BIOTHERAPY IN DENTISTRY

TRAIAN BODNAR [1], DANA CRISTINA BODNAR[2], DUMITRU FERECHIDE[3], LILIANA BURLIBAŞA[4], MIHAI MIŢARIU[5], MIHAELA CERNUŞCĂ-MIŢARIU[6]

[1,2,3]"Carol Davila" University of Medicine and Pharmacy Bucureşti, [4]University of Bucureşti, [5,6]"Lucian Blaga" University of Sibiu

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Abstract: *Today, thanks to the progress of the research on stem cells and biomaterials, it is possible to develop new kinds of therapies in the field of dentistry. These therapies are called biotherapies. The recently highlighted stem cells within the different pulp organ tissues and especially those in the dental pulp have made possible the development of new therapeutic possibilities, for treating dental pulp injuries. In the case of moderate pulpal lesions, it has become possible to stimulate the persistent pulpal stem cell reservoir with the help of biomolecules. In the case of more severe lesions, which require a total removal of pulpal tissue, a cellular therapy should be considered. The objective of this paper is to present these future therapeutic methods. The results of the research conducted on the dental pulp stem cells, combined with the overall progress of stem cell research, as well as that of tissue engineering, will allow the development of therapeutic alternatives to the current treatments of dental pulp lesions.*

Cuvinte cheie: *pulpa dentară, bioterapie, celule suşe pulpare, peptide*

Rezumat: *Astăzi, datorită progresului cercetărilor în domeniul celulelor suşe şi biomaterialelor, este posibilă dezvoltarea de noi terapii, bioterapiile, în domeniul dentar. Punerea recentă în evidenţă a celulelor suşe din diferite ţesuturi ale organului pulpar şi în particular din pulpa dentară, a permis dezvoltarea de noi posibilităţi terapeutice a leziunilor pulpodentinare. În cazul leziunilor pulpare moderate, se are în vedere o stimulare a rezervorului de celule suşe pulpare persistente cu ajutorul unor biomolecule. În leziunile mai severe, care cer o îndepărtare totală a ţesutului pulpar, se prevede o terapie celulară. Obiectivul acestui material este acela de a prezenta aceste metode terapeutice de viitor. Rezultatele cercetărilor privind celulele suşe ale pulpei dentare, combinate cu progresul cercetărilor în domeniul celulelor suşe în general şi al ingineriei tisulare, va permite dezvoltarea unor alternative terapeutice, pentru tratamentele actuale ale leziunilor dentopulpare.*

Stem cells, undifferentiated cells, have the ability to reproduce for long periods of time. These cells are not specialized. Such cells can be obtained from an embryo or from certain tissues belonging to adult individuals. In the first case, the cells are pluripotent, which means that they are able to turn into any type of cell in the human body. In the second case, these are cells that are part of differentiated body tissues and are designed to produce new cells to replace aging ones. Such cells are multipotent cells, capable of producing only the cell type from a specific tissue or organ.

In a laboratory, under controlled conditions, stem cells can be induced to differentiate. Today, there are known the stem cells derived from the haematopoietic system or undifferentiated mesenchymal cells, all of which have the potential to differentiate into cardiac and skeletal muscle, brain, gastrointestinal tract, liver, kidney. This potential has been demonstrated in vitro and subsequently in vivo.

Today, with the help of biotherapies, medicine has become the recipient of new therapeutic additions. Biotherapies are involved in the treatment of diseased organs or tissues by using cell therapy, gene therapy or other combined biomolecules, as well as various biomaterials.(1) In recent years, these studies were extended to the teeth and especially to the pulpal tissue.

The tooth, viewed as a morphological unit, removed from the structure to which it belongs, might give the impression that it is irrelevant, but if we analyze it in conjunction with the dento-maxillary apparatus, from which it is a part of, we find that it has a unique structural and functional character, determined by the complex and less then friendly environment in which it conducts its activities.

The tooth would not be able to withstand specific elements of its natural habitat if its histological structure is not well suited for this purpose. The tooth structure, together with its components, is very complex, unique within the body and an adaptation of its structure in response to the environment and its complex functions is the only explanation for it.(2)

In different clinical situations, the teeth are subjected to multiple aggressions such as severe dentoalveolar trauma, dental caries, dental wear, or cases where the dental pulp may suffer irreversible damage. The connective tissue, consisting of cells, fibers, essential substance, the vasculonervous and lymphatic system, as well as dental pulp, reveals great structural instability.

