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# Use of stem cells in the regeneration of dental tissues: narrative review

Faculdade de Ciências da Saúde

Universidade Fernando Pessoa

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Thesis presented to the Faculty of Health Sciences of Fernando Pessoa University as part of the requirements for the obtention of Dental Medicine master's degree

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**ABSTRACT**

**Introduction:** Stem cells have come to light as a promising field of research in various medical areas, including dentistry. Their unique characteristics, such as self-renewal and differentiation abilities, make them a valuable resource for regenerative medicine and tissue engineering. In the recent years, there has been a growing interest in exploring the potential applications of stem cells in odontology.

**Objective:** This narrative review aims to examine the characteristics of stem cells relevant to dentistry, summarize the latest research advancements, discuss their current applications, assess the state of research, and explore the potential future uses of stem cells in odontology.

**Methodology:** The narrative review conducted for this study was based on Pubmed, ScienceDirect, Scielo, NCBI and ResearchGate, in English and Portuguese. 38 articles were used in the writing of this work.

**Conclusion:** Stem cells show promise in dentistry, reproducing various cells and creating complex tissues. Despite challenges, they offer potential solutions for dental limitations and personalized treatments. They already have some practical applications in other fields of medicine. There are several ongoing clinical trials and research aimed at bringing new applications in stem cell therapies.

**Keywords:** Stem cells, dentistry, periodontal ligament, tooth, dental pulp, tissue engineering, clinical applications.

**RESUMO**

**Introdução**: As células-tronco surgiram como um promissor campo de pesquisa em diversas áreas médicas, incluindo a medicina dentária. As suas características únicas, como a capacidade de auto-renovação e diferenciação, fazem delas um recurso valioso para a medicina regenerativa e a engenharia de tecidos. Nos últimos anos, tem havido um crescente interesse na exploração das potenciais aplicações das células-tronco em medicina dentária.

**Objetivo:** Esta revisão narrativa visa examinar as características das células-tronco relevantes para a medicina dentária, resumir os últimos avanços da pesquisa, discutir suas aplicações atuais, avaliar o estado da pesquisa e explorar os possíveis usos futuros das células-tronco em medicina dentária.

**Metodologia:** A revisão narrativa realizada para este estudo foi baseada na pesquisa da Pubmed,ScienceDirect, Scielo, NCBI e ResearchGate, em inglês e português. 38 artigos foram utilizados na redação deste trabalho.

**Conclusão:** As células-tronco são promissoras em medicina dentária, reproduzindo várias células e criando tecidos complexos. Apesar dos desafios, elas oferecem potenciais soluções para as limitações dentárias e tratamentos personalizados. Elas já têm algumas aplicações práticas noutros campos da medicina. Existem vários ensaios clínicos e pesquisas em decurso que visam trazer novas aplicações em terapias com células-tronco.

**Palavras-chave:** Células-tronco, medicina dentária, ligamento periodontal, dente, polpa dentária, engenharia de tecidos.

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**INDEX**

**INDEX OF ABBREVIATIONS**

ASC – Adult Stem Cell

BFPSC – Bone fat pad stem cell

BM-MSC – Bone marrow derived mesenchymal stem cells

DPSC – Dental pulp stem cell

DSC – Dental stem cell

EMC – Embryonic Stem Cell

FDBA – Freeze-dried bone allograft

iPSC – Induced pluripotent stem cell

MSC – Mesenchymal Stem Cell

PDL – Periodontal ligament

PDLSC – Periodontal ligament-derived stem cell

SC – Stem Cell

## I. INTRODUCTION

Regenerative dentistry is an innovative field of dentistry that aims to restore and repair damaged or lost dental tissues. Traditional dental treatments such as fillings, root canals, and tooth replacements have limitations in terms of durability, aesthetics, and function. The emergence of stem cell research and tissue engineering techniques has opened up new possibilities for natural tooth regeneration.

