[3], M. İbrahim Tuğlu[2]

[1]*Department of Biology, Faculty of Sciences & Letters, Celal Bayar University, Manisa, Turkey*
[2]*Department of Histology-Embryology, Faculty of Medicine, Celal Bayar University, Manisa, Turkey*
[3]*Department of Anatomy, Faculty of Medicine, Celal Bayar University, Manisa, Turkey*

Abstract

Human embryonic stem cells are important for the understanding of biologic mechanisms and their potential for treatment, and for toxicology studies. Mesenchymal stem cells can produce a good environment with chemical factors and signals to serve as anti-apoptotic, immune modulator and angiogenic, and can support regeneration in damaged tissues and induce faster and better wound healing. Stem cells have recently been shown in cancer tissue; these play a major role in the progression of cancer and the principal obstacle in treatment due to their resistance. Stem cells may participate in tissue homeostasis and regeneration which shows their capacity for cell therapies which makes them an amazing source for the clinical translation to treatment of diseases. Therefore, better understanding of the behavior of these cells and the mechanisms they use are important.

Keywords: cancer; embryonic; hematopoietic; mesenchymal; pluripotent; stem cell

Anatomy 2015;9(2):86–90

Introduction

Stem cells are pluripotent cells that proliferate indefinitely with appropriate growth factor and nutrients, and appropriate environment. Stem cells have been believed to originate from primordial germ cells which normally produce the sperm or oocyte. These cells differentiate to all types cells types of mature tissues, into all derivatives of the three primary germ layers: ectoderm, endoderm and mesoderm. Stem cells can be categorized according to their potential to differentiate into different cell types such as totipotent which can give rise to a complete and functional organism, and pluripotent which can give rise to every cell in the embryo and multipotent which can give rise into the cell types of tissues they belong to. Stem cells can also be categorized as embryonic or adult. Embryonic stem cells can be isolated from blastocysts whereas adult stem cells can be obtained from the umblical cord blood and all tissues of mature organs such as the adipose tissue, cornea, teeth and skin. Moreover, recent studies have shown that are stem cells in cancer tissue.[1,2]

Stem cells can be isolated from the inner cell mass of blastocyst or on the basis of their adhesive properties in the mature tissue. They can be sorted by immunosurgery with their affinity to antibodies or just with their ability to stick mechanically. Embryonic stem cells can survive and proliferate on a fibroblast feeder layer in an appropriate culture environment. The function of feeder layer is to provide matrix environment for embryonic stem cells. This environment can also be found as an artificial product like matrigel. Embryonic stem cells can be sorted by drop culture and differentiated to any desirable cell. Proliferation of these cells can be induced by factors like LIF, tyrosine kinases JAK, transcription factors for example STAT or other related agents. Embryonic stem cells can also be identified with alkaline phosphatase activity or high-level telomerase activity. They are also positive for SSEA, TRA-1 osteopontin and PCAM-1 factors. Transcription factors such as Oct4, Sox2, FoxD3, Fbx15, Nanog, Fgf4, Utf1, Rex-1, Tdgf-1 can also be useful for their description.[3]

Mesenchymal Stem Cells

Mesenchymal stem cells can be sorted with their adhesive capacity to stick to plastic culture dish (**Figure 1a**). These cells on tissue culture plate can migrate, proliferate and expand. Using different medium and growth fac-

tors, it is possible to differentiate them to any desired cell which could be a very valuable tool in regenerative medicine. Mesenchymal stem cells can produce a good environment with chemical factors and signals to serve as anti-apoptotic, immune modulator and angiogenic. This restructured environment can support regeneration in damaged tissues and induce faster and better wound healing.[4]

Cancer Stem Cells

Cancer stem cells play a major role in the progression of cancer and the principal obstacle in treatment due to their resistance. Mesenchymal stem cells around the tumor tissue can be identified either as cancer stem cells or normal stem cells. These two different stem cells can behave as inhibitor or inductor through their secretions in the inflammatory microenvironment. Normal mesenchymal stem cells can inhibit proliferation of tumor cells by activating immune cells whereas cancer stem cells can induce proliferation and migration by the help of inflammatory mediators. The transition from epithelial to mesenchymal cancer stem cells is proposed to originate through embryonic differentiation.[5,6]

