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Literature Review Article

Stem cells carrier scaffolds for tissue engineering

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Abstract

Introduction: Mesenchymal Stem Cells (MSCs) can be isolated from several body tissues, including dental tissues. As a result of being capable of differentiating into a variety of cell types, it can be presumed that stem cell therapy has an advantage compared to other tissue repair methods. **Objective:** The aim of this paper is to provide a review about current and future materials for scaffolds to carry stem cells in tissue engineering in Dentistry, especially for bone tissue repair. **Literature review:** MSCs have great therapeutic potential in tissue engineering, they can be expanded *in vitro*, and combined with scaffolds to be inserted into defects to promote healing and tissue replacement. **Conclusion:** Stem cells from dental tissues have a real potential in Advanced Therapies. The combination of inductive scaffold materials with stem cells might optimize the approaches for bone regeneration. Although there are numerous available biomaterials potentially compatible to combine with MSCs, more studies need to be performed, due to the fact that for each indication there will be a more suitable material according to the defect's biological and mechanical requirement.

Introduction

The potential therapeutic use of stem cells has been the focus of much research in recent years. The ability to restore cells and tissues function without the need to use immunosuppressive drugs and without concern for tissue compatibility makes mesenchymal stem cells (MSCs, usual acronym) a strong promise for the future. Until now, several progenitor cells derived from dental tissues have been isolated and characterized (table I).

Table I – Sources of stem-cells from dental tissues

- Dental pulp stem-cells (DPSCs) [12]
- Stem-cells from human exfoliated deciduous teeth (SHED) [23]
- Periodontal ligament stem-cells (PDLSCs) [28]
- Precursor cells from human dental follicle (PCs) [25]
- Oral keratinocyte stem-cells [17]
- Mandibular bone marrow stem-cells (MBMSC) [18]
- Apical papilla stem-cells [31]
- Supernumerary tooth pulp stem-cells [15]
- Human tooth bud stem-cells [33]
- Human natal dental pulp stem-cells (hNDPs) [19]
- Human oral mucosa stem-cells (hOMSC) [22]
- Gingiva hyperplasia stem-cells [34]

Stem cells derived from dental tissue are isolated from specialized tissues and have a strong ability to give rise to other cell lines, but with a different potential of stem cells derived from bone marrow [16].

For stem cells to be used in tissue engineering a scaffold is essential to provide the necessary support for the transport of nutrients and oxygen and the elimination of metabolic waste [30], promoting an conducive environment for cell growth and differentiation.

The development of new biomaterials for use in tissue engineering provides a scientific basis for the creation of scaffolds that provide appropriate regeneration and tissue repair [14].

This study aimed to provide a literature review of current and future materials for use as scaffolds for carrying stem cells in tissue engineering, especially in the bone tissue regeneration.

Literature review

Stem cells are divided primarily into two categories: embryonic stem cells, which are found in the embryo and adult stem cells found in adult tissues. Embryonic stem cells are present only in the early stages of development and are able to generate any cell type (pluripotent). Adult stem cells are found in differentiated tissues and are able to generate specialized cell types in some tissues (multipotent - MSCs). Adult stem cells can be isolated from many tissues in the human body; we may cite bone marrow, umbilical cord, periosteum, cancellous bone, adipose tissue, brain, dental pulp, pulp of deciduous teeth, the periodontal ligament, etc. [6].

MSCs have a clinical attractiveness because they are easy to expand, have the ability to differentiate into various types of tissues [5], and may be directed to become osteocytes, chondrocytes and adipocytes. The high regenerator potential has aroused a great interest of the scientific community [3], because of its many clinical applications in cell therapy or tissue engineering.

Cell therapy is defined as the therapy that aims to put a population of cells directly into the injured area or systemically, to promote local repair or restore systemic health. Tissue engineering is the science that combines the principles of biology and engineering techniques in order to obtain biological substitutes for regenerating, replacing, modifying, repairing or restoring the function of organs and tissues arranged three-dimensionally.