In this paper, we will discuss the diverse categories of stem cells and their characteristics, alongside their prospective applications and utilities in regenerative dentistry. We will specifically focus on the regeneration of periodontal tissues, dental pulp, craniofacial bone defects and entire teeth.

Today, conventional treatments are limited in their effectiveness and longevity. With the advancement of stem cell research and tissue engineering, we are now able to explore new possibilities for natural tooth regeneration. In the future, stem cells have the potential to change the way we approach and treat the loss of dental tissues.

### 1. Material and Methods

This work is a narrative review, which intends to systematize information about the use of stem cells in the regeneration of dental tissues.
Articles obtained from online databases such as Pubmed, ScienceDirect, Scielo, NCBI and ResearchGate were used. The terms used for the research were stem cells, dentistry, dentistry, periodontal ligament, tooth, dental pulp, tissue engineering, stem cell therapy. Whenever necessary, Boolean operators were used.
To reduce the number of articles and also to make the search more specific, articles were selected that more specified the objectives of the theme and filters were applied, such as the language of the articles, which in this case was English and Portuguese, the text of the article available in full and published in the last 13 years (2011-2023).

## II. DEVELOPMENT

### 1. Stem cells

### 1.1. Definition

Stem cells (SCs) are a group of cells distinguished by their exceptional ability to undergo extensive proliferation, transform into various cell types, and play a crucial role in the regeneration and repair of tissues and organs (Kolios & Moodley, 2013).

SCs possess three key features: self-renewal, clonality, and potency:

• Self-renewal is the ability to undergo multiple cell divisions and generate identical daughter cells without differentiating (Kolios & Moodley, 2013).

• Clonality refers to their ability to form identical cells from a single cell (Kolios & Moodley, 2013).

• Potency describes the ability of SCs to differentiate into different cell types, such as neural, cardiac, muscular, and bone cells, among others (Kolios & Moodley, 2013).

SCs are undifferentiated cells found in all stages of life, from the embryonic state to adulthood, and their specific properties and characteristics vary among different types: hematopoietic stem cells for instance located in the bone marrow can differentiate into any of the blood cell types which makes them less potent than embryonic stem cells (ESCs) (Kolios & Moodley, 2013; Mosaddad *et al.*, 2022).

SCs have the potential to revolutionize the domain of reparative medicine, offering a new approach for treating various injuries and diseases that involve the loss or damage of specific tissues or organs. In dentistry, SC-based therapies have been explored for the regeneration of periodontal tissues, dental pulp, craniofacial bone defects, and entire teeth (Kolios & Moodley, 2013; Mosaddad *et al.*, 2022).

## 1.2. Types of stem cells and characteristics

### 1.2.1. Classification based on origin

The two primary sources of natural stem cells are: adult stem cells (ASCs) and embryonic stem cells.

**Adult Stem Cells**: ASCs, also known as somatic stem cells or postnatal stem cells, are a crucial component of tissue homeostasis and repair in adults. ASCs are present in various tissues and organs. They multiply and differentiate to maintain and repair the tissues. Through the years, multiple sources of ASC were located in specific areas of the maxillofacial region (Hiroshi *et al.*, 2012).

The word ASC is a broad term that encompasses all SCs found in specialized tissues, although there is no consensus for their exact definition or a definitive identification and isolation protocol. They can be further classified by potency into hematopoietic stem cells, neuronal stem cells, mesenchymal stem cells (MSCs), intestinal stem cells, epidermal stem cells, and multiple others, with even more that researchers have not found yet. MSCs are particularly interesting for researchers due to their presence in various tissues, and more specifically for dentistry (Prochazkova *et al.*, 2015; Ullah *et al.*, 2015).

The main criteria for MSCs today, according to the International Society for Stem Cell Research, is their plastic adherence in standard cultures, it is worth noting that while all MSCs are adherent, not all adherent cells are necessarily MSCs (Hiroshi *et al.*, 2012; Baghaei *et al.*, 2017).

