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Review Article

Current Status and Future Prospects of Stem Cells in Dentistry-A Review

Anindita Kundoo and Vidya Dodwad*

Department of Periodontology, Bharati Vidyapeeth (Deemed to be) University, Dental College and Hospital, Pune, India

***Corresponding Author:** Vidya Dodwad; Department of Periodontology, Bharati Vidyapeeth (Deemed to be) University, Dental College and Hospital, Pune, India.

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Abstract

Stem cells are able to multiply and create cell lines that can develop into different cell lineages. Depending on their source, stem cells can either be adult or embryonic stem cells and can be taken from a variety of locations. Due to their capacity for self-renewal, they are employed to treat significant flaws brought about by diseases, injuries, or surgical procedures. They are nevertheless constrained by moral and ethical issues as well as the challenges of isolation, culturing, and implantation. The regeneration of orofacial structures uses dental stem cells, which still have the ability to differentiate into neurogenic, adipogenic, and odontogenic components. Prior to stem cell implantation, scaffolding that has been treated with bone morphogenic proteins and growth factors is crucial. The introduction of 3D scaffolding with biomatrix into the therapeutic setting will aid in the regeneration of tissues. The pulp, apical papilla, dental follicle, periodontal ligament, deciduous teeth, and mucosa in the maxillofacial region are possible sources of stem cells. They can be applied to the bioengineering of periodontal tissues, soft tissues, bone, and the temporomandibular joint. To fully use the enormous potential of stem cell therapy and ensure future treatment outcomes, a multispecialty strategy integrating cell biologists, pharmacologists, and bioengineers is necessary. As a result, this review provides a narrative of the development of stem cell use over time and clarifies the bioethical stance of today's various religions in relation to social ones with regard to the study and application of embryonic and adult stem cells.

Keywords: Periodontal Regeneration; Stem Cell; Stem Cell Therapy

Introduction

Stem cells are undifferentiated cells that are unique to a particular type of cell or tissue and have not yet developed structures or proteins. Thus, they serve as the building blocks for each cell, tissue, and organ in the human body and contribute to the development of all adult cells. A stem cell can ensure both self-renewal and differentiation.

A group of undifferentiated cells, stem cells are distinguished by

- Their capacity for rapid proliferation and tissue differentiation.
- Typically develop from a solitary cell.

Medical researchers employ stem cells to treat a variety of illnesses, including hematological (bone marrow transplantation), ophthalmological (age-related macular degeneration), endocrinological (diabetes), neurological, genetically modified fat cells, and medication development (Figure 1).

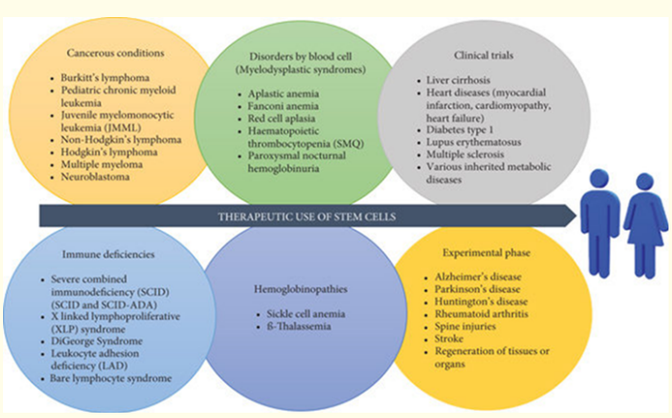

Figure 1: A list of the ailments that have been treated, along with any medicines, clinical research, or stem cell studies.

Three stem cell-based treatments have been taken into consideration

- The transplantation of already differentiated cells, such as insulin-producing cells for the treatment of diabetes, derived from embryonic or somatic stem cells as well as the patient's own stem cells.
- Enhancing or triggering the processes of self-repair by stimulating a person's own endogenous stem cells (by giving them growth hormones).
- Giving stem cells directly to the patient, causing them to colonize the targeted body region and continue to differentiate into the desired cell type. (Figure 2) [1].

