

Biological Approach of Pulp Revascularization: A Literature Review

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Abstract

The discovery of pulp stem cells by Gronthos in 2000 highlighted a new therapeutic alternative to current endodontic treatments. Biology researchers have been able to develop dental revascularization protocols and have, in particular, focused much attention on the revascularization of necrotic immature permanent teeth. The aim of this paper is to accomplish a literature review concerning this issue.

advantage is the possibility of further root development and the reinforcement of the root canal walls by depositing hard tissue, reinforcing the root against fracture [6].

The aim of this paper is to provide a detailed update on the pulp revascularization process. It is divided into two main parts. An overview of the pulp is first presented, the different types of dental stem cells are then described; and the second part investigates the process of pulp revascularization and the various experimental approaches.

The Dental Pulp

The pulp is a very heterogeneous loose connective tissue, composed of different cell types and an extra-cellular matrix rich in collagen [7].

It is located in the centre of the tooth in an enclosed and inextensible space called the pulp cavity, and contains vessels and nerves. It is the living part of the tooth, it has a crucial role in the nutrition of odontoblasts and the elimination of waste to produce a quality dentin, it is also responsible for the protection of the tooth because pulp innervation allows on the one hand to transmit alarm messages (pain) against many aggressive elements (mechanical, chemical and biological), and on the other hand to regulate the blood flow which allows an adapted activity of odontoblasts.

Like the rest of the body's tissues, human dental pulp has a network of immune cells that can be mobilized against pathogens when they invade the tooth. Very few data, mainly obtained using conventional histological methods, have reported their quantities and relative percentages [8].

Alongside nerve, endothelial and immune cells, the pulp contains other cell types, in particular Höhl cells which are derived from the last mitosis of pre-odontoblasts, this kind of cells is able to initiate a scarring process [9]. We also find fibroblasts which the main function is to synthesize and regenerate the extra-cellular matrix; they are derived from pulp parenchyma; these fibroblasts can synthesize cytokines in response to various stimuli; for instance, after an attack, they

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Introduction

Tissue engineering is a set of techniques that use engineering and life science principles to develop biological substitutes to restore, maintain or improve tissue functions [1]. The emergence of this new strategy dates back to the late 1980s with recent research on cell culture and growth factors. In 2000, work conducted by Gronthos' team identified the presence of stem cells in dental pulp and isolated them [2].

A new alternative for tissue bioengineering exists and is attempting to develop, namely revitalization, better known as revascularization [3].

All root canal filling techniques use non-biological, non-resorbable materials of the family of bioceramics; their sole purpose is to provide root canal sealing to prevent the passage of bacteria from the oral cavity to the underlying bone [4].

Despite their properties, these materials remain an artificial filling [4]. The recent explosion of tissue engineering techniques now makes it possible to devise surgical techniques whose objective is to close the channels with regenerated biological tissue.

Pulp revascularization has been identified as a new treatment method for irritated, inflamed or necrotic pulp [5]. Its main

are involved in the healing of pulpal lesions with the secretion of pro-angiogenic factors [10].

The dental pulp is equipped by an extra-cellular matrix made of a fundamental substance in which collagen fibres, glycosaminoglycans, glycoproteins, elastin, matrix metalloproteases (MMPs) and lipids are found; It ensures exchange of nutrients, metabolites and debris between cells and pulp vessels; it has a high viscoelasticity that allows it to adapt to intrapulpal pressure variations during inflammatory reactions.

The Dental Stem Cells

Pulpal stem cells have a high capacity for proliferation and differentiation. They represent an important therapeutic interest in tissue regeneration [11].

The identification of these cells within the dental pulp has opened up new perspectives in dentistry. They could be used in the regeneration of the dentino-pulpal complex, the regeneration of the dental organ, and the pulp revascularization [11,12].

Although stem cells have been identified in most oral tissues, stem cells mainly involved in regeneration work include:

Dental pulp stem cells (DPSCs)

They were highlighted by Gronthos in 2000 from the cameral and root canal pulp of a 3rd molar [2]. Pulpal stem cells have a phenotype similar to bone marrow stem cells, they are large cells, with a large central nucleus and a large cytoplasm. In addition, DPSCs have a 30% higher proliferation rate than bone marrow stem cells and a better growth potential. DPSCs can be reprogrammed in multiple cell lines such as: odontoblasts, osteoblasts, chondrocytes, myocytes, neurocytes, adipocytes, corneal cells. DPSCs express some markers that can be used to identify and locate these as CD44, CD146, 3G5 and integrin β [13].

Stem-cell from human exfoliated deciduous teeth (SHED)

A second kind of stem cell, SHEDs are isolated from deciduous teeth. These could be an excellent source of stem cell banking [14]. Both SHEDs and DPSCs express dentine sialophosphoprotein (DSPP) [15]. These cells have the ability to induce bone and dentine formation and to differentiate into other non-dental mesenchymal cell derivatives *in vitro* [16]. They have greater proliferation rates than DPSCs [17].

Apical papilla stem cells (SCAP)

Another type of mesenchymal stem cell from the apical papilla of immature permanent teeth has been isolated: SCAPs (Stem Cell of the Apical Papilla). This population of cells is different from DPSCs [11]. The apical papilla is a tissue present at the apex of the developing root and can be easily detached. Cells that originate from them have a capacity to double their population, a proliferation rate, telomerase activity and a cell migration capacity superior to DPSCs [18]. This high proliferation

potential of SCAPs makes them suitable for dental tissue regeneration and preferably for root formation. They have specific STRO-1 and CD24 markers [11].

