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ТКАНЕВАЯ ИНЖЕНЕРИЯ В СТОМАТОЛОГИИ

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TISSUE ENGINEERING IN DENTISTRY

Аннотация. Данная статья посвящена методам тканевой инженерии, применяемым для выращивания зубов из стволовых клеток. Основная цель статьи это собрать информацию о типах клеток с потенциалом многолинейной дифференциации, оценить возможность применения данной технологии в стоматологической практике. Также в статье выявлены требования к скаффолдам для наиболее успешной реконструкции тканей и основные проблемы трансляции экспериментальных разработок в стоматологическую клинику.

Ключевые слова: тканевая инженерия, стоматология, стволовые клетки.

Abstract. This article is devoted to the methods of tissue engineering which are used for growing teeth from stem cells. The main goal of the article is to collect information about cell types with multi-linear differentiation potential, and to estimate the possibility of using this technology in dental practice. The requirements to scaffolds for the most successful reconstruction of tissue and the main problems of translation of experimental developments to the dental clinic are revealed in this article.

Keywords: tissue engineering, dentistry, stem cells.

Introduction

Tissue engineering is a set of methods and procedures aimed at biological tissue regeneration. It includes a triad of basic elements: stem cells, extracellular matrix or scaffold, growth factors and signaling pathways. The purpose of tissue engineering is to replace lost cells, tissues and organs, either to promote their regeneration or simply to restore their damaged function.

Stem cells

Stem cells are undifferentiated embryonic or adult (postnatal) cells capable of passing through a huge number of cell divisions, being in an undifferentiated state, as well as of forming intermediate cell types - precursors that can differentiate into different cells and create complete tissues and organs. Stem cells are not only embryonