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Review Article

Stem Cell and Its Applications in Prosthodontics

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ABSTRACT

Stem cells are much of keen interest in the recent era. Undifferentiated stem cells do have pluripotent nature in which they can turn into characteristic cell as per in-situ requirement of the body. Genetic engineering field currently works on "reprogramming" techniques by exploring the scope of stem cells.This article reviews about stem cells and its extended application in the field of prosthodontics.

INTRODUCTION

Life is diverse and so are the forms and functions of cells. Cell is the basic unit of life.

HISTORY

1663-ROBERT HOOKE identified and named CELL.

1838-MATHIAS SCHEILDEN(German botanist)-cell is the basic unit of all vegetable matter.

1839-THEODOR SCHWANN cell are organisms and entire animals and plants are aggregates of these organisms arranged according to definite laws.

1960 - ERNEST A. MCCULLOCH and JAMES E. TILL at the University of Toronto were the first to venture into the field of stem cells research

THE STEM CELLS

A cell that has the potential to regenerate tissue over a lifetime is termed as Stem Cell.

A stem cell must be able to reproduce new blood cells and immune cells over a long term, demonstrating potency. It should also be possible to isolate stem cells from the transplanted individual, which can themselves be transplanted into another individual demonstrating that the stem cell was able to self-renew.(1)

ORIGINS

1.) Pluripotent Stem Cells: The pluripotent stem cells includes investigation on the biology and regenerative treatments due to their pluripotency and self-renewal.

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Dental research is focused on obtaining oral lineages from the differentiation of pluripotent stem cells which is applied clinically (2).

1.1) Embryonic Stem Cells (ES Cells): ES cells which are produced from the culturing cells, precede from the blastocyst, particularly from its undifferentiated inner cell mass (the early stage of embryonic development after fertilization) (3). They are of great interest because of the particular distinguishing quality of differentiating into all somatic cell lineages and germ cells.

1.2) iPS Cells (Pluripotent Stem Cells): iPS cells have the aptitude to develop into various types' tissue and organs. This technology is very promising, which can revolutionize medicine and create a biocompatible medicine that uses patients' cells to supply individual and biocompatible treatments. iPS cells can be obtained from multiple oral mesenchymal cells: SCAP, DPSCs and SHED, TGPCs, buccal mucosa fibroblasts, gingiva fibroblasts, and periodontal ligament fibroblasts (5). It is expected that oral cells can be an ideal iPS cell source, which can be applied in regenerative procedures for periodontal tissue, salivary glands, missing jaw bone, and tooth loss (6).

2.) Adult Stem Cells: Embryonic stem (ES) and adult stem cells are two of the leading sources of stem cells present in humans. Further sources can be obtained synthetically from somatic cells, which are known as pluripotent stem (iPS) cells. Adult stem cells can only develop into a certain number of kinds of cells. On the other hand, ES cells or IPS cells are pluripotent stem cells, which means that they can differentiate into all kinds of cells from all three germinal layers. (7, 8)

Studies on stem cells have revealed that the oral and maxillofacial region has a number of adult stem cell sources.(9)

2.1) Mesenchymal Stem Cells (MSCs): Even though bone marrow was the original source of MSCs, there are alternatives which have been drawn from other adult tissues(10). Friedenstein et al. described in the 70s that the approach of using adherent fibroblastic cells that were drawn from the bone marrow (11) and their capacity to differentiate into several mesenchymal tissues. Years later, Pittenger et al. described human mesenchymal stem cells from the iliac rest bone marrow as multipotent cells, explaining their isolation, expansion in culture, and differentiation into chondrogenic, adipogenic, and osteogenic lineages (12) Mesenchymal stem cells can be attached to tissue culture-treated plastic when maintained in standard culture conditions (13) as stated in ISCT (The International Society for Cellular Therapy) criteria. In addition, MSCs shouldexpress CD105, CD73, and CD90 and lack the expression of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR surface molecules. MSCs must also be able to differentiate into chondroblasts, adipocytes, and osteoblasts (14).