The stem cells from exfoliated deciduous teeth (SHEDs) have a great potential for therapeutic use because of its differentiation capability and its easy access, since the collection is performed at the physiological exfoliation of deciduous tooth. The tissues before discarded may serve as a basis for scientific research and clinical use in tissue regeneration and treatment of various diseases [23].

The easy access, the absence of ethical conflicts, and especially the potential for systemic use in tissue engineering and cell therapy motivate many researchers to better understand how these cells work and why they present peculiarities in relation to stem cells found in other sources [16].

For use in tissue engineering, it is essential that the cells are arranged in a matrix capable of facilitating the transport of nutrients and oxygen and the removal of metabolic waste [30]. The matrix will promote a conducive environment for growth and cell differentiation.

The scaffolds can be classified as permanent or resorbable. The permanent scaffolds are stable *in vivo*, while the resorbable scaffolds are reabsorbed *in vivo*, metabolized by the body.

Cell scaffolds can be cultured in vitro to synthesize tissue which can be implanted at the site of injury, using the organism itself, where the regeneration of tissue or organ is induced *in vivo* [26].

Scaffolds can be made of various types of materials, but there are some considerations to create or determine the suitability of a scaffold for use in tissue engineering. According to O'Brien (2011) [26], these considerations are biocompatibility, biodegradability, mechanical properties consistent with the anatomical site that will receive the scaffold architecture that enables a cellular penetration and diffusion of nutrients, and the technology used to enable the production on a smaller scale

In situations of large tissue defects, it is difficult to obtain repair and natural regeneration using only local administration of cells because in these situations not only the cells, but also the extracellular matrix and the surrounding environment (anatomical contour) may have been lost. Thus, to induce tissue regeneration, an artificial environment to the cells (scaffolds) may be used in order to assist in cell adhesion and consequent proliferation and differentiation [32].

Biomaterials play an important role in tissue regeneration, because they will hold the space for tissue growth and will also facilitate the integration with the host [8], it is a substitute of the extracellular matrix. Typically, three groups of biomaterials are used to manufacture scaffolds: ceramic, synthetic polymers, and natural polymers [26] (table II).

Table II – Main characteristics of biomaterials with potential application for tissue engineering

	Material type	**Main characteristics**
Natural polymers	Collagen Fibrin Platelet-rich plasma Silk	Low toxicity, low chronic inflammatory response, can be combined with other natural or synthetic materials. Its main disadvantage is the low mechanical strength [35].
Synthetic polymers	PGA PLA PCL	Can be manufactured with different times of degradation, mechanical properties, shape and porosity, but have low cell adhesion [21], low ductility [1] and low bioactivity [37].
Ceramics	Hydroxyapatite Tricalcium phosphate	Biocompatible, similar to the inorganic component of bone, osteoconductiveness, absence of protein (providing lack of immune response) and high degradation time *in vivo* [2]. However, they have poor mechanical properties [27].

The ceramics scaffolds such as hydroxyapatite and tricalcium phosphate, have been widely used in bone regeneration because of their biocompatibility, similarity to the inorganic component of bone, osteoconductiveness, absence of protein in their composition (providing lack of immune response) and because of its high degradation time *in vivo* [2], which allows bone remodeling at the site of grafting. Its disadvantages are its low structural stiffness (and may not be used in large mechanical stresses regions) and its porous nature, which increases the risk of fractures [36]. They are quite used in orthopedics and dentistry to repair bone defects, maintenance of the alveolar ridge as well as orthopedic and dental implants [20].

Despite its advantages, the hydroxyapatite and tricalcium phosphate are not osteoinductive materials; hydroxyapatite is resorbed more slowly than the tricalcium phosphate, and their mechanical properties are poor, resulting in the inability to use on large bone defects which require stabilization [27]. In such cases synthetic and natural polymers may be used to overcome these limitations. The most studied synthetic polymers for bone reconstruction include: polyglycolic acid (PGA), polylactic acid (PLA), and polycaprolactone (PCL) [2].