Embryonic Stem Cells

Embryonic stem cells have a very high potential for use in domestic animals, agricultural products and biomedical industry. Experimental studies are very useful due to similar behavior and parallel mechanisms of these cells.[7] Currently, human embryonic stem cells can survive and proliferate even without a feeder layer due to advances in technology allowing us to analyze protein alterations at DNA, RNA or micro RNA level revealing the mechanisms of gene expression and signal transduction. Moreover, understanding of the differentiation process in stem cells by proteomics data could lead to better understanding of their regeneration capacity.[8]

Human embryonic stem cells are important for the understanding of biologic mechanisms and their potential for treatment. They are also important for toxicology studies. TGF, BMP, Nodal, Aktivin and FGF are important factors for the function of human embryonic stem cells. Most important resource for these cells is unused embryos from assisted reproductive technology clinics, but these have chromosome abnormalities, because healthy embryos cannot be used in stem cell studies due to ethical considerations. Cells from the blastomer stage obtained for preimplantation genetic diagnosis can also be used. Currently, it is advisable to use good manufacturing principles for the isolation of human embryonic stem cells. These cells can be very useful for the treatment of all types of diseases but there are ethical issues, problems in finding good quality embryos and animal origin culture materials, risk of forming teratomas and risk of rejection.[9] Human embryonic stem cells can also be useful for the treatment of nervous system diseases where there is modal culture environment for neurogenesis and synaptogenesis with the help of inducible pluripotent stem cells. In these modal system, action potentials, synaptic connections and neurotransmitter responses can be investigated for

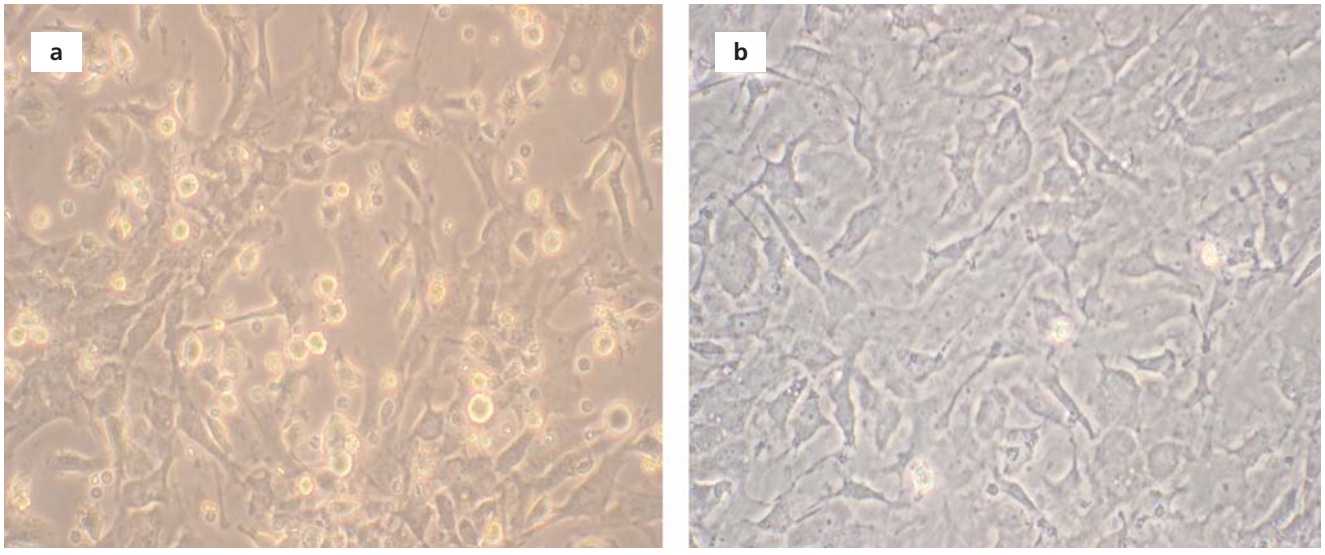

Figure 1. Inverted phase contrast morphology of (**a**) mesenchymal stem cell, and (**b**) differentation to osteoblasts, X400 magnification.

nervous system pathologies.[10] Therefore, cells therapies are quite good, effective and safe treatments against neurological diseases with possibility of personalized therapeutic applications.[11]