2.2) Bone Marrow-Derived MSCs (BMSCs): BMSCs are multipotent progenitor cells present in adult bone marrow. Due to their replicative capacity, they can also differentiate into numerous cells of the connective tissue. BMSCs can be isolated from the iliac crest (15). Even though the process of isolating BMSCs from the bonem arrow is a relatively simple process, but the drawback is the need for amajor surgical and invasive operation. Nevertheless, this procedure is the most common and it has been used in dental bone regeneration for many years. (16)We can obtain BMSCs from orofacial bones as well. Human BMSCs can be isolated from the maxilla and mandible bone marrow suctioned during dental treatments like dental implantation, third molar extraction, orthodontic osteotomy, or cyst extirpation(17). These cells have the possibility to be attained from both young patients (6–53 years old) and from older patients (57–62 years old), (18). Animal (19) and human studies (20) have described that grafted bone from the craniofacial area for autologous bone grafting at craniofacial locations produces greater results and considerably higher bone volume than bone extracted from the endochondral bone, such as rib or iliac crest.

Following embryology, cranial neural crest cells create maxilla and mandible bones, and the mesoderm originates the iliac crest bone. This embryological explanation may be the reason why there are functional differences between the iliac crest human and orofacial BMSCs (21)

2.3) Dental Tissue-Derived Stem Cells: Epithelial stem cells and MSCs have been described in dental tissues. In 1999, through organ culture of the apical end of the mouse incisor, the first epithelial stem cell niche was established. The cervical loopof thetooth apex where theniche islocated possibly contains dental epithelial stem cells, which have the abilitytoturnintoenamel-producingamelobasts.Thereisno further information available about human dental epithelial stem cells. Having the suitable conditions after dental procedures, dental tissues such as dental pulp and periodontal tissues are able to regenerate and form reparative dentine. We can find mesenchymal progenitor or stem cells in these types of tissues (22).

2.4) Periosteum – Derived Stem/Progenitor Cells: Periosteum is the name given to the specialized connective tissue whose function is to cover the outer surface of the bone tissue. In 1932, author Fell firstly described the osteogenic potential of long bones periosteum and its membrane, having suggested its capacity to form a mineralized extracellular matrix if there were the suitable in vitro circumstances (23). The external area contains elastic fibers and fibroblasts, and the interior area contains MSCs, fibroblasts and osteoblasts,osteogenic progenitor cells, microvessels, and sympathetic nerves (24). These cells have the ability to differentiate into adipocytes, osteoblasts, and chondrocytes and to express the typical MSC markers. Clinical research has demonstrated positive results when cells derived from the periosteum were applied for sinus or alveolar ridge augmentation, which showed reliable implant insertion, withimprovedbone remodelling andlamellarbone production, and also demonstrated that shorter postoperative waiting time was needed after implantation. As a result, in case of large bone defects, the periosteum could be a source of stem/progenitor cells (25).

2.5) Salivary Gland-Derived Stem Cells: Salivary glandderived stem cells have been studied to be used for autologous transplantation treatment, for gland tissue engineering, and for cell treatments. The endoderm originates from the salivary glands, which compose the epithelial cells from the ductus and acinar cells with exocrine capacity. The epithelium proliferates when the link of the salivary gland duct occurs, and the acinar cells undergoes apoptosis. (26) Studies suggest that salivary glands are a promising source for stem cells that can be used for therapy in patients that suffer from cancer to the head and neck and who have undergone radiotherapy. Human salivary gland primitive MSC-like cells were isolated, evidently showing that embryonic candadultstemcellmarkers and can be guided to differentiate into chondrogenic, osteogenic, and adipogenic cells (27).

2.6) Adipose Tissue-Derived Stem Cells (ASCs): Adipose tissue has been studied as a stem cell source in regenerative medicine, and it is considered an abundant MSC source. ASCs can be obtained through lipectomy or from lipoaspiration from areas such as the chin, hips, upper arms, and abdomen with low donor-site morbidity, as liposuction is a very common cosmetic procedure (28). ASC sare expected to bean alternative source of MSCs in bone regeneration in the dental field, as theypresent arobust osteogenesis (29). The practicability of using ASCs in GBR and in implant surgery has already been tested (30).

Clinical Applications in Dentistry

The focus of stem cell research in dentistry is mostly in the regeneration of missing oral tissues. Its application in dentistry is varied.