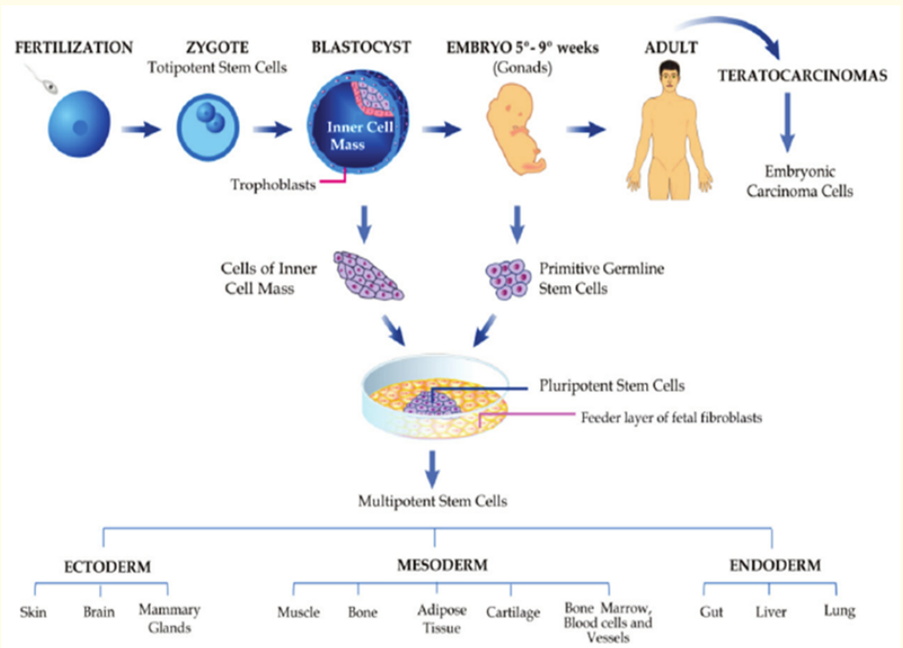

Figure 2: The genesis, collecting process, and plasticity of stem cells: pluripotent embryonic stem cells are produced as an internal cell mass inside a blastocyst following fertilisation of the natural egg or *in vitro*.

Stem cells in the history

The term "stem cell" was first used to refer to cells committed to generating the germline by two zoologists Theodor Heinrich Boveri (1862-1915) and Valentin Häcker (1864-1927). Boveri, a comparative anatomist, also revealed that some cells may regenerate with subsequent functional differentiation during his cytology and genetic research.

Ernest Armstrong McCulloch (1926-2011), a biophysicist, and James Edgar till (1931), a cell biologist, were the forerunners in the quantitative clonal approach to studying stem cells in the early 1960s. They noticed nodules at the level of the spleen after introducing the cells into the bone marrow of the previously irradiated laboratory mice. Just one progenitor cell was the source of each of these cell colonies [2]. They later discovered that cells may functionally self-renew by forming these colonies, working with the molecular biologist Lou Siminovitch [3].

Towards the evolution of the 21st century era

In 1981, the two biologists Sir Martin John Evans (1941) and Matthew Kaufman (1942-2013) created mouse embryonic stem cells in a lab setting for the first time. The first umbilical cord blood stem cell transplant occurred in 1988 on a kid suffering from Fanconi anemia. Since then, more than 6,000 transplants involving a relative or another stem cell recipient have been carried out, provided there is compatibility (heterologous transplant) [4].

James Alexander Thomson, a biologist, discovered human embryonic stem cells through his research in 1998. In 2007 he also discovered a method for creating human-induced pluripotent stem cells (iPS), which involves transforming skin cells into cells that closely resemble human embryonic stem cells [5]. The first study on umbilical cord stem cell transplantation in adults was released in 2001, and Gesine Koegler and colleagues discovered that pluripotent stem cells can also be detected in umbilical cord blood in addition to hematopoietic stem cells in 2004 [6].

Finally, in 2012 Shinya Yamanaka and John Gurdon shared the Nobel Prize in Physiology or Medicine for their work showing that mature cells may be transformed into stem cells and then modified to become pluripotent.