Adult Stem Cells

Adult stem cells can be identified by the expression of cell surface markers such as CD34, CD14, CD45 and CD133. Stem cells from mesenchymal origin can also be identified with expression of CD73, CD54, CD105, CD39 and CD49e. Stem cells differentiate with the influence of the niche to adipocytes, osteoblasts (**Figure 1b**) and chondrocytes and also can be de-differentiated back to their origin. There is no clear definition for the level of differentiation but there are markers to identify to degree of differentiation. For osteoblasts, ALP (**Figure 2a**), calcium accumulation (**Figure 2b**), osteonectin (**Figure 2c**), osteocalcine (**Figure 2d**) and osteopontin are useful markers for the level of osteoblastic differentiation with the influence of factors such as BMP, TGF, kinases and WNT. Therefore, this kind of differentiation can be very useful for tissue regeneration, gene therapies, sorting immunological problems and regeneration in the treated organs with cell therapies. For example, osteogenesis imperfecta is a degenerative disease that can be treated with stem cell therapy.[12]

Stem cells from different origins can be defined with different markers.[13] Differentiation of these cells for the use of cell therapies are influenced by adhesion molecules, matrix molecules and signals transductions.[14] By this way, vessels, liver cells, myocytes and osteoblasts can be produced in culture[15] for the treatment of diseases such as large bone defects.[16–19]