Relation Between Stem Cells & Orthodontic Tooth Movement - It is a documented example of cell differentiation into the "wrong" lineage by applied static forces, given the observation that non-cartilage cells in the periodontal ligament are transformed into chondrocytes, thus temporarily halting orthodontic tooth movement. Research is still on to understand the intricacies of differentiation of stem cell into osteoblast, osteoclast, chondroblast etc. and cyclic orthodonticforces to:-

- Accelerates the tooth movement
- Reduce retention time

Stem cells & Tooth Eruption - Stem cells can differentiate into osteoblasts, osteoclasts, fibroblasts, fibroclastsetc. which can aid in eruption of tooth. Results of different studies are controversial

Role of Stem Cell In Craniofacial Defects - Research has shown that use of stem cells along with Distraction Osteogenesis gives promising results in respect of quality of bone produced.Study has shown that use of stem cells to reconstruct calvarial defect resulted in near complete calvarial continuity.(31, 32)

Role of Stem Cell In TMD - Mesenchymal stem cells can be used to regenerate the cartilage, synovial membrane and the articulating surfaces.

Another Applications (32)

- Maxillofacial Soft tissue Regeneration
- Implants and Ridge augmentation
- Stereolithography
- Tissue specific Base scaffold
- Bone tissue regeneration
- Cartilage tissue formation
- Adipose tissue regeneration
- Muscular tissue regeneration
- Tooth/root regeneration
- Salivary gland regeneration
- Mandible condyle regeneration
- Tongue regeneration

Clinical Applications in Prosthodontics

In particular, the restoration of alveolar ridge height is a major concern to prosthodontists because bone defects that arise after tooth loss usually result in further horizontal and vertical bone loss which limits the effectiveness of dental implants and other prosthodontic treatments (1). Therefore, stem-cell-based regenerative technology is considered to represent a new frontier in prosthodontics (33). In the field of prosthodontics, especially in the clinic, material-based reconstruction without major surgical procedures was the main approach to treatment.However, emerging stem cell technologies and the requirements of alveolar ridge augmentation associated with implant dentistry have expanded the clinical concept to include stem-cell based regeneration. Stem cell technologies have even permitted dental scientists to imagine the development of bioengineered teeth to replace the patient's missing teeth.

Furthermore, ‘‘dental stem cell banking’’ is already on the market for possible future use in regenerative therapies. Thus, clinicians as well as researchers in the prosthodontic field should understand basic aspects of stem cells and the implications of stem cell technologies in the future of dentistry.

Tooth regeneration - The regeneration of adult teeth will be possible in future with the help of tissue engineering and newer expansion in stem cell therapy. Regenerative procedures would be improved fitting and substitutes in place of dental implants. Experimental studies with animal models have exposed that the tooth crown formation can be regenerated using tissue engineering techniques that merge stem cells and recyclable scaffolds. Three key elements are involvein tooth regeneration which include: Inductive morphogenes, Stem cells and Scaffold

Following steps are involved in regeneration of tooth:

1) Harvesting and spreading out of adultstem cells. 2) Seeding the stem cells into scaffold which provides optimize environment. 3) Cells are instructed with targeted soluble molecular signals spatially. 4) The gene expression profile is confirming by the cells for next phase in odontogenesis. 5)Duailibi et al., in their studies were able to form tooth from single cell suspensions of cultured rat tooth bud cells. They confirmed bioengineered rat teeth grown in 12 weeks with PLGA and PGA scaffold. Honda et al. developed tissue engineered teeth, when implanted into omentum of rat utilizing porcine tooth bud cells and PGA fiber engage scaffold that reminds of the model of odontogenesis. Young et al., using porcine tooth bud cells, PLGA and PGA scaffolds produced a crossbreed tooth bone for the cure of tooth loss beside with alveolar bone resorption.(34, 35, 36, 37)

Periodontal regeneration - Due to the difficult structure of the periodontium (having hard and soft tissues), its entire regeneration has always beena challenge. All the present regenerative techniques such as allografts, autologous bonegrafts, or alloplastic materials have restrictions and cannot be utilized in all clinical condition. Therefore, a cell mediated bone regeneration technique will be a possible therapeutic alternative. Kawaguchi et al. verified that the transplantation of ex vivo prolonged autologous MSCs can regenerate fresh cementum, periodontal ligament and alveolar bone in class III periodontal deficit in dogs. (38)

