ECRONICON OPEN ACCESS

EC ORTHOPAEDICS
Editorial

Utilization of Different Osteogenic Cells in Cell Therapy in Bone Healing

A Oryan* and S Sahvieh

Department of Pathology, School of Veterinary Medicine, Shiraz University, Shiraz, Iran

***Corresponding Author:** A Oryan, Department of Pathology, School of Veterinary Medicine, Shiraz University, Shiraz, Iran.

Received: November 17, 2020; **Published:** December 28, 2020

The main concern of the researchers and orthopedic surgeons is to find an efficient method for bone healing. Because of some conditions such as accidents, trauma, burns, non-union bone defects, myeloma-related bone diseases, osteotomies, arthritis, bone tumor resections, osteomyelitis, pathologic fractures, osteoporosis, chronic bone infections, osteoarthritis, and bone cancer which cause extensive bone defects, bone tissue regeneration and reconstruction is notable. In addition to impact the quality of life and health of the patients, the multibillion-dollar cost of bone fractures is also significant [1-4].

A productive bone healing is distinguished by a well-vascularized and remodeled newly formed bone tissue that fills the defect region. It is finally led to an efficient skeletal function with adequate stability [5-7]. Bone formation is reduced by infection, diabetes, non-steroid anti-inflammatory drugs (NSAIDs), and smoking. There is a complex set of regulated signaling pathways that have a crucial role in bone healing via resorption of the damaged bone matrix and simultaneously controlling the new bone matrix synthesis by balanced anabolic and catabolic processes. Manipulation of these two pathways with pharmacological, mechanical, and biological interventions leads to enhanced bone healing [5].

The first step in bone healing is characterized by blood clot formation or hematoma formation which is followed by acute and chronic inflammation. Serotonin, leukotrienes, thromboxane, histamine, and bradykinin are released by basophils, platelets, and mast cells resulting in vasodilation and cell infiltration to the defect region. The cytokines and growth factors that are released from the inflammatory cells activate the osteoprogenitor cells to proliferate, differentiate, and migrate to the injured area [8,9]. They finally differentiate to the chondroblasts, chondrocytes, osteoblasts, and osteocytes and form fibrocartilaginous, cartilaginous, and bony tissues [6,10].

Pathologic and traumatic injuries cause massive bone defect which needs bone transplantation and reconstructive surgery. Some methods such as intramedullary pins, dynamic external fixation, and plating are needed to enhance the local osteoprogenitors to heal the defect. Autograft, allograft, and xenograft are also other methods in bone regeneration, but they have disadvantages such as the need for further surgery, disease transmission, immunogenicity, pain, and graft rejection that limit their utilization [11]. The autologous bones have beneficial characteristics such as osteointegration, osteoinduction, osteogenesis, and osteoconduction that are crucial for the tissue-engineered bone constructs but morbidity of the donor site, necrosis, pain, and infection are its limitation [1]. Tissue engineering is the most reliable method in regenerative medicine in plastic surgery, orthopedic surgery, and reconstructive fields. In this method, a combination of osteoinductive and/or osteogenic components with scaffolds would enhance bone regeneration especially in extensive defects [12,13]. One of the principal ingredients that is utilized in bone regeneration in tissue engineering is cells in addition to the extracellular matrices and growth factors [9,11]. Some metabolic diseases and other abnormalities such as diabetes, irradiation, severe trauma, osteoporosis, and aging are cured by cell-based therapies [9].

Many cell types are used in bone tissue engineering to enhance healing. One important source of cell therapy for regenerative medicine is mesenchymal stem cells (MSCs) in human clinical trials and animal models. This cell line could migrate to the defect site and has the potential to differentiate into the components of the original tissue in the defect site. They also can secrete growth factors, cytokines, and chemokines which are efficacious in bone healing [14,15]. MSCs are migrated and recruited from the surrounding tissues to the defect area to differentiate to the osteogenic precursor cells, but this endogenous source of mesenchymal cells might be insufficient. Therefore, applying MSCs alone or loading to scaffolds, and further differentiation of these cell type to osteoprogenitor cells like osteoblasts at the defect region would enhance and lead to promoted bone regeneration [16].

MSCs differentiate to various mesenchymal lineages such as fibroblasts, fibrocytes, adipoblasts, adipocytes, chondroblasts, chondrocytes, osteoblasts, osteocytes, marrow stroma, and other musculoskeletal tissue cell lines [17]. Some tissues such as adipose tissue, umbilical cord, and dental pulp contain substantial amounts of MSCs. Amongst all these tissues, the umbilical cord not only has the most plentiful source of stem cells for musculoskeletal defects but also it has the lower immunogenic reactions to the body of patients. The MSCs extracted from the umbilical cord have a differentiation potential to the adipogenic, chondrogenic, and osteogenic lineages [18]. The umbilical cord matrix-derived MSCs have osteogenic potential in 3-dimensional and 2-dimensional differentiation conditions. Loading the combination of endothelial and undifferentiated MSCs lineage cells onto the scaffolds has shown the bone healing capacity of MSCs [19]. Based upon the MSCs' ability to migrate to the defect site and differentiate to the osteogenic precursor cells, the MSCs are utilized in stem cell transplantation and tissue engineering properly [20,21]. As the MSCs would differentiate to the endothelial cells, implantation of the MSCs in the defect region could enhance angiogenesis. By implanting the MSCs in the defect region, endochondral ossification would occur; however, implantation of the osteoblasts in the defect region would result in intramembranous ossification [22].

