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Mini Review

Application of Stem Cells in Periodontal Regeneration

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Abstract

Periodontal regeneration is one of the major achievements that have been done in modern periodontics, however, this concept is still developing and requires a better understanding of the human tissues. The aim of this review is to discuss the recent advancement in the clinical application of stem cells in periodontal regeneration. Different types of stem cells were described in literature but mesenchymal stem cells are still considered the most applicable cells in regenerative procedures.

Keywords: *Stem Cells; Periodontal Regeneration; Periodontium; Repair; Periodontal Tissues*

Abbreviations

DPSCs: Dental Pulp Stem Cells; PDSCs: Periodontal Stem Cells; SCs: Stem Cells; DFCSs: Dental Follicle Stem Cells

Introduction

Periodontal ligaments originate from neural crest cells and are derived from the dental follicle. They are highly specialized connective tissues that provide anchorage for the tooth root within the alveolar socket bone [1]. Their regeneration using stem cells offers an intriguing alternative to existing therapies for the regeneration and repair of the periodontium. These new approaches are constantly being refreshed and updated. Here's a brief review about everything you'd need to know for a better understanding of this topic. This particular type of stem cells may have a promising and encouraging impact in the future of periodontal regeneration.

Periodontium

The two main components of the periodontium are the soft and the hard tissues. The soft being the periodontal ligaments and the connective tissues, whereas the hard tissues are the alveolar bone and the cementum covering the tooth root [2]. Hence, an investment in the stem cells targeting the regeneration of any of these tissues is supporting the periodontal regeneration as a whole. As described by Philstrom BL, periodontal tissues constitute an essential role in supporting tooth function and providing the roots with anchorage rendering them with an importance similar to that of the tooth itself [3]. Among all the parts of the periodontium, the periodontal ligaments constitute the highest interest in these studies. Why so? Because these specialized connective tissues are highly fibrous and vascular and are known by their increased turnover rates in the body. Anatomically speaking, these periodontal ligaments stabilize and anchor the roots within their bony sockets of the alveolar bone [1]. Histologically, the periodontal cells are the osteoblasts, cementoblasts, fibroblasts, epithelial cells, endothelial cells and the progenitor cells which carry some mesenchymal cell features and they're all derived from the dental follicles going back in origin to the neural crest cells [4].

Periodontal Diseases

A periodontal disease is any pathological inflammatory reaction caused by a bacterial-induced chronic inflammation [5]. Periodontitis is the most common one, it can be simply described as an inflammation in the periodontium consequently leading to the loss of the surrounding and supporting dental tissues [6]. The original stimuli triggering periodontitis are the oral bacteria which cause damage to the gingival attachment and the alveolar bone resulting in tooth loss [7]. Rendering this type of disease the 6th most prevailing health condition worldwide [5].

Materials and Methods

Electronic literature searches were using Medline, and Embase for articles up to June 2017 reporting the classification of stem cells and their application in periodontal regeneration the search terms "(Stem Cells OR Mesenchymal Stem Cells) AND Periodontal Regeneration" were used.

Results and Discussion

Periodontal Regeneration

Many studies and trials have proven that scaling and subgingival root planning does not reverse tissue loss that was induced by periodontal destruction, it rather stabilizes it because these are traditional methods that focus mainly on eliminating bacterial pathogens and modulating the host's response to lessen or arrest the role of progression [8]. However, an adequate knowledge and understanding of the arising field of tissue engineering must be gained, improved and invested in order to develop a certain biological substitute to be able to regenerate periodontium and restore the original function and from of the lost tissues [8].

The concept of regeneration first started to arise and develop in the early 1980s. A guided and controlled tissue regeneration was developed by using an occlusive membrane that blocks any ectopic growth of epithelial cells in a periodontal defect, thus making a space for the regeneration of periodontal cells at site [9]. However, the regenerative cells must be putative mesenchymal stem cells because in this field not any type of stem cells can be used [10].

Several recent studies have stated that establishing a regenerative procedure requires the presence of 3 most effective measures which are growth factors, scaffolds, and investing cells. Examples on growth factors are epidermal fibroblasts, polypeptide growth factors, platelet derived growth factors and bone morphogenic proteins [11]. It is preferable for scaffolds to be biodegradable and to be applied through the harvesting, expanding and differentiating of cells *in vitro,* then seeding them into scaffolds and implanting them *in vivo* [12]. Several investigations have found that β-TCP is an ideal scaffold due to its superior bioactivity, nontoxicity, and biocompatibility [13].