Most ASCs, including MSCs, are considered either multipotent or unipotent, meaning that they can differentiate into any of the cells from a particular lineage (multipotent) or only a single lineage (unipotent). Despite the small number of ASCs present in the adult tissues, they are vital components involved into the maintenance of tissue homeostasis and repair. Thus, their identification and isolation have significant implications for regenerative medicine and tissue engineering (Hiroshi *et al.*, 2012; Sobhani *et al.*, 2017).

**Embryonic Stem Cells**: ESCs are one of the prime SCs that are derived from the inner cell mass early-stage pre-implantation embryo (blastocyst). These cells have unique properties that make them highly valuable for the purposes of tissue engineering and cell therapy. ESCs are pluripotent, which means that they are capable of dividing and then differentiating into any of the three embryonic layers: ectoderm, endoderm, mesoderm, they can eventually become specialized body cells or tissues, except for the extraembryonic cells such as the placenta. The derivation of ESCs from human embryos by James Thomson in 1998 has drawn significant attention to these cells. However, the use of ESCs has raised moral, religious and ethical concerns, as some individuals believe that "human life begins at the fertilization of an oocyte and sperm, and thus an embryo is a person with human rights". From this perspective, the removal of the inner cell mass of a blastocyte to derive ESCs is equivalent to killing, which has imposed several limitations on their use (Hiroshi *et al.*, 2012; Golchin *et al.*, 2021).

Induced pluripotent stem cells (iPSCs) on the other hand are another variety of SCs that were discovered by Dr. Shinya Yamanaka in 2006. These cells are artificially reprogrammed from adult skin fibroblasts, by introducing four genetic factors involved in the regulation of gene expression; Oct3/4, Sox2, Klf4, and c-Myc. The resulting cells have a similar potency to ESCs and are considered a promising alternative to ESCs, as they can be generated from patient-specific cells. The ability to produce iPSCs from somatic cells has opened doors to a new era of research and therapies, without the moral and ethical concerns that accompany the use of ESCs (Hiroshi *et al.*, 2012; Golchin *et al.*, 2021).

### 1.2.2. Major sources of mesenchymal stem cells

**Bone marrow derived MSCs** (BM-MSC): BM-MSCs are considered multipotent ASCs, mainly extracted from the iliac crest bone, these MSCs have an extensive arsenal of cell lineages making them highly desired for multiple purposes despite their major drawbacks:

- Highly invasive extraction procedure
- Cell potency highly dependent on the age of the donor

In comparison, BM-MSC harvested from orofacial structures can circumvent these aforementioned drawbacks by being easily accessible and less age-dependent, though their relatively scarce volume limits their usage (Polymeri *et al*., 2016; Mosaddad *et al*., 2022).

**Gingival MSCs**: Human gingival MSCs in comparison to other sources of MSCs from the oral cavity have the clear advantages due to their easy accessibility and rapid wound healing of the donor area. It is however unknown whether GMSCs have the same growth ability and safety when compared with other intra-oral MSCs such as periodontal ligament-derived mesenchymal cells (PDLSC), they do however display a higher proliferation rate in suboptimal conditions on top of their availability (Santamaria *et al*., 2017).

**Dental follicle SCs**: Dental follicle SCs were first identified as mesenchymal stem/progenitor cells in the first molars of the neonatal rat and they have been shown to be able to differentiate into osteoblasts, cementoblasts, adipocytes and neural cells. These cells are thought to be good candidate cell types for the regeneration of periodontal tissue injury (Oshima & Tsuji, 2014).

**Dental pulp SCs** (DPSCs): Dental pulp, a soft connective tissue within the dental crown, is an interesting source of adult stem cells because of the large amount of cells present and the non-invasiveness of the isolation methods compared to other adult tissue sources. Dental pulp contains mesenchymal stem cells defined as DPSCs obtained from human permanent and primary teeth, human wisdom teeth, apical papilla and human exfoliated deciduous teeth which are normally a biological waste, making the latter a free source of DPSCs without extra procedures on the patient when applicable (La Noce *et al*., 2014).