Periodontal ligament stem cells (PDLSC)

The periodontal ligament contains a specific population of stem cells, called PDLSC (PerioDontal Ligament Stem Cell) which are mesenchymal stem cells the origin of its formation. This population is able to differentiate into multiple mesenchymal cell lines (cementoblasts, adipocytes, fibroblasts). The stem cells of the periodontal ligament express the surface markers characteristic of mesenchymal stem cells (STRO-1/CD146/CD44). Their potential for differentiation is similar to that of stromal stem cells in bone marrow and DPSCs.

Pulp Revascularization

Regeneration of the dental organ is still being studied, but the use of pulp stem cells in pulp revascularization is a topical issue.

Pulp revascularization is a regenerative treatment of necrotic immature teeth that involves inducing the formation of a blood clot within the previously disinfected canal, by involving the recruitment of stem cells from the apical region. The objective of this therapeutic approach is to regenerate tissue comparable to pulp tissue and to reactivate dentinogenesis, which has become non-existent following the necrosis of pulp tissue, and subsequently allows the development of the root [19].

The indication for pulpal revascularization is currently limited to immature teeth, but this treatment has been successful in some cases, performed on mature teeth [20].

From the tissue engineering perspective, pulp regeneration of mature teeth have the advantage of restoring the neurovascular system of the root canals, which provides the tooth with an immune system to defend against the microbial defiance [21].

The problem of the revascularization of mature teeth is that they have fewer progenitor cells than immature teeth, a difficulty in inducing bleeding because of the closed apex, a difficulty in disinfecting the root canals; the closed apex of mature teeth gives less chance to stem cells to migrate to the canals [21,22].

Pulp revascularization of mature teeth is related to the amount of progenitor cells, it depend of the aging of the tooth [23].

Protocol

Many papers have proposed protocols that were both very similar but also very divergent. To take stock, the two endodontic scientific societies, the American and the European one, published their recommendations with protocols validated by a committee of experts [24].

In summary, there are two main steps for the pulp revascularization protocol. The first one called disinfection and a second one called regeneration [10].

For disinfection it is no longer advisable to use a mixture of antibiotics as initially recommended (metronidazole, ciprofloxacin, and minocycline); [12] this blend has an indisputable bactericidal effect but its side effects: development of resistance, staining etc. [25-27] make the benefit/safety ratio unfavourable to their use [28].

Disinfection is now achieved with both low sodium hypochlorite irrigation at a low concentration of 1.5% and intra-channel calcium hydroxide medication left in place for 15 days [23].

The regeneration step is performed two to three weeks later, and after removal of the medication, the root canal is rinsed with a solution of sodium hypochlorite at 1.5%; then with a solution of EDTA at 17%, left in place for two minutes.

This EDTA treatment has two objectives: on the one hand, it will eliminate the first layer of dentin, the one which was in contact with sodium hypochlorite and which is contaminated by residual chlor, the latter being toxic to future cells; and on the other hand, it will release the intrinsic growth factors of dentin which will subsequently participate in the regeneration process [29].

At the infected canal, revascularization is performed with a strongly pre-bent file that is placed beyond the foramen of the tooth, this file is then animated by a continuous rotational movement, the part of this instrument that is beyond the apex will tear the apical papilla and cause a bleeding that is allowed to rise up within the canal to the amelococementary junction.

After a few minutes a blood clot will be formed and covered with a collagen sponge before the cavity can be filled with biodentine or MTA [30].

Discussion

Intra-channel tissue regeneration is a real challenge, as it involves many domains of competence, such as biology to define the choice and mode of recruiting the progenitor cells and signalling molecules to use, biochemistry, and biomaterial science to develop the ideal matrix scaffold [31].

Too many case reports published in the literature tends to demonstrate the clinical interest of these therapies, [5,31-34] but the variability of the results obtained encourages us to focus on the nature of the biological tissue formed in the root canal, and to raise the issue of whether the implementation of root canal vascularization alone can be considered as a regeneration or a simple repair [35].

Some clinical cases report the return of tooth sensitivity, with positive responses to the vitality test, probably confirming the regeneration of nerve tissue in the root tissue filling the canal, as well as a resumption of root edification and the thickening of its walls [34].

All these elements therefore tend to suggest that real pulp tissue has been regenerated within the tooth. However, histological differentiation of the tissues formed still impossible with only clinical and radiological examinations.

This examination revealed the presence of free connective tissue in the root canal space. This tissue appears to be an extension of the periapical tissue. The cells in the canal and periapical area were young fibroblasts or mesenchymal cells. A layer of polarized cells had organized along the predentine in the canal, similar to odontoblasts. A layer of cells, similar to Hertwig's epithelial cells, surrounded the apex of the root [36].

Histological observation of this human tooth showed that a periodontal mineralized tissue was placed in contact with the root walls [37].

These histological sections reveal that in some cases, the tissues formed in the root canal space after revascularization are cementitious in nature. Regeneration of intracanal cement can occur despite the presence of inflammatory infiltration at the root apex. This intra-canal cement is similar to the cellular cement [35].

In other cases, the tissue formed in the canal is osseous in nature.

Conclusion

These authors explain that the root thickening and maturation obtained after revascularization is due to the deposition of cementitious and bony tissue in the canal.

These histological observations suggest that the tissue regenerated in the canal is therefore more closely related to a periodontal structure than to pulpal structure. In these cases, progenitor cells recruited from the apical region differentiate to periodontal cells but not to pulpal ones.

For this reason, it is impossible to affirm that the tissue formed in the treated canal is dental pulp.

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