Stem Cells Biology

Diving in the Stem Cells Biology is a necessity for a better understanding of the mechanism and value behind stem cells. They are divided into four types: "Embryonic stem cells" which come from embryos, "Adult stem cells" that come from adults, "Perinatal stem cells" existing in the amniotic fluid and last but not least "Induced Pluripotent stem cells" that have formerly been regular adult cells that transformed into stem cells by genetic reprogramming. Embryonic stem cells which are the inner mass of a blastocyst, have proven their pluripotent efficiency. Yet their usage and application is unethical and illegal along with huge medical limitations because the collection of embryonic stem cells requires the destruction of an embryo [14]. Further studying of amniotic stem cells is needed for a better understanding of its potential, whereas post-natal stem cells (for example bone marrow, adipose and teeth-derived stem cells) can be applied in regenerative procedures. IPS and adult stem cells provide repairing oral and maxillofacial defects with great benefits [7]. Reprogrammed stem cells are being used by altering genetic program (phenotypic modulation using the most recent four methods that are: Nuclear transfer from the somatic cells to the oocytes, direct conversion, overexpression of a certain pathway, and lineage switching). Those cells will be referred to as IPS cells which are characterized by the plasticity of their skeletal cells; multipotent cells which differentiate into three mesenchymal cell lineages. The recent present classification is illustrated in figure 1.

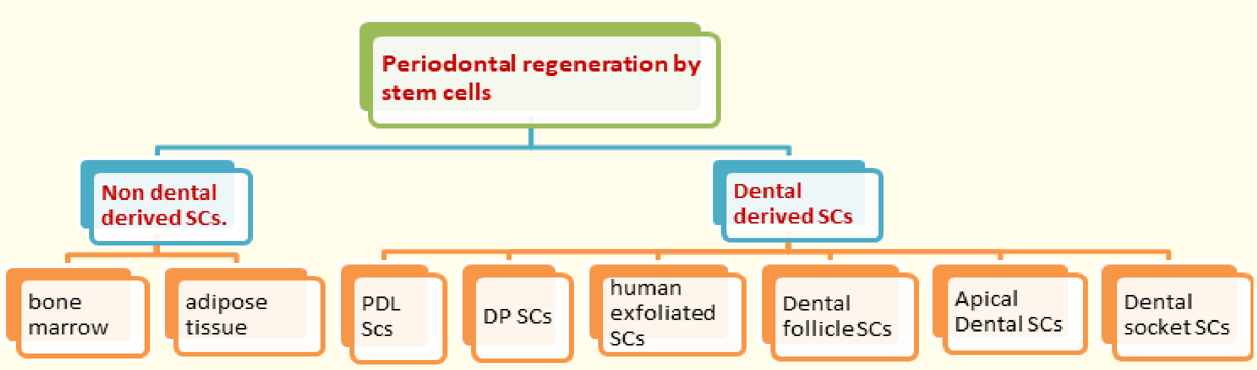

Figure 1: *Classification of the Dental and Non-Dental Stem Cells (Yang et al.).*

Non-dental derived stem cells

Bone Marrow Stem Cells

It was evidenced that the autologous BM mesenchymal-derived cells present a confirmed effect on the regeneration of alveolar bone and periodontal ligament-like structures after transplantation [10]. The multiple specialized cell types that are given by the mesenchymal stem cells (adult cells) are the common connective factor, they are extensively disturbed in a number of adult tissues including those of dental origin. That is the main reason of backing up targeting MSCs in the regeneration of periodontal tissue [15]. This proves that the mesenchymal stem cells are the future of cell-based therapy due to their huge effect on periodontal regeneration because of the few cytokines that have contributed in the process, and it may even become the alternative tissue regenerative therapy itself [16]. An experimental study done in 2004 on dogs with class III defects, have shown that 20% of the regeneration of the cementum and alveolar bone was promoted by auto-transplantation of BM-MSCs [17]. Also, an autologous bone marrow with collagen gel and an alginate carrier was tried on a class III furcation defect where the BMSSCs differentiated into fibroblasts and osteoblasts. However the primary problem in these cases is that the autologous stem cells' number undergo a reduction with age and hence decreasing their proliferative potential. A proposed alternative solution is the cryopreservation due to its ability to preserve autologous BMMSCs, yet freshly isolated ones would have a higher potential than those that are cryopreserved. An alternative source is displayed by the Allogeneic Bone Marrow Non-Dental Derived Stem Cells; it was tested on rats labelled with a green fluorescent protein GFP, the test results presented: Defect regeneration, new bone formation and increase in the number of the functionally oriented periodontal tissues [18]. The GFP labelled BMSSCs have directly contributed to periodontal regeneration and differentiated into specific cells including periodontal osteoblasts and fibroblasts. A heterogeneous cell population results from the isolation and enrichment of the bone marrow derived SSCs. However, it's not clear whether the newly formed bone, cementum and PDL are formed by the lineage specific progenitor cells or multipotent stem cells. Many studies were made specifically on the bone marrow stem cells concerning periodontal regeneration and have supported this concept. This proves that not only can BM-MSCs be a part of periodontal regeneration, but can modulate it as well [19].