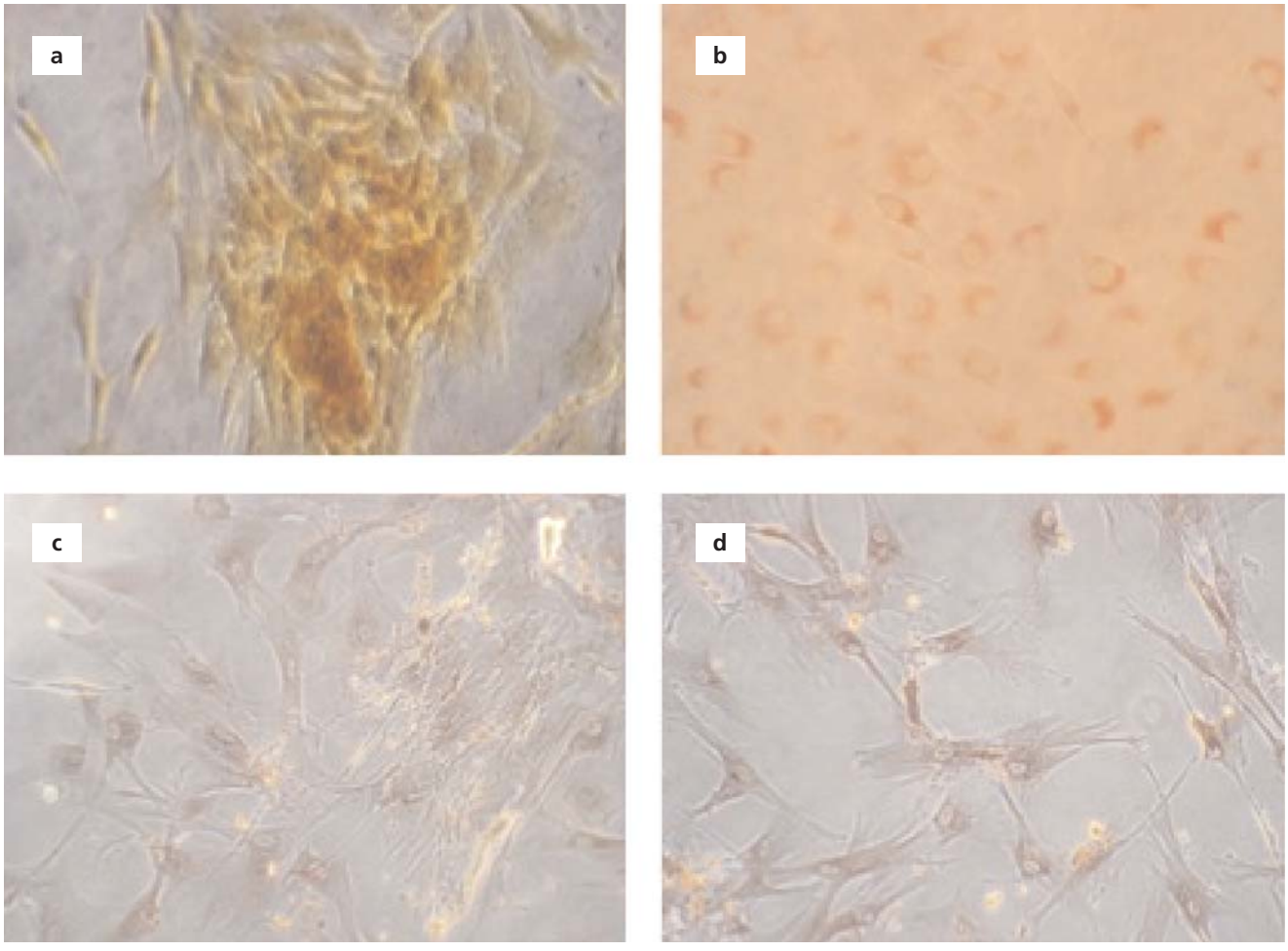

Figure 2. Histochemistry of (**a**) ALP, (**b**) Alizarin Red with calcium accumulation, and immunocytochemistry of (**c**) osteonectin and (**d**) osteocalcin, X400 magnification.

Hematopoetic Stem Cells

Hematopoetic stem cells are the blood cells that give rise to all the other blood cells and they can be identified by using the fluorescence activated cell sorting method. These cells can be labeled with fluorescence monoclonal antibodies against cell surface antigens such as CD34, CD38, CD43, CD45, CD59, CD90, CD109, CD117, CD133, CD166 and HLA-DL, or a combination of two or three of these. Progenitors of hematopoetic stem cells in the bone marrow produce a mutual source for lymphoid and myeloid series to make mature myeloid and erythroid cells. They have self-renewal capacity, but are very difficult to culture. Their proliferation can be activated by stem cell inducers. Hematopoetic stem cells can also be induced to proliferate by Hox genes in Wnt/fzd/beta-catenin pathway. Their differentiation and migration can be directed by growth factors and cytokines. They use different mechanisms such as apoptosis. These cells can migrate to hematopoetic regions such as spleen, liver and bone marrow where they start hematopoesis. The source of hematopoetic stem cells are peripheral blood, cord blood and bone marrow. Plasticity of these cells are very similar to mesencymal stem cells, both have been shown to differentiate to many different cells. Their clinical use has been known for a long time and bone marrow transplantation is used in hematologic, solid tumor cancers and high-dose chemotherapy treatments. They are getting more important lately for immunologic problems and organ failures, and in graft-versus-host disease because of their immunologic capabilities. They are also useful in autoimmune diseases such as Type 1 diabetes.[20]

The relation between signal factors and cell differentiation can be observed widely during stages of embryonic development which are similar to stem cell differentiation. The fate of stem cells can be determined by specific signal pathways such as WNT, BMP, Hedgehog and Notch.[21] It has been shown that use of both hematopoetic and mesencymal stem cells can prevent tissue rejection in graft-versus-host disease.[22,23]

Conclusion

Stem cells may participate in tissue homeostasis and regeneration which shows their capacity for cell therapies. It has been shown that local and systemic application of these cells with repetition makes this cell therapy even more effective. This is an amazing source for the clinical translation to treat every possible disease. Because of their no adverse side-effects especially for the adult mesencymal stem cells makes this source a safe, effective and successful treatment for the life quality of patients. Therefore, we need to examine the behavior of these cells and understand the mechanisms that they use to make them more efficient for the patient.