Classification of stem cells

Stem cells are classified according to their origin.

- **Embryonic stem cells (ESCs):** They are populations of pluripotent cells that can create the primitive ectoderm during development. They are extracted from the interior cell mass of the blastocyst. Dental-derived stem cells (d-DSCs), a special subset of stem cells, have the capacity to develop *in vitro* into layer-like tissues of the mesoderm, endoderm, and ectoderm, including those of adipocytes and neural cells [7].
- **Amniotic epithelial cells (AECs):** They arise from the human placenta's amniotic membrane. They do not express telomerase, or develop teratomas *in vivo* after transplantation, and express multivalent ESC markers such as oct-4, Nanog, and alkaline phosphatase. They can differ *in vitro* from ectoderm, which is found in nerve cells, mesoderm, and endoderm (such as pancreatic endocrine cells and hepatocytes) [8].
- **Fetal stem cells (FSCs):** Mostly isolated from tissue-specific embryonic stem cells or from organs of embryonic cadavers up to 12 weeks of pregnancy. They, therefore, have the therapeutic benefit over ESCs in that they do not result in teratomas *in vivo*, allowing for transplantation without rejection reactions [9].
- **The umbilical cord epithelium (UCE):** It is a source of pluripotent stem cells and is derived from the epithelial amniotic membrane. They can develop into a variety of progenitor cells with distinct functions.
- **Induced pluripotent stem cells:** Despite sharing the same ability to divide as embryonic stem cells, induced pluripotent stem cells are not subject to ethical restrictions since they are created by using vectors to transfer genes from embryonic stem cells into a donor cell. Here, patient-specific embryonic stem cells derived from autologous somatic cells open the door to treatments that are individually customized to the patient's needs [10].
- **Adult somatic stem cells:** It is a product of ontogenesis [11]. Almost all mammalian organs and tissues contain them in specific locations, including the bone marrow, heart, kidneys, brain, skin, eyes, gastrointestinal system, liver, pancreas, lungs, breasts, prostate, testicles, and ovaries.
- **Mesenchymal stem cells:** Adult stem cells known as mesenchymal stem cells (MSC) are also known as mesenchymal stromal cells. They exist in adipose tissue, skin, mouth and maxillofacial tissues, and bone marrow and are multipotent [12]. They are autologous and have no chance of being rejected.
- **Adipose-derived stem cells:** These cells are isolated after being removed through liposuction, lipectomy, or lipo-aspiration [12]. They are plentiful, easily accessible, multipotent, and have a broad lineage following differentiation.
- **Bone marrow-derived mesenchymal stem cells:** Because of their multipotency, they are a subset of adult stem cells that are plentiful in the bone marrow and frequently employed in clinical settings. One of the most popular places to obtain stem cells for regenerative medicine is from iliac crest bone marrow. They can also develop from the synovial membrane or periosteum to generate cancellous bone [10].
- **Dental tissue-derived stem cells:** One of the easiest to obtain stem cell types are those generated from dental tissue, which may be isolated from pulp, apical papilla, periodontal ligament, gingiva, permanent or growing teeth, tooth follicles, removed or exfoliated teeth, and pulpal tissues. During development, they arise from the neural crest and mesenchymal cells. The mesenchymal cell lines give rise to dentin through odontoblasts, whereas the epithelial cell lines form enamel through ameloblasts [10].
- **Dental pulp-derived stem cells (DPSC):** These are derived from the pulp of permanent teeth and are the most prevalent source of dental tissue-derived stem cells. They exhibit STRO-1, CD 44, and CD 146 MSC markers and are multipotent [13].
- **Stem cells from human exfoliated deciduous teeth (SHED):** They are more proliferative than DPSC and originate from exfoliated teeth. They are utilized for tissue regeneration involving orofacial bone structures after differentiating into neurogenic, adipogenic, and odontogenic components. They contain glial and neuronal markers including Nestin and III Tubulin as well as MSC markers like STRO-1 and CD 146.
- **Periodontal ligament stem cells (PDLSC):** They are derived from human third molars separated periodontal ligaments and contain progenitors for the self-renewal of oral tissues like cementum and bone [14]. Seo., *et al*. isolated them initially and discovered their multipotency.
- **Dental follicle stem cells (DFSC):** They are pluripotent and derived from the follicle that surrounds human third molars. They consist of ectomesenchyme and are marked by the presence of Notch1, STRO-1, and Nestin. *In vitro*, they can differentiate into osteoblasts, adipocytes, and neuroblasts, and *in vivo*, they can differentiate into periodontal ligament [14].
- **Stem Cells from the Apical Part of Papilla (SCAP):** They have significant proliferative, migrating, and regeneration capacities and are derived from the apical region of a developing tooth [13]. They contain cells that resemble fibroblasts and odontoblasts and have MSC markers such as STRO-1, CD 24, CD 44, and CD 146.
- **Periosteum-derived stem cells:** The multipotent, odontogenic, chondrogenic, adipogenic, and myogenic potential of human periosteum-derived stem cells is demonstrated.
- **Salivary gland-derived stem cells:** *In vitro*, salivary gland-derived cells can develop into duct and acinar cells yet still have the ability to make amylase and mucin.

The division of stem cells into embryonic and somatic stem cells based on their origin and degree of developmental plasticity provides an easier way to distinguish between them (Table 1).

Stem cell use in medicine

One of the most significant developments in medicine could come from stem cells. Improper differentiation or cell division can lead to a number of serious medical disorders, including cancer or birth abnormalities. There are currently a number of stem cell

Totipotent/omnipotent	Pluripotent	Multipotent	Oligopotent	Unipotent
When an embryo is developing up until the first blastomeres (i.e., three to four days after fertilization), these cells have the least differentiated cell shape. Can create a new organism if given enough maternal assistance. Produces all bodily tissues, germline tissues, including extraembryonic tissues.	The ectoderm, endoderm, and mesoderm can differentiate into distinct cell types. They generate all cell types for all tissues and organs. The most well-known pluripotent stem cells are embryonic stem cells.	They can differentiate into distinct cell kinds, such as several types of blood cell-like lymphocytes, monocytes, neutrophils, bone cells, or another non-blood cell type. The best mesenchymal cells (MSCs) can be found in bone marrow, adipose tissue, Wharton's jelly in umbilical cord blood, dental tissues, and peripheral blood.	These stem cells (hematopoietic stem cells and bronchioalveolar stem cells) can self-renew and develop into two or more cells that belong to a certain type of tissue.	They have the ability to self-renew and differentiate into just one kind of cell, creating just one cell line (such as the muscle stem cells).

Table 1: The division of stem cells into embryonic and somatic stem cells based on their origin and degree of developmental plasticity provides an easier way to distinguish between them.

therapies that can be used to treat conditions like spinal cord injury, heart failure, retinal and macular degeneration, tendon ruptures, and type 1 diabetes [15].