Adipose tissue stem Cells

Adipose tissue stem cells and bone marrow stem cells have similar properties. They possess the ability to differentiate into adipogenic, myogenic, chondrogenic, osteogenic and neurogenic cells [20]. They don't express hematopoietic markers, but they do possess the expression of mesenchymal cell surface markers [21]. Their primary advantage over BMSSCs is that they are easily harvested with minimal donor site morbidity [22].

Dental derived Postnatal Stem Cells

This part is the most important one, dealing with the employment of dental tissues in dental regeneration. These dental-derived stem cells are obtained from discarded dental tissues in the clinics, hence lower morbidity rates are noticed compared to non-dental derived stem cells due to their isolation.

Periodontal Ligament Stem Cells

PDL exhibit a heterogeneous cell population consisting of fibroblasts, cementoblasts and osteoblasts. The first validation on the presence of multipotent stem cells was confirmed from the extracted third molars' periodontal ligaments [23]. However, PDL stem cells exhibit a self-renewal multipotent mesenchymal self-marker, resulting in PDL and cementum like tissues following an ectopic transplant. These cells are superior to the other skeletal stem cells because of their multilineage differentiation capacity, lack of hematopoietic markers, mesenchymal cell-surface markers, self-renewal, higher proliferation rate and the expression of scleraxis (a ligament/tendon specific transcription factor) [23]. Another characteristic of PDLSCs is their ability to repress immune response in inflammatory reactions leading to a decrease in the immune response. They can also form Sharpey's fibers which are considered to be a primary cell source that give PDL attachment in vivo. In 2008, Liu., et al. had demonstrated a periodontal defect that was surgically created by the removal of the alveolar bone around the tooth. Autologous periodontal ligaments from pigs following alloplasts have exhibited the ability to treat periodontal defects [24].

Although the PDLSCs present promising results, two major limitations challenge them. The limitation of their sources because of the involvement of extracted teeth, and the PDLSCs that are affected by the age and disease statuses of the donor [25]. Age influences the PDLSCs by affecting their proliferative capacity, multilineage differentiation ability and their migratory potential [26].

Dental pulp stem cells

This criteria was first recognized in the 2000s. It represents a heterogeneous population obtained from a richly vascularized area of extracted teeth (young or old). However, one of its characteristics is the lack of cell surface mesenchymal markers as well as hematopoietic factors and its limited capacity in the formation of cementum. Due to these limitations, DPSCs haven't increased the utilization of PDLSCs that are still considered the most ideal choice. A study done in 2014 has exclusively stated that autologous DPSCs are highly relevant in deep and non-contained periodontal and infrabony defects, but because of their poor histologic analysis, caution should be taken in the interpretation of regeneration [27].

Human exfoliated dental stem cells

Speaking here about a multipotent group with pulp remnants. Unlike the DPSCs, human exfoliated stem cells exhibit mesenchymal surface markers but not hematopoietic. Studies have proven its higher proliferative rate than the DPSCs and BMSSCs. It is promising in the field of bone regeneration because following an ectopic transplant, it has the ability to form dentin-cementum complex and not dentin-pulp complex [8].

Dental follicle stem cells

They come from the loose connective tissue from the ectomesenchymal cells, differentiate and express cell surface markers but do not express hematopoietic markers similar to the DPSCs. Dental follicle stem cells exhibit a potential in periodontal regeneration. Formation of new PDL has been confirmed following an ectopic transplant + collagen I fibrin of the autologous DFSC [28].

Apical dental stem cells

They are obtained from the soft tissues of teeth apices during root development only or from the developing third molars. Similar to the DPSCs, apical dental stem cells express mesenchymal self-markers, but lack hematopoietic markers [29].

Dental socket stem cells

This category presents no hematopoietic markers, it's osteogenic in activity. From the analysis of bone cones that were removed from post-extraction healed sockets, osteoblasts and osteoid are found during weeks 4 - 8 after the extraction [8].

Conclusion

To be deeply involved in the latest advances of periodontal dentistry, you must have full knowledge and a background on the periodontal regeneration based on the broad concepts and entering through the classifications and types. Stem cells take a massive part of periodontal tissue regeneration, and so this review aims to sum up all the basic information and show the gradual improvement in the scientific evolution of regenerative therapy over traditional and surgical therapy.

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Conflict of Interest

No conflict of interest to declare.

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