References

1. Kurt FO, Vatansever HS. Potential clinical use of differentiated cells from embryonic or mesenchymal stem cells in orthopeadic problems. Curr Stem Cell Res Ther 2015;Mar 31. doi:10.2174/1574888X10666150401104259
2. Can A, Balci D. Isolation, culture, and characterization of human umbilical cord stroma-derived mesenchymal stem cells. Methods Mol Biol 2011;698:51–62.
3. Vatansever HS, Gumus B, Aydogdu O, Sivrikoz ON, Türköz-Uluer E, Kivanç M, Ateşçi YZ, Bugdayci H. The role of stem/progenitor cells and Wnt/β-catenin signaling pathway in the patients with prostate cancer. Minerva Urol Nefrol 2014;66:249–55.
4. Meirelles Lda S, Nardi NB. Methodology, biology and clinical applications of mesenchymal stem cells. Front Biosci 2009;14:4281–98.
5. Ansieau S. EMT in breast cancer stem cell generation. Cancer Lett 2013;338:63-8.
6. Sun Z, Wang S, Zhao RC. The roles of mesenchymal stem cells in tumor inflammatory microenvironment. J Hematol Oncol 2014;7:14.
7. Brevini TA, Pennarossa G, Attanasio L, Vanelli A, Gasparrini B, Gandolfi F. Culture conditions and signalling networks promoting the establishment of cell lines from parthenogenetic and biparental pig embryos. Stem Cell Rev 2010;6:484–95.
8. King CC. Culture and preparation of human embryonic stem cells for proteomics-based applications. Methods Mol Biol 2010;584:151–77.
9. Findikli N, Candan NZ, Kahraman S. Human embryonic stem cell culture: current limitations and novel strategies. Reprod Biomed Online 2006;13:581–90.
10. Telias M, Ben-Yosef D. Modeling neurodevelopmental disorders using human pluripotent stem cells. Stem Cell Rev 2014;10:494–511.
11. Ha HY, Jang SH, Jung JW. The use of pluripotent stem cell for personalized cell therapies against neurological disorders. J Biomed Biotechnol 2011;2011.520816.
12. Can A, Karahuseyinoglu S. Concise review: human umbilical cord stroma with regard to the source of fetus-derived stem cells. Stem Cells 2007;25:2886–95.
13. Saito MT, Silvério KG, Casati MZ, Sallum EA, Nociti FH Jr. Tooth-derived stem cells: update and perspectives. World J Stem Cells 2015;7:399–407.
14. Roll L, Faissner A. Influence of the extracellular matrix on endogenous and transplanted stem cells after brain damage. Front Cell Neurosci 2014;8:219.
15. Nadal-Ginard B, Ellison GM, Torella D. The cardiac stem cell compartment is indispensable for myocardial cell homeostasis, repair and regeneration in the adult. Stem Cell Res 2014;13:615–30.
16. Sándor GK, Tuovinen VJ, Wolff J, Patrikoski M, Jokinen J, Nieminen E, Mannerström B, Lappalainen OP, Seppänen R,

Miettinen S. Adipose stem cell tissue-engineered construct used to treat large anterior mandibular defect: a case report and review of the clinical application of good manufacturing practice-level adipose stem cells for bone regeneration. J Oral Maxillofac Surg 2013; 71:938–50.

17. Vestentoft PS. Development and molecular composition of the hepatic progenitor cell niche. Dan Med J 2013;60:B4640.
18. Murray IR, West CC, Hardy WR, James AW, Park TS, Nguyen A, Tawonsawatruk T, Lazzari L, Soo C, Péault B. Natural history of mesenchymal stem cells, from vessel walls to culture vessels. Cell Mol Life Sci 2014;71:1353–74.
19. Wang X, Zachman AL, Haglund NA, Maltais S, Sung HJ. Combined usage of stem cells in end-stage heart failure therapies. J Cell Biochem 2014;115:1217–24.
20. Gülen H, Tüzün F, Ayhan Y, Erbay A, Oztürk E, Inan S, Vergin C. The evaluation of blood donor deferral causes. Pediatr Hematol Oncol 2006;23:91–4.
21. Van Camp JK, Beckers S, Zegers D, Van Hul W. Wnt signaling and the control of human stem cell fate. Stem Cell Rev 2014;10:207–29.
22. Sawitzki B, Brunstein C, Meisel C, Schumann J, Vogt K, Appelt C, Curtsinger JM, Verneris MR, Miller JS, Wagner JE, Blazar BR. Prevention of graft-versus-host disease by adoptive T regulatory therapy is associated with active repression of peripheral blood Toll-like receptor 5 mRNA expression. Biol Blood Marrow Transplant 2014;20:173–82.
23. Introna M, Rambaldi A. Mesenchymal stromal cells for prevention and treatment of graft-versus-host disease: successes and hurdles. Curr Opin Organ Transplant 2015;20:72–8.

Online available at:
www.anatomy.org.tr
doi:10.2399/ana.15.014
QR code:

Correspondence to: M. İbrahim Tuğlu, MD
Department of Histology-Embryology, Faculty of Medicine,
Celal Bayar University, 45020, Manisa, Turkey
Phone: +90 533 337 38 21
e-mail: mituglu@yahoo.com

Conflict of interest statement: No conflicts declared.