Craniofacial regeneration - Regenerative medicine aims to use tissue engineering to restore damaged and lost tissue (39). TRCs were grafted into osseous defects of the jaw and biopsies harvested for analyses at 6 and 12 weeks. Reconstruction of these sites was completed with oral implant therapy and treatment sites were followed for 12 months postoperatively. Clinical and laboratory analyses of treatment sites demonstrated that the cell therapy accelerated the regenerative response as determined clinically, radiographically, and histologically. Further, there was a significantly reduced need for secondary bone grafting procedures in the group that originally received the cell therapy. (40)

Alveolar bone regeneration - Bone development involves the aggregation of MSCs into mesenchymal condensations, which is partly similar to tooth development but without the epithelial invagination. There are two typesof bone formation: intramembranous and endochondral. In endochondral bone formation, the mesenchymal condensations first undergo chondrogenesis and then ossification to form cartilage and bone. (41) During adulthood, bone possesses the intrinsic capacity for regeneration throughout life. In most bone injuries (fractures), the damaged bone tissue can be functionally regenerated by the local cells (including chondroblasts, osteoblasts, endotheliocytes and fibroblasts). However, when the fractures are serious (such as large bone defects created by trauma, infection, tumorresection, and skeletal abnormalities) enough that self-healing cannot repair, an adequate supply of stem cells (such as bone marrow stem cells) is required for efficient bone regeneration. (42) Oral MSCs seem to be ideal candidates for bone regeneration. Both dental and non-dental MSCs are able to differentiate into chondroblastsand osteoblastsunder inductive condition. (43)

Muscle regeneration - Some research groups have focused on the muscle and tendon-forming properties of oral stem cells. Armiñán et al (44) first reported that DPSCs could differentiate into cardiomyocyte-like cells when cultivated with neonatal rat cardiomyocytes for about 4 weeks.

CONCLUSION

After decades of experiments, stem cell therapy has become a magnificent game changer not only for medicine but also for dental treatments. Stem cells can be obtained as discarded biological materials. Their excellent regenerative ability can be applied not only in dentistry but also in various fields of regenerative medicine. Tissue banks are becoming popular day by day, as they gather cells in a struggle against present and future diseases. The oral stem cells has the capability to repair cornea, dental pulp, periodontal, neural, bone, muscle, tendon, cartilage, and endothelial tissues without neoplasm formation. Prosthodontists rarely perform basic biological studies. However, the increased requirement for new technologies for implant dentistry is encouraging prosthodontists to be involved in or at least understand regenerative medicine, including stem cell biology. With advancements in stem cell therapy and all its regenerative benefits, we are better able to prolong human life.

REFERENCES

1. "iPS cells in dentistry,". Egusa H. Clinical Calcium. 2012; 22:67-73.
2. "The ground state of pluripotency". J. Wray, T. Kalkan, and A. G. Smith,. 4, 2010, Biochemical Society Transactions, Vol. 38, pp. 1027-1032.
3. "Embryonic stem cell lines derived from human blastocysts,". J.A. Thomson, J.Itskovitz-Eldor, S.S. Shapiroetal.,. 5391, 1998, Science, Vol. 282, pp. 1145-1147.
4. "Induced pluripotent stem cell lines derived from human gingival fibroblasts and periodontal ligament fibroblasts". N. Wada, B. Wang, N. H. Lin, A. L. Laslett, S. Gronthos, and P. M. Bartold. 4, 2011, Journal of Periodontal Research, Vol. 46, pp. 438-447.
5. "Differentiation of induced pluripotent stem cells into dental mesenchymal cells,". K. Otsu, R. Kishigami, A. Oikawa-Sasaki et al. 7, 2012, Stem Cells and Development, Vol. 21, pp. 1156-1164.
6. "Adult stem cells,". H. E. Young and A. C. Black Jr. 1, 2004, The Anatomical Record. Part A, Discoveries in Molecular, Cellular, and Evolutionary Biology, Vol. 276A, pp. 75-102.
7. "Stem cells in dentistry – part I : stem cell sources,". [H. Egusa, W. Sonoyama, M. Nishimura, I. Atsuta, and K. Akiyama,. 3, 2012, Journal of Prosthodontic Research, Vol. 56, pp. 151-165.