**Periodontal ligament-derived SC**: PDLSCs were first reported by Seo et al. in 2004 and have been a subject of substantial research since then, they play a dominant role in maintaining the periodontal ligament (PDL) tissues making them the star of the PDL regeneration research. They have shown their regenerative potential numerous times both *in vivo* and *in vitro* (Santamaria *et al*., 2017; Yang et al., 2020)

## 2. Applications of stem cells in regenerative dentistry

SCs have shown remarkable potential in regenerative medicine due to their ability to differentiate into a wide range of cells. In dentistry, they hold great promise for the repair and regeneration of damaged or lost oral tissues, including teeth, bone, and gums. With the ongoing research and development, SC-based therapies could revolutionize the field of regenerative dentistry and provide effective solutions and alternatives for a variety of dental conditions. SC-based therapies have already shown promising results in preclinical and clinical studies, with several ongoing trials investigating their efficacy and safety. In the future, the advances could potentially provide new treatment options for patients with dental conditions that are currently difficult or impossible to treat using conventional approaches (Kolios & Moodley, 2013; Soudi *et al.*, 2021).

**2.1. Stem cells in the regeneration of periodontal tissues**

The periodontal tissue, consisting of the cementum, the periodontal ligament and alveolar bone, is a multilayered structure formed from dental follicle tissue during tooth development. The PDL fiber connects the cementum and alveolar bone, creating a biological bond. The periodontal tissue is frequently damaged by excessive forces and periodontal diseases such as periodontitis and effective treatments to fix the lost tissues is yet to be found. Due to their complex structure, effectively regenerating periodontal tissues would mean regenerating all 3 tissues, attaching them to the existing alveolar bone and ensuring the functional link between these tissues (Oshima *& Tsuji*, 2014; Liu *et al*., 2019).

The SCs contained within the PDL, also known as PDLSC were isolated by Shi et al. in 2018 from extracted healthy human teeth due to orthodontic reasons. These cells were then treated, incubated and added to a biphasic calcium phosphate scaffold. The resulting construct was later surgically implanted into 8 dogs' surgically created alveolar bone loss to simulate clinical defects seen in humans. Four months after the procedure, it was observed that not only did the alveolar bone regenerate almost fully, but that the newly formed tissue had also matured (Shi *et al*., 2018).

During an experiment on adult nude mice, a portion of the tissues surrounding their first mandibular molars was removed, effectively denuding their roots from periodontal tissues: PDL, external cementum layer, and surrounding alveolar bone, simulating an artificial furcation defect. An apatite-coated silk fibroin scaffold mixed with iPS mice cells as well as enamel matrix derivative was subsequently implanted in lieu of the removed tissues. The results were evaluated 2-3 weeks after the procedure: the control group with just the scaffold implanted had filled the defect sites with connective tissues and linear bone formations, the experimental group on the other hand almost repaired the whole defect. The denuded root's surface regenerated the lost cementum, the alveolar bone recovered and was connected to the newly formed cementum through new PDL tissues (Duan *et al*., 2011).

Similarly, traumatic tooth avulsion is among the most common oral injuries, all PDL are torn, severing their connection to the alveolar bone. Currently, reimplanting the affected tooth is the only treatment that exists if we want to maintain the natural tooth and current research suggests that time is of a paramount importance in this case with the best results occurring when the tooth is reimplanted in the few minutes after the trauma (<5 minutes), which is realistically hard to achieve more often than not. The more the reimplantation is delayed, the higher the risk of complications, resorption being one of the most recurrent, it often leads to the loss of the affected tooth (Zhu *et al*., 2015).