- **Haematopoietic stem cell transplantation:** Because they are by far the most extensively studied tissue-specific stem cells, hematopoietic stem cells are significant. The most widely used stem cell therapy now is multipotent hematopoietic stem cell (HSC) transplantation. Target cells are often derived from bone marrow, peripheral blood, or umbilical cord blood [16]. Problems with the hematopoietic system, which includes illnesses like leukemia and anemia, are resolved through HSC transplantation.
- **Stem cells as an alternative for arthroplasty:** The ability of the tendons to regenerate is where the problems begin. After an injury, tendons do not functionally regenerate; instead, they merely recover by creating scar tissues that do not function like healthy tissues. Hypervascularization, calcific material deposition, discomfort, or edema are the causes of the inadequate healing response. Due to the articular cartilage's limited capacity for regeneration and its avascular nature, osteoarthritis is a prevalent condition. Although arthroplasty is already a standard technique for treating osteoarthritis, it is not recommended for younger patients since they may outlive the implant and require many surgical procedures in the future. In these circumstances, stem cell therapy can aid by delaying the onset of osteoarthritis [17]. However, these techniques need more development, and long-term hyaline cartilage maintenance research is needed.
- **Cell-based therapies:** Stem cells appear to be the ideal solution for the problem of an excess demand for transplantable tissues and organs compared to the potential supply. Macular degeneration, strokes, osteoarthritis, neurological illnesses, and diabetes are the most frequent conditions that benefit from such treatment. An autoimmune response in people with type 1 diabetes causes the destruction of insulin-producing cells in the pancreas. Inducing stem cells to develop into insulin-producing cells can be used as a treatment alternative to transplantation [18].
- **Fertility diseases:** In an experiment using mice, Katsuhiko Hayashi., *et al*. [19] demonstrated in 2011 that it is possible to create sperm from iPSCs. They were successful in giving infertile mice healthy, fruitful offspring. The primary target population for testicular tissue cryopreservation and auto transplantation is young individuals who are at risk of losing their spermatogonial stem cells, most commonly cancer patients.
- **Dental perspectives of stem cell therapy**
- For regenerative medicine, teeth are a highly challenging material. They can be tough to replicate because of their complex structural makeup and function in areas like articulation, mastication, or aesthetics.
- The primary cause of tooth loss is periodontitis, an inflamed, infected oral condition that damages periodontal tissues. Dentists have been successful in reducing periodontal inflammation with standard treatments, but they have failed to repair the periodontium that has been harmed. The goal of periodontal regenerative therapy is to regenerate periodontal supporting tissues, such as alveolar bone, gingiva, periodontal ligaments, and cementum, in order to restore the physiological function of teeth.
- **Pulp regeneration in endodontics:** Odontoblasts can develop from dental pulp stem cells. There are several techniques that can regenerate pulp. Ex vivo testing is the first way. Before being inserted into the root canal, appropriate stem cells are produced on a scaffold [20]. The second technique is an *in vivo* one. This approach focuses on infusing stem cells into clean, open apical channels of the roots. Techniques for inserting stem cells into the root channel fall under the categories of soft scaffolding or using stem cells for apexogenesis or apexification.
- **Acquiring non-dental tissue cells by dental stem cell differentiation:** It was revealed in 2013 that it is possible to produce teeth from stem cells collected extra orally, such as from urine [21]. However, because it is non-invasive, somewhat in-

expensive, and allows for the use of somatic cells rather than embryonic cells, it seems to be a very promising technology. More importantly, stem cells made from urine did not develop into tumors, and using autologous cells lessens the likelihood of rejection.

- **Use of graphene in stem cell therapy:** In order to mediate stem cell development and differentiation, graphene and its derivatives have become substantially more frequently used as scaffold materials in recent years. Cells adhere properly to graphene and it is biocompatible with them. Additionally, it was found to be effective at promoting stem cell differentiation or proliferation [22].
- **Therapeutic potential of extracellular vesicle-based therapies:** Virtually all cells in an organism, including stem cells, have the ability to release extracellular vesicles, which are used to communicate between cells by carrying their mRNAs, lipids, and proteins. As demonstrated by Oh., *et al*., stem cells and the exosomes of their paracrine factor can be used as possible therapies in the management of skin aging.

Stem cells in periodontal tissues

The discovery and manipulation of stem cells have significantly advanced regenerative medicine and aided in the development of tissue engineering-based therapeutic medicines. The introduction of ex vivo enlarged progenitor populations or the mobilization of endogenous progenitor cells capable of proliferating and differentiating into the desired tissues is a crucial prerequisite for a tissue engineering technique.

Human dental stem cells obtained from dental pulp tissue of extracted third-molar teeth were compared to bone marrow mesenchymal stem cells for the first time [23]. Periodontal ligament stem cells have been demonstrated to give rise to adherent clonogenic clusters that resemble fibroblasts and can grow *in vitro* into adipocytes, osteoblast-like cells, and cementoblast-like cells, as well as cementum-like and periodontal ligament-like tissues. They are similar to dental pulp stem cells and bone marrow mesenchymal stem cells.