The non-hematopoietic stem cells which exist in bone marrow have a multipotential differentiating ability. These cells are utilized for cell therapy in regenerative medicine and tissue engineering [23]. This cell line is proper for bone healing because of its high *in vitro* amplification potential and low immunogenicity. They also differentiate into osteoblasts which are known as the principal elements of bone regeneration [24]. In Weiab and colleagues' study, the BMSCs implantation on the calcinated cancellous bone promoted angiogenesis and also improved new bone tissue formation [25]. This cell line differentiated to different cell lineages such as chondroblasts, chondrocytes, osteoblasts, osteocytes and adipocytes and also demonstrated a self-renewal potential [26]. Based upon knowing that the BMCs have a role in cell-based therapy, Zhang., *et al.* [27] depicted that the BMSCs-laden hydrogel makes a proper microenvironment that result in the promotion of cell proliferation, attachment, and differentiation and finally enhance bone healing. In a previous study, we showed the effect of BMSCs loaded on the polylactic acid/polycaprolactone/hydroxyapatite scaffold on bone healing and compared it with the cell free scaffold. The BMSCs was differentiated into the osteoblasts and osteocytes and the best regeneration was seen in the group that was treated with BMSCs-seeded onto the scaffold [28].

The nonunion, malunion, delayed union, and incomplete bone regeneration is resulted from poor cell migration, proliferation, differentiation, and inept conversion of MSCs to the osteogenic precursor cells [29]. The scaffold degradation rate was enhanced due to the secretion of some specific extracellular matrix ingredients by BMSCs [21]. The mineralized area, gene expression of Runx-2, BMP-2, Col 1a1, and b-FGF, and the OSX, and ALP activity was also promoted following treatment by these cells [30]. Liuac., *et al.* [31] showed that the BMSCs-sheet resulted in better bone regeneration in comparison to the untreated animals. It was also demonstrated that the proliferated bone marrow cells generated the fibroblast-like cells colonies which were also generated via the MSCs [32]. The stem cells reside at the stem cell niche which contains high contents of chemical and physical components such as extracellular matrix, adhesion cells and molecules, and soluble factors. The components of stem cells work interactively to preserve their properties and induce differentiation, proliferation, and migration of these cells in response to the physiological necessities. Based on the importance of knowing the properties and compositions of the stem cell niches, the researchers utilized cell tracking and genetic labeling to show the differences between the BMSCs' behavior in the bone marrow and the culture [26].

Osteoclast lineages have a principal role in bone resorption and remodeling but they are not used for clinical application. The differentiated osteogenic cells are used in cell therapy in bone healing because of their potential to differentiate to the osteogenic cells [32]. Due to the extent utilization of cell therapy in regenerative medicine, especially bone healing, understanding the capacity of various cell lines in this field is notable. In this manner, by combining one of these cell lineages with other components in bone regeneration, bone healing is promoted. Altogether, we propose the MSCs as the most suitable cell lineage in bone regeneration when compared to other cell lines because of their potential to differ to the endothelial cell and based upon this property, the angiogenesis is properly established beside the differentiation capacity of MSCs to the osteogenic cells.

Bibliography

1. Oryan A., *et al*. "Bone regenerative medicine: Classic options, novel strategies, and future directions". *Journal of Orthopaedic Surgery and Research* 9 (2014): 18.

2. Oryan A., *et al*. "Effects of osteogenic medium on healing of the experimental critical bone defect in a rabbit model". *Bone* 63 (2014): 53-60.

3. Moshiri A., *et al*. "An overview on bone tissue engineering and regenerative medicine: current challenges, future directions and strategies". *Journal of Sports Medicine and Doping Studies* 5 (2015): 144.

4. Alidadi S., *et al*. "Comparative study on the healing potential of chitosan, polymethylmethacrylateand demineralized bone matrix in radial bone defects of rat". *Carbohydrate Polymers* 166 (2017): 236-248.

5. Mathavan N., *et al*. "Investigating the synergistic efficacy of BMP-7 and zoledronate on bone allografts using an open rat osteotomy model". *Bone* 56 (2013): 440-448.

6. Kyllonen L., *et al*. "Local drug delivery for enhancing fracture healing in osteoporotic bone". *Acta Biomaterialia* 11 (2015): 412-434.

7. Oryan A., *et al*. "Effectiveness of mesenchymal stem cell-seeded onto the 3D polylactic acid/polycaprolactone/hydroxyapatite scaffold on the radius bone defect in rat". *Life Sciences* 257 (2020): 118038. doi: 10.1016/j.lfs.2020.118038.

8. Oryan A., *et al*. "Bone Injury and Fracture Healing Biology". *Biomedical and Environmental Sciences* 28 (2015): 57-71.