In order to evaluate the potential use of SCs in these cases and assess their effectiveness compared to the traditional approach, an experiment has been conducted on dogs to artificially mimic traumatic tooth avulsion. Mandibular dog premolars were surgically luxated and then extracted, air-dried for 2 hours to ensure the absence of any living PDL cells. The PDL cells were then removed by mechanical friction and the crown was also removed to limit any potential interferences of mechanical nature. The teeth were then demineralized with EDTA and coated with bone morphogenic protein 7 and stromal cell derived factor 1 before being reimplanted autologously and fixated to their socket more than two days after the initial extraction. The results were evaluated 6 months after the procedure: a new PDL-like connective tissue was created with sharpey-like fibers following a similar spatial pattern as their natural counterpart (perpendicular to the nearby alveolar bone), enhanced angiogenesis activity was also observed. Though it should also be noted that some of the new fibers were not perfect as a few of them were interpenetrating the cementum (Zhu *et al*., 2015).

### 2.2. Stem cells in the regeneration of craniofacial bone defects

SCs from the maxillofacial region hold great promise for addressing various craniofacial bone defects, whether it is minor periodontal defects, severe traumatic bone loss, surgical defects, or congenital malformations like clefts. Besides their negative functional impact, these abnormalities also have a profound social and psychological impact on the patient's life (Deborah *et al*., 2020).

The ‘gold standard’ for treating severe bone loss, including maxillofacial bone loss, is autologous bone transplant and the most common harvesting site is the iliac crest. The harvesting procedure itself is well documented and widely used, but it is an extra surgical procedure coming with its fair share of complications: pain, temporary sensorial disturbance, potential fractures, potential major hematoma or seroma, among others (Almaiman *et al*., 2013).

Bioengineered bony tissues can be potentially used to avoid the aforementioned complications as well as other disadvantages not related to the harvesting but to the whole autologous bone transplant procedure like tissue availability, the rejection due to an immune response and cost. Several studies have evaluated the potential of SC in these situations, the results were mostly similar to autologous grafts and, in some cases, they have been shown to be superior. However, SC graft and autologous bone transplants are not necessarily mutually exclusive as SCs appear to provide the best results when used in conjunction with other bone substitutes rather than by themselves, that theory on the superiority of a hybrid approach was later confirmed by a meta-analysis (Chauca-Bajaña *et al*., 2023; Deborah *et al*., 2020, Bertolai *et al*., 2015).

One such study was conducted on human subjects with severe maxillary atrophy, freeze-dried bone allograft (FDBA) was harvested from the iliac crest was soaked in activated platelet-rich plasma and then conditioned with MSCs of unspecified origins, freeze-drying destroys the cells and organic matrix present, therefore the bone allograft pretty much served as a simple scaffold. The bone was then grafted and fixated on the maxillary bone; the results were evaluated 3 months after the procedure. While no complications occurred for any of the patients and both the control and test area had successful results, the test area with the platelet-rich plasma and MSCs induced substantially more osteogenesis compared to the test area with just the FDBA, as well as a better osteointegration. Overall, the results were comparable to a complete autologous bone graft and better than the control group with just the FDBA (Bertolai *et al*., 2015).

In another similar study on patients with severe jaw atrophy, bone fat pad stem cells (BFPSC) were incorporated into commercial FDBA (SureOss) and surgically grafted on half the patients alongside the other test group half which received the same treatment without the BFPSC. The test group using BFPSC displayed 15% higher bone formation. Even though the results were not conclusive due to the small sample size (4 per group), the study seems to suggest that BFPSC somewhat lowers the secondary bone resorption (Khojatesh & Sadeghi, 2016).

### 2.3. Stem cells in the regeneration of dental pulp

For odontology, a wide variety of materials have been used as substitutes to regenerate the dentin-pulp complex, these materials include ceramics, titanium or even collagen. However, their low flexibility greatly limits their applicability in the dental pulp capping procedure. This is where the emergence of tissue bioengineering techniques presents a promising solution for the development of natural dental tissue substitutes (Yang *et al*., 2012).

Currently, mature teeth with pulpal involvement are often considered a “lost cause” and receive a root canal treatment involving the replacement of the dental pulp with a filling material, usually gutta-percha (Meza *et al*., 2019).

Multiple issues have been associated with the loss of the live pulp:

• increased risks for tooth caries and periodontal diseases;

• brittleness;

• color changes (aesthetical impact) among others.