8. “Human dental pulp stem cells hook into biocoral scaffold forming an engineered biocomplex,” . C. Mangano, F. Paino, R. d'Aquino et al. 4, 2011, PLoS One, Vol. 6, p. e18721.
9. “In vivo osteogenic differentiation of human adipose-derived stem cells in an injectable in situ–forming gel scaffold,”. H. H. Ahn, K. S. Kim, J. H. Lee et al.,. 7, 2009, Tissue Engineering Part A, Vol. 15, pp. 1821-1832.
10. “The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells,” ,. A.J.Friedenstein, R.K.Chailakhjan,andK.S.Lalykina,. 4, 1970, Cell and Tissue Kinetics, Vol. 3, pp. 393-403.
11. “Multilineage potential of adult human mesenchymal stem cells,” . M.F.Pittenger, A.M. Mackay,S.C.Becketal.,. 5411, 1999, Science, Vol. 284, pp. 143-147.
12. “Clarification of the nomenclature for MSC: the International Society for Cellular Therapy position statement,” . E. M. Horwitz, K. le Blanc, M. Dominici et al.,. 5, 2005, Cytotherapy, Vol. 7, pp. 393-395.
13. “Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement,”. M. Dominici, K. le Blanc, I. Mueller et al.,. 4, 2006, Cytotherapy, Vol. 8, pp. 315-317.
14. “Bone marrow stromal cells (BMSCs) in bone engineering: limitations and recent advances,”. A. R. Derubeis and R. Cancedda. 1, 2004, Annals of Biomedical Engineering, Vol. 32, pp. 160-165.
15. “Bone marrow stromal cells generate muscle cells and repair muscle degeneration,”. M. Dezawa, H. Ishikawa, Y. Itokazu et al.,. 5732, 2005, Science, Vol. 309, pp. 314-317.
16. “Age-related decline in the osteogenic potential of human bone marrow cells cultured in three-dimensional collagen sponges,”. S. M. Mueller and J. Glowacki. 4, 2001, Journal of Cellular Biochemistry, Vol. 82, pp. 583-590.
17. “Alveolar bone marrow as a cell source for regenerative medicine: differences between alveolar and iliac bone marrow stromal cells,”. T. Matsubara, K. Suardita, M. Ishii et al.,. 3, 2005, Journal of Bone and Mineral Research, Vol. 20, pp. 399-409.
18. “Membranous vs endochondral bone autografts: implications for craniofacial reconstruction,”. J.E.Zins and L.A.Whitaker. 1979, Surgical Forum, Vol. 30, pp. 521-523.
19. “Calvarial versus iliac crest for autologous bone graft material for a sinus lift procedure: a histomorphometric study,". R. Crespi, R. Vinci, P. Cappare, E. Gherlone, and G. E. Romanos,. 4, 2007. , The International Journal of Oral & Maxillofacial Implants, Vol. 22, pp. 527-532.
20. “Early secondary bone grafting of alveolar cleft defects. A comparison between chin and rib grafts,”. W. A. Borstlap, K. L. W. M. Heidbuchel, H. P. M. Freihofer, and A. M. Kuijpers-Jagtman,. 5, 1990, Journal of Cranio-Maxillofacial Surgery, Vol. 18, pp. 201-205.
21. “Regenerative periodontal therapy,”. D. W. Kao and J. P. Fiorellini. 2012, Frontiers of Oral Biology, Vol. 15, pp. 149-159.
22. “The osteogenic capacity in vitro of periosteum and endosteum isolated from the limb skeleton of fowl embryos and young chicks,”. H.B.Fell. 1932, Journal of Anatomy, Vol. 66, pp. 157-180.
23. “Human periosteum is a source of cells for orthopaedic tissue engineering: a pilot study,”. M. D. Ball, I. C. Bonzani, M. J. Bovis, A. Williams, and