9. Oryan A and Sahvieh S. "Effectiveness of chitosan scaffold in skin, bone and cartilage healing". *International Journal of Biological Macromolecules* 104 (2017): 1003-1011.

10. Oryan A and Moshiri A. "A long term study on the role of exogenous human recombinant basic fibroblast growth factor on the superficial digital flexor tendon healing in rabbits". *Journal of Musculoskeletal and Neuronal Interactions* 11 (2011): 185-195.

11. Oryan A., *et al*. "Effectiveness of tissue engineered chitosan-gelatin composite scaffold loaded with human platelet gel in regeneration of critical sized radial bone defect in rat". *Journal of Controlled Release* 254 (2017): 65-77.

12. Moshiri A., *et al*. "Role of tissue-engineered artificial tendon in healing of a large achilles tendon defect model in rabbits". *Journal of American Collage Surgeons* 217 (2013): 421-441.

13. Shahrezaie M., *et al*. "Effectiveness of tissue engineered three dimensional bioactive graft on bone healing and regeneration: an *In vivo* study with significant clinical value". *Journal of Tissue Engineering and Regenerative Medicine* 12 (2017): 936-960.

14. Xing Z., *et al*. "Multiple roles for CCR2 during fracture healing". *Disease Models and Mechanism* 3 (2010): 451-458.

15. Cho SW. "Role of osteal macrophages in bone metabolism". *Journal of Pathology and Translational Medicine* 49 (2015): 102-104.

16. Oryan A., *et al*. "Chemical crosslinking of biopolymeric scaffolds: current knowledge and future directions of crosslinked engineered bone scaffolds" *International Journal of Biological Macromolecules* 107 (2017): 678-688.

17. Malgieri A., *et al*. "Bone marrow and umbilical cord blood human mesenchymal stem cells: state of the art". *International Journal of Clinical and Experimental Medicine* 3 (2010): 248-269.

18. Jager M., *et al*. "Bone Healing and Migration of Cord Blood-Derived Stem Cells Into a Critical Size Femoral Defect After Xenotransplantation". *Journal of Bone and Mineral Research* 22 (2007): 1224-1233.

19. Jones E and Yang X. "Mesenchymal stem cells and bone regeneration: Current status". *Injury* 42 (2011): 562-568.

20. Baghaban-Eslaminejad M., *et al*. "Type I collagen gel in seeding medium improves murine mesencymal stem cell loading onto the scaffold, increases their subsequent proliferation, and enhances culture mineralization". *Journal of Biomedical Materials Research B Appllied Biomaterial* 90 (2009): 659-667.

21. Oryan A., *et al*. "Synergistic effect of strontium, bioactive glass and nano-hydroxyapatite promotes bone regeneration of critical-sized radial bone defects". *Journal of Biomedical Materials Research Part B* 107 (2018): 50-64.

22. Tortelli F., *et al*. "The development of tissue engineered bone of different origin through endochondral and intramembranous ossification following the implantation of mesenchymal stem cells and osteoblasts in a murine model". *Biomaterials* 31 (2010): 242-249.

23. Fu X., *et al*. "Mesenchymal stem cell migration and tissue repair". *Cells* 8 (2019): 784-800.

24. Luo CH., *et al*. "Biomimetic open porous structured core-shell microtissue with enhanced mechanical properties for bottom-up bone tissue engineering". *Theranostics* 9 (2019): 4663-4677.

25. Weiab JQ., *et al*. "Enhanced critical-sized bone defect repair efficiency by combining deproteinized antler cancellous bone and autologous BMSCs". *Chinese Chemical Letters* 28 (2017): 845-850.

26. Tsai TL and Li WJ. "Identification of bone marrow-derived soluble factors regulating human mesenchymal stem cells for bone regeneration". *Stem Cell Reports Journal* 8 (2017): 387-400.

27. Zhang Y., *et al*. "Injectable hydrogels from enzyme-catalyzed crosslinking as BMSCs-laden scaffold for bone repair and regeneration". *Materials Science and Engineering C* 96 (2019): 841-849.

28. Oryan A., *et al*. "Role of mesenchymal stem cells in bone regenerative medicine: What is the evidence?" *Cells Tissues Organs* 204 (2017): 59-83.

29. Sahvieh S., *et al*. "Role of bone 1stem cell-seeded 3D polylactic acid/polycaprolactone/hydroxyapatite scaffold on a critical-sized radial bone defect in rat". *Cell and Tissue Research* (2020): 32924069. doi: 10.1007/s00441-020-03284-9.

30. Chatterjee K., *et al*. "The effect of 3D hydrogel scaffold modulus on osteoblast differentiation and mineralization revealed by combinatorial screening". *Biomaterials* 31 (2010): 5051-5062.

31. Liuac Y., *et al*. "Integration of a calcined bovine bone and BMSC-sheet 3D scaffold and the promotion of bone regeneration in large defects". *Biomaterials* 34 (2013): 9998-10006.

32. Rosset P., *et al*. "Cell therapy for bone repair". *Orthopaedics and Traumatology: Surgery and Research* 100 (2014): S107-S112.

Volume 12 Issue 1 January 2021