As such, the potential of SCs in regenerating lost tissues in teeth devoid of their pulp has attracted attention as potential superior alternatives (Torabinejad *et al*., 2016; Itoh *et al*., 2018)

In a recent study, human DPSC isolated from the third molars were cultured and incubated inside a favorable growth environment. They were later made into a scaffold free hydrogel-based construct and then either tested *in vitro* or *in vivo* on immunodeficient mice and evaluated 6 weeks following the procedure. Vascularized tissues resembling the human dental pulp were found in the root canals implanted into the mice, additionally, it was found that the DPSC localized near the internal wall of the dentin also differentiated into odontoblast like cells with mineralization capabilities (Itoh *et al*., 2018).

During another trial, conducted on a human patient this time, a 50 years old man was diagnosed with irreversible pulpitis which, under normal circumstances, would require a standard root canal treatment was treated differently in this case; a construct from the patient's platelet-rich fibrin (widely considered a superior alternative to platelet-rich plasma) and their DPSCs was deposited in the canal after standard instrumentation and cleaning. The crown received a normal definitive restauration with Biodentine (synthetic dentine replacement material) and a composite resin. The results were evaluated twice: Once after a month and another 3 years after the procedure. The patient remained completely asymptomatic during the entire period, and clinical examination didn't show any signs of pain during palpation or percussion, nor the presence of pockets > 3 mm or altered mobility. However, during the second evaluation (3 years), a delayed response to cold was observed and a calcification in the apical third, so laser testing for vitality was conducted to confirm the vitality of the root, the treated tooth displayed pulse characteristics displaying the circulation of blood in the root. The trial, despite the associated high cost and the low sample size (1) has shown the potential of SCs in overcoming the limitations of standard treatments (Meza *et al.*, 2019).

**2.4. Stem cells in the regeneration of entire teeth**

The discovery of modern dental implants has revolutionized the field of dentistry and greatly improved the occlusal and masticatory functions by providing a functional 'artificial' replacement to the lost teeth. SCs have the potential to improve upon what implants offer by replacing the lost tooth with a fully functional 'natural' alternative. To be considered as such, the new tooth has to replicate all of features that its predecessor had, including the periodontal tissues and sensory perception. Since their initial discovery, and to this day, SCs has been the target of extensive research for multiple potential applications, but the most promising application is neo-organogenesis. More particularly for this work, their potential in neo-odontogenesis (Nakahara *et al.*, 2011; Oshima & Tsuji, 2014).

Achieving perfect neo-odontogenesis should be seen more as the holy-grail of prosthodontics, accomplishing it is a culmination of all the knowledge about bioengineering the involved tissues. With the current advances, regenerating a perfectly sized crown with a proper shape seems impossible and unfeasible, so the expectations for "regenerating entire teeth" should be lowered to the bioengineering of a functional root canal and artificially restoring the crown with conventional restorative methods. More realistically the tooth should be engineered *ex vivo* and implanted in the subject (Jussila *et al*., 2012; Oshima *et al*., 2011).

Epithelial SCs and MSCs were extracted from mice's tooth germs, they were later used to bioengineer a new dental germ using a three-dimensional cell manipulation technique developed by Nakao et al. in 2007 allowing a better three-dimensional organization and control of the different cells forming the germ. After cultivating the germ in a plastic structure to limit their size and control their shape, the resulting germ was implanted in the subrenal capsule of female mice for 2 months in order to form a mature tooth. Following the surgical extraction of the first mandibular molars of different mice and then removing the surrounding alveolar bone in order to simulate an extensive bone loss, the newly formed teeth were implanted into the created socket and the results were evaluated regularly during the two months following the procedure. The new tooth was able to successfully develop all the appropriate dental tissues including the pulp cavity and supporting periodontal structures. Upon implantation, a full osteointegration was observed within two weeks after the procedure, and in 40 days the alveolar bone created *in vitro* was seen to completely resorb in the host's mouth leaving place to new ossified structure formation. The engineered tooth had similar hardness to normal teeth. Blood flow, sensory perception to external stimuli and PDL response to mechanical stress was also restored (Oshima *et al*., 2011).