Inside the pulpal tissue, there is a continuous transformation of the cell typology, which is primarily the biological adaptation and the renewal of depleted, aging or damaged elements, following an aggressive element. Dental

[1]Corresponding author: Liliana Burlibaşa, Bulevardul Mărăşeşti, Nr. 2B, Bl. A, Sc. 2, Et. 5, Ap. 17, Sect. 4, Bucureşti, România, E-mail: mburlibasa@gmail.com, Tel: +40723 472632
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pulp cells are able to move from one side of the pulp to the other, with all pulpal cells being mobile or being able to be made mobile, as well as some of them being able to differentiate from one cell type to another.

Primitive undifferentiated mesenchymal cells can take the form and function of any type of pulpal cell. Undifferentiated mesenchymal cells are found in the subodontoblastic area, which is rich in cells, as well as in the central pulp area. They are usually located near blood vessels, have a polyhedral shape, with a bulky central core, plentiful cytoplasm and peripheral cytoplasmic extensions. Depending on the stimuli, these cells can differentiate into odontoblasts or fibroblasts.(3)

The complex game of physical states, which affect the components of the dental pulp, the extraordinary variations of chemical structures and stunning plastic transformations of various movable and immovable elements, determine the quality of the pulpal tissue to respond, at any given time and in various ways, to the stimuli that it receives. Everywhere, throughout the body, where there is connecting tissue, where the function is differentiated and specialized, the processes are similar.

Nevertheless, the dental pulp is a miracle in terms of perfecting its physiological processes, at such a small volume and in topographic conditions, which are not always beneficial.(4)

Obviously, as it happens in other tissues and organs, short or long duration illnesses can also occur within the pulpal tissue. At times, it may even become necessary to use an endodontic treatment, which completely removes the pulpal tissue, followed by filling the resulting endodontic space with a material which does not have any apparent biological effect.

This is very important, considering that the dental pulp, through its structural complexity, has well defined roles in immune defence, nutrition, sensory detection and repair.

Specifically, after devitalisation, the tooth loses these roles, namely vascularisation and innervation and it becomes vulnerable to fracture due to its embitterment, all of which leads to its premature loss, due to complications requiring premature extraction. It can also lead to infectious complications of periapical periodontitis type, which are susceptible to the bacterial seeding of various other tissues within the body. Such a microbial seeding can be the basis of serious diseases, such as endocarditis, nephropathies or rheumatic fever.(1)

In recent years, research on the biological properties of the dental pulp and its cells, have opened the way towards the development of biological therapies for several diseases of the dental pulp.

It has long been known that pulp tissue has a high capacity for regeneration. The mechanisms and cells involved in this process continue to be the subject of debate among experts.

The first description on the presence of mesenchymal stem cells within the pulpal tissue appeared in the year 2000, enabling advances towards understanding the mechanisms involved in the repair of pulpal tissue. Since then, it has become clear that a population of pulpal cells, DPSCs (Dental Pulp Stem Cells), exhibit classic attributes of mesenchymal, selfrenewing, multipotent stem cells, similar to bone marrow stromal cells.(5,6)

Highlighting the adult dental pulp stem cells, allowed the initiation of research aimed at biotherapies, which use the potential of these cells to repair dental lesions.

To this day, two types of biotherapies are described in dental odontology.(1,7). These are:

- biotherapy by peptides, which stimulate the existing pulpal stem cell reservoir, capable of stimulating the natural repair ability of the dental pulp;
- cell biotherapy to restore the functions of damaged pulpal tissue, which was removed through total extirpation, by implanting cells, previously amplified in vitro, into the endodontic space which was created.

In the case of moderate lesions of the pulpal tissue, biotherapy involves a biological treatment aimed at the repair / regeneration of the injured dental pulp tissue. The treatment involves stimulating the pulpal stem cell reservoir located inside the pulpal tissue. This is achieved by implanting “biomolecules capable of stimulating the natural pulpal repair capacity”.

The research focused on the proteins of the extracellular matrix of the dental enamel, bone or dentine, which are carriers of a proteical dominance (an amino acid sequence showing a particular structure or function), able to induce or stop the process of biomineralization. On the one hand, they serve to initiate the proliferation of pulpal cells as well as the formation of odontoblastic progenitor cells.(1)

In principle, the evidence regarding the efficiency of the peptides, which were derived from molecules found in the extracellular matrix of the mineralized tissue, was obtained from animals, by stimulating dentine repair. It requires much work, as well as a partnership between academic and industrial research in order to transfer this laboratory experiment to a clinical application and to organize studies at a scale larger than even before.