M. M. Stevens. 11, 2011, Clinical Orthopaedics and Related Research, Vol. 469, pp. 3085-3093.

24. “A comparative qualitative histological analysis of tissue-engineered bone using bone marrow mesenchymal stem cells, alveolar bone cells, and periosteal cells,”. S. J. Zhu, B. H. Choi, J. Y. Huh, J. H. Jung, B. Y. Kim, and S. H. Lee,. 2, 2006, Oral Surgery,Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics, Vol. 101, pp. 164-169.
25. “Contributions of intercalated duct cells to the normal parenchyma of submandibular glands of adult rats,”. Y.G.Man, W.D.Ball, L.Marchetti and A.R.Hand. 2, 2001, The Anatomical Record, Vol. 263, pp. 202-214.
26. “Glandular tissue from human pancreas and salivary gland yields similar stem cell populations,”. E. Gorjup, S. Danner, N. Rotter et al.,. 7, 2009, European Journal of Cell Biology, Vol. 88, pp. 409-421.
27. “Concise review: adipose-derived stem cells as a novel tool for future regenerative medicine,”. H. Mizuno, M. Tobita, and A. C. Uysal,. 5, 2012, Stem Cells, Vol. 30, pp. 804-810.
28. “Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue,”. S. Kern, H. Eichler, J. Stoeve, H. Kluter, and K. Bieback,. 5, 2006, Stem Cells, Vol. 24, pp. 1294-1301.
29. “Novel maxillary reconstruction with ectopic bone formation by GMP adipose stem cells,”. K. Mesimäki, B. Lindroos,J. Törnwallet al.,. 3, 2009, International Journal of Oral and Maxillofacial Surgery, Vol. 38, pp. 201-209.
30. Autologous Stem cells (adipose) and fibrin glue used to treat widespread traumatic calvarial defects: Case report. Lendeckel S, Jodicke A, Christophis P, et al:. 2004, J Craniomaxillofac Surg , Vol. 32, p. 370.
31. Bone marrow derived mesenchymal stem cells for regenerative medicine in craniofacial region. M Miura, Y Miura,W Sonomaya T Yamaza,S Granthos, S Shi. 2006, Oral diseases, Vol. 12, pp. 514-522.
32. Toward a new era in prosthodontic medicine. K., Koyano. 2012, J Prosthodont Res, Vol. 56, pp. 1-2.
33. Stem Cells In Dentistry- A Review. Chandra Mouli PE, Kumar S Manoj, Senthil B, Parthiban S, Priya R, Subha R. 4, 2012, J. Pharm. Sci. & Res., Vol. 7, pp. 1872-1876.
34. Tooth Regeneration: Implications For The Use Of Bioengineered Organs In Irst-Wave Organ Replacement. . Nakahara T, Ide Y. 2007, Hum Cell, Vol. 20, pp. 63-70.
35. Bioengineered Teeth From Cultured Rat Tooth Bud Cells. Duailibi Mt, Duailibi Se, Young Cs, Bartlett Jd, Vacanti Jp, Yelick Pc. 2004, J Dent Res, Vol. 83, pp. 523-528.
36. Histological And Immunohistochemical Studies . Honda Mj, Sumita Y, Kagami H, Ueda M.
37. Role of Stem Cells in Prosthodontics Rehabilitation . Ashika Rachael Samuel, Dr. Revathy Gounder. 4, 2017, J. Pharm. Sci. & Res. , Vol. 9, pp. 497-500.
38. Tissue engineering. Langer R, Vacanti JP. 5110, 1993, Science, Vol. 260, pp. 920-926.
39. Clinical and histomorphometric evaluation of extraction sockets treated with an autologous bone marrow graft. Pelegrine AA, da Costa CE, Correa ME, Marques JF Jr. 5, 2010, Clin Oral Implants Res., Vol. 21, pp. 535-542.
40. JS., Khurana.Bone pathology. 2nd ed. Philadephia, PA : Springer, 2009.

41. Bone regeneration: current concepts and future directions. . Dimitriou R, Jones E, McGonagle D, Giannoudis PV. 2011, BMC Med, Vol. 9, p. 66.
42. Dental pulp stem cells: a promising tool for bone regeneration. Graziano A, d'Aquino R, Laino G, Papaccio G. 1, 2008, Stem Cell Rev., Vol. 4, pp. 21-26.
43. Cardiac differentiation is driven by NKX2.5 and GATA4 nuclear translocation in tissue specific mesenchymal stem cells. . Armiñán A, Gandía C, Bartual M, et al. 6, 2009, Stem Cells Dev., Vol. 18, pp. 907-918.
44. Physiological Reviews, pp. 635-678.