### 3. Stem cells: a better alternative to conventional treatments

SC experimentation being a relatively recent branch of research, their applications in general and more specifically for dental purposes are mostly limited to preclinical studies or phase I / II trials. However, in certain disciplines, various purposes are being served by SCs on a bigger scale.

Hematopoietic SCs:  for treating certain malignant tumors like some types of leukemias, multiple myelomas and lymphomas are used in conjunction with chemotherapy and radiotherapy in the restoration of bone marrow functions when the aforementioned procedures cause intensive damage. In some cases of allogeneic grafts, the SCs have been shown to not only help with their regenerative role, but to also actively fight cancerous cells (National Cancer Institute, 2015).

MSCs: Heart failure is the leading cause of death among the elderly worldwide and is steadily increasing even among younger generations. Currently, there is no cure for cardiomyopathy and its treatment revolves around slowing its progression through lifestyle changes and medications, or, implants in some extreme cases. And while most MSC trials are still in the early phases of clinical trials (phase I / II), there are phase III and phase IV trials with very promising results in the improvement of the cardiac functions and capacity of affected patients effectively increasing their wellbeing (Rodríguez-Fuentes *et al*., 2021).

## 4. Limitations of stem cells

Despite their prowess, researchers have yet to overcome multiple challenges and issues in order to standardize the applicability of SCs, some intrinsic, others extrinsic.

- Extrinsic:

Other than the ethical, moral and religious concerns for the use of ESCs which are debated even for SCs of non-embryonic origins to a lesser extent, the most obvious limitation would be the lack of data on the effects of SCs on humans. Most of the promising research has been conducted either *in vitro* or on lab animals, and as much as we try to mimic real human conditions and limit external interference (the use of human SCs for instance), the proper human conditions can’t be perfectly reproduced. But there are also less obvious issues related to the pre-experimental conditions; many of the subjects used in testing come from inbreeding severely impeding the genetic diversity of the animals (Wnorowski *et al*., 2019).

Appropriate biocompatible and resolvable scaffolds, through guided tissue formation by serving as a space-holder and growth environment to prevent scar tissues from colonizing the targeted area among other benefits or similar techniques (cell sheet constructions for instance) are required to ensure proper regeneration of the missing tissue, particularly for complex tissues (Brozek *et al.*, 2018; Buduru *et al.*, 2019).

- Intrinsic:

The greatest asset of SCs is their ability renew in an unlimited manner, if left uncontrolled however, that same therapeutic advantage can turn into a tumorous cellular mass, so ensuring the safety of their host is of uttermost priority. Furthermore, one of their main advantages, their ability to effectively eliminate rejection risk when grafted autologously is, in practice, the least favored compared to allogenic grafts especially when time and economic resources are factored in (Yamanaka, 2020).

**III. CONCLUSION**

The progress made in SC based regenerative medicine so far is encouraging. Studies have shown that SCs have the power to reproduce various types of cells and their functions. Moreover, when their exceptional capabilities are combined with the structural support of scaffolds, more complex tissues can be created adding more therapeutic options for afflictions that the current medicine can’t treat effectively. Their potential applications in the field of dentistry are particularly active research-wise as evidenced by the recent surge of scientific papers in the last decade.

Though there are still numerous challenges to overcome before then, such as the need for a reliable scaffold material that can mimic the natural extracellular matrix of the tooth, the progress made so far suggests that the future of tooth regeneration may lie in the use of stem cells and bioengineering techniques. SC bioengineering is a promising solution for some of the limitations of dentistry and a great potential addition to its therapeutic options.

Additionally, SC based treatments have the potential to offer a more organic, safe and personalized approach to orofacial tissue restauration, as it can utilize the patient's own cells, thereby reducing the risk of rejection or immune responses. As research in this field continues, we can expect to see more advancements and innovations that will bring us closer to realizing the full potential of stem cell-based tooth regeneration.

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