This collaboration would enable the development of base materials for the implantation of biomolecules, adapted for the use in dentristy, as well as making laboratory and clinical trials possible in order to verify and elaborate the optimal conditions for their use in therapy.(1)

This kind of biotherapy was initially realised by capping with calcium hydroxide, and more recently with calcium silicate cement (MTA™, Biodentine™).

It was observed that the bioactive molecules brought by these materials can increase the rate of repair, but they can also offer a good treatment choice for the more stable pulpal lesions.(1)

The cell therapy used today, involves restoring the functions of the injured tissue or organ by implanting cells, which were initially amplified in vitro, into the injured organ or tissue.

The research conducted with the help of cell therapy is used today in various fields. One example would be the treatment of large scale burns. It is estimated that a rare appearance of an uncontrollable effect of the multipotent cells is possible, through ectopic differentiation and the development of tumours.(1)

In dentistry, the use of stem cells is not yet developed. At the level of the pulpal tissue, a relatively isolated organ, the dispersion risk of the implanted cells is apparently lower than in other organs.

Cell therapy should be considered in the case of severe pulpal lesions, which are regarded as irreversible and whose treatment is the total removal of the pulpal tissue.

Dental pulp is a reservoir of mesenchymal stem cells, more accessible than those found inside the bone marrow. These can be obtained without major injury, for example, from exfoliated deciduous teeth or from premolars and teeth, which are going to be extracted for orthodontic purposes.

Several stem cell populations have been found inside the dental pulp, suggesting the existence, as within the bone marrow, of a hierarchy of specimens with a lesser or greater potential for differentiation.(8,9)

Pulpal stem cells are obtained trough the usage of isolation procedures, which differ depending on the laboratory (enzymatic digestion versus explant culture), as well as trough a

selection based on their expression of surface markers, which all mesenchymal stem cells have in common (STRO-1 +). Cells from deciduous teeth or SHEDs (Stem cells from Human Exfoliated deciduous teeth) have a higher proliferation potential and a larger differentiating capacity than the isolated pulpal cells, which were obtained from permanent teeth, thus sparking a greater interest for cell therapy.(8,9)

The cell therapy for severely injured dental pulp, involves implanting a tissue, which was artificially formed from a three-dimensional matrix inseminated with pulpal stem cells, into the empty pulpal space, which formed as a result of the techniques used for the total removal of the pulpal tissue.

The purpose of this implantation is to maintain the vitality of the tooth, trough the formation of new vascular and nervous tissue inside the pulpal space, which was formed as a result of the total removal techniques, allowing the avoidance of difficulties arising from the conventional endodontic treatment. In the development of an artificial dental tissue, the following aspects must be observed:

- Rapid neovascularisation capacity of implanted tissue, essential for maintaining itself;
- Conversion of the new differentiated cells into odontoblastic type cells under the existing dentinal wall, inside the pulpal chamber space;
- Formation of dentin at the pulp periphery, by these new differentiated cells.

Despite the difficulties caused by the implantation of such tissue into the pulpal chamber, due to:

- closed space;
- severe hypoxia;
- the difficulty of tracking cells in a highly mineralized tissue with conventional imaging methods used for cell tracking, this cell therapy is now studied by several research teams within the international scientific community. Its feasibility has already been proven through studies performed on animals.

It is considered that there is room for other uses for the DPSCs in cell therapy, given the fact that these cells are capable of producing osteogenesis, chondrogenesis, adipose tissues, endothelial and neural tissue. This ability puts DPSCs as alternative cells to bone marrow mesenchymal cells and expanding their therapeutic potential to other tissues than the teeth, should be considered.

In this regard, a lot of clinical and laboratory research has been done. The first published therapeutic trial shows that the implantation, into the mandibular bone defects, of collagen sponges impregnated with dental pulpal cells, allows a faster and more substantial bone healing, than the untreated side of the mandible.(10)

Conclusions:

An innovative therapeutic field is opened by the treatment of dental pulp lesions through biotherapy, which involves the activation of pulpal stem cells with the help of biomolecules or by the direct implantation of pulpal stem cells. Depending on the choice (judgment) of the public authorities and the position of the Ethics Committee, the therapeutic use of adult pulpal stem cells can be applied to humans. At the same time, a depository of potential cells can be established and these can be managed by university hospitals or with the help of public institutions.

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