Stem Cells in Periodontal Regeneration

The primary goal of periodontal therapy is to restore damaged tissues to their native design and function. Under certain situations, any cell type with a high proliferative capacity and a multipotent character, particularly stem cells, can be employed to replenish damaged cells [24].

The discovery and therapeutic application of stem cells have provided a novel approach to periodontal regeneration. Current stem cell-based therapies in periodontics focus primarily on the transfer of culture-expanded cells to the periodontal defect to improve wound healing, and several elegant studies have proven favorable effects utilizing either intraoral or extraoral stem cells [25].

An early phase investigation also suggested that in the clinic, transplantation of enlarged autologous fibroblasts could be effective in treating papillary insufficiency after a papilla priming surgery. However, there are certain disadvantages to injecting cell suspensions, such as insufficient cell supply following an injection, poor engraftment, dissemination of injected cells to neighbouring healthy tissue, and loss of cell fate control.

To strengthen the stability of the cells within the defect, stem cell sheets are often implanted into the injured periodontium along with bone substitutes such as hydroxyapatite/tricalcium phosphate, bovine bone, synthetic hydrogels, and their composites.

Tissue engineering techniques have been used to repair injured periodontium. Following transplantation, autologous bone marrow mesenchymal and adipose-derived stem cells repair alveolar bone and periodontal ligament-like structures [26]. Human adult dermal fibroblasts reprogrammed to pluripotency and the generation of enough cells for regenerative periodontal therapy could be an ideal source [27].

Although human case studies and randomized clinical trials have shown that stem cells are feasible and safe, more well-designed human research should be conducted to investigate the therapeutic benefits of stem cells on periodontal regeneration.

The negative aspect of mesenchymal stem cell biology

Consideration should be given to all potential negative effects while employing stem cell-based therapy. The danger of tumor development following stem cell transplantation is well-covered in the literature. Because of their proliferating for a long time, high vitality, and resistance to apoptosis, stem cells can be likened to tumor cells in certain ways [28].

The age of the donor, the host tissue, growth regulators produced by the recipient tissue, and mechanisms that regulate the behavior of the MSCs at the target location are only a few of the factors that may have an impact on the possibility of cancer following MSC transplantation. Additionally, long-term *in vitro* cultivation of MSCs and modifications might result in chromosomal aberrations and genetic instability [29]. A reaction in the form of a spontaneous tumor transformation might be caused by several cumulative circumstances. Patients who get stem cell transplants frequently have prolonged chemotherapy or radiation, which impairs the function of their immune systems and may increase the risk of tumorigenesis.

Numerous studies also show that MSC engraftment is minimal because of the MSCs' transient vitality after injection [30]. Additionally, it has been shown that following transplantation, a large number of MSCs become stuck in the lungs, reducing the number of cells that inhabit the target region.

Cell transplantation is well tolerated by the recipient organism thanks to the MSCs' low immunogenicity, which lowers the risk of transplant rejection. Differentiated MSCs, however, could only have weak or no therapeutic benefits.

Future perspectives for stem cells in periodontal regeneration

To overcome some of the limitations of current cell treatment and based on the promising outcomes of animal and human stem cell research, researchers have proposed a new step forward: exogenous human MSCs.

In order to overcome the limitations of using stem cells in elderly persons, whose regenerative capacity is restricted, the use of exogenous or allogenic stem cells has been recommended. Exogenous human MSCs have already been evaluated in cases of biologic resistant luminal Crohn's disease with fistula formation, cranial abnormalities, cardiac regeneration, and individuals with aging frailty. Exogenous MSC infusion seems to be very well tolerated, with relatively minor and short-term side effects and, in many cases, no adverse reaction at all. Thus, exogenous MSCs appear to be a viable method for periodontal and regenerative therapy in general. Pluripotent stem cells derived from somatic cells (iPSCs) are one possible stem cell lineage to investigate for periodontal regeneration. They have the ability to develop into a wide range of various cells and tissues. Scientists have been very interested in iPSC-derived mesenchymal cells and osteoprogenitor cells in dentistry research. These cells must go through a trans-differentiation process before they may be utilized. In this procedure, adult somatic cells undergo a metamorphosis to a distinct somatic cell without going through a pluripotent or progenitor phase. This technique is also known as lineage switching or lineage conversion. Epigenetic changes, which directly reprogramme non-osteoblast cells into functional osteoblasts, have begun to be explored as a new treatment option for alveolar bone regeneration as a result of this process.