Natural biomaterials used in scaffolds may be made from components found in the extracellular matrix, such as collagen, fibrinogen, hyaluronic acid, etc., thus having the advantage of being biocompatible, and having mechanical properties similar to natural tissue [7].

The advantages of natural polymers include low toxicity and low chronic inflammatory response, in

addition to the possibility of being combined with other natural or synthetic materials [35]. These materials also provides a good environment for stem cell culture [7]. Its disadvantages include low mechanical strength, difficult to handle and need for chemical modification [35].

Among the natural polymers, we can mention the platelet-rich plasma (PRP) and platelet-rich fibrin (PRF). The platelet concentrates are widely used in tissue regeneration because of its high content of growth factors and their easy processing [9]. The combined use of stem cells and platelet concentrates causes that the factors secreted by concentrated enrich the culture medium, enhancing tissue regeneration capacity [24], but it has low stability for regenerative medicine [29].

Each tissue requires specific requirements resulting from the type of tissue cell site, function, and mechanical properties. For bone remodeling, it is necessary that the scaffold material has a porosity and also can be produced in a three-dimensional anatomic shape [35]. Best results were obtained with the combination of MSCs and porous ceramics, in which the properties of ceramics have been integrated with the properties of the osteoprogenitor cells to form a vital and vascularized bone tissue, with biomechanical properties [4].

The success of osteoinductive grafts depends on the efficiency of the scaffold material. The ideal scaffold should increase the exposure of the host tissue to the growth substance and ensure uniform distribution. It should be safe, biocompatible, biodegradable, and resorbable as will occur bone formation [13].

Discussion

Stem cells are undifferentiated cells capable of unlimited self-renewal and to differentiate into several cell types. Stem cells show great therapeutic potential, is promising in tissue repair area in order to regenerate and restore the normal function [10].

The large potential capacity for differentiation of the MSCs, the possibility of graft, the immunosuppressive effects, and expansion in culture led to increased clinical interest in the use of these cells via intravenous infusion or site-directed administration in many situations pathological [4].

The design of the scaffold is critical since it must be capable of supporting cell adhesion and proliferation, and have favorable mechanical properties. In addition, there are parameters that must be considered for building a scaffold, including porosity, mechanical integrity, and effect of the surface morphology in cell adhesion and proliferation [38].

Currently, the autogenous bone graft has been used as the gold standard for repair and bone replacement. However, the use of this type of graft has several disadvantages, including cost, the trauma, the possibility of donor site morbidity, limited availability, and resorption. These disadvantages can be eliminated by the use of allografts, which are obtained from living donors or tissue banks. Despite increased availability and donor site morbidity disposal, this type of graft is associated with the transmission of diseases, bacterial infection, and immune rejection, in addition to presenting a limited osteoconductiveness [11]. Thus, the creation of the ideal material for bone replacement is necessary [20].

The selection of the biomaterial to be used in the scaffold is also of extreme importance; in addition to being biocompatible, promote chemical stability, having good physical properties, have a controlled degradation, allowing cell adhesion and proliferation, the biomaterial should mimic completely or partially the extracellular matrix of the tissue that will be replaced [38].

One of the major advantages of tissue engineering is the possibility of creating tissue so that they correspond exactly to the individual requirements such as size, shape, and immunological compatibility while minimizing the need for further treatment [35].

Conclusion

Stem cells point to a promising future in dentistry to replicate dental tissues, in order to repair or recover them, especially in endodontics, periodontics and surgery (grafting).

The use of biomaterials in bone tissue engineering has many advantages over traditional surgical procedures. The possibility of using biomaterials to repair large bone defects replace the need for traditional surgery grafting, giving a new chance for bone repair. Among the scaffolds, ceramics receive a lot of attention when you want to restore the bone tissue, especially hydroxyapatite and tricalcium phosphate.

Although studies with stem cells are at an early stage, they have a great therapeutic potential. It is expected that in future the isolation of stem cells from various parts of the human body would be possible, and, along with appropriate scaffolds, MSCs could be applied for the treatment of numerous disorders in dentistry and medicine.

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