Studies related to stem cells.

- Narang S. and Sehgal N. (2012). conducted a study to examine the important ongoing stem cell research in regenerative dentistry. It was established that stem cells have the capacity to differentiate into specialized dentin, bone, and brain cells and develop quickly. They concluded that these neuronal cells can be utilized in dental treatments and can give patients greater treatment alternatives. The use of stem cell-based treatments may lead to new developments in the treatment of damaged teeth, the promotion of bone regrowth, and the management of neurological injury.

- Zhu W and Liang M (2014) conducted a review study to discuss the standard criteria for the culture and identification of PDLSCs and a review of the most recent results about PDLSCs are covered in the present. The review concludes by recommending that the safety of PDLSC transplantation be carefully considered. Given the lack of research on long-term transplanted PDLSCs, they concluded that ongoing recipient monitoring is essential. In an ovine periodontal deficiency, autologous PDLSCs that had been BrdU-labeled were shown to be identifiable eight weeks after transplantation, according to research by Gronthos' team. Kim and colleagues' findings from another experiment, however, were different: Two weeks following the implantation of allogeneic teeth, no donor cells were found in the periodontal ligament gap because donor cells from lacZ transgenic ROSA26 mice did not exhibit the same blue color as the host cells after X-gal staining.

- Bansal R and Jain A (2015) conducted a review article in which they evaluated the ever-expanding literature on dental stem cells, regenerative dentistry, dental stem cells, banking dental stem cells, and stem cells from human exfoliated deciduous teeth, which was archived in Medline. This article's goal was to cover the history of stem cells, various dental stem cells, their methods for separation, collection, and storage, as well as the state of dental and medical applications today. They concluded that while dental stem cells have a variety of uses, they also have certain restrictions. Long-term clinical investigations are still needed to assess the oncogenic potential of these cells.
- Charitos I.A, Ballini A, Cantore S, Boccellino M., *et al.* (2021) conducted a review study in which they sought to provide a narrative of the development of stem cells uses to this point as well as to clarify the current bioethical stance of different faiths in relation to societal ones regarding the study and usage of embryonic and adult ones. They are therefore contrasted to the fundamental theological beliefs in terms of their biological hypostasis regarding the ideas of "conception" and "fertilization," as well as their development and therapeutic application. They concluded that one of the most significant scientific advances in recent years is the use of stem cells to cure illness. It is difficult to separate foetal and adult stem cells. Since umbilical cord blood stem cells are extracted from placental blood after delivery when the umbilical cord is cut, isolating them is less difficult. Adult stem cells may now be reprogrammed to become pluripotent again. In this branch of science, this is a significant development.

Conclusion

Stem cell therapy is becoming a major game changer for medicine after decades of research. The potential of stem cells is expanding with every experiment, but there are still numerous challenges to be solved. Regardless, stem cells have a significant impact on transplantology and regenerative medicine. The coordinated interaction of stem cells, biomaterials, and the host immune system results in the complicated healing cascade known as periodontal tissue regeneration. Regardless of the cell source or method used to harvest the cells, stem cell therapies and tissue engineering in the field of periodontics are still in their infancy. Despite some encouraging clinical observations, there is yet no ideal cell regeneration paradigm that is ready for clinical application.

One of the concerns that needs to be carefully considered is immune rejection, although using autologous cells can solve this problem. Finally, compared to embryonic stem cells, progenitor cells are relatively less potent. Since artificial teeth cannot be used as a substitute, much research and development is needed to enhance dental regenerative treatments. To make teeth completely functioning, scientists still need to figure out how to increase their blood and nerve supply. Despite not being readily available right now, these methods could someday be employed as biological substitutes for the synthetic materials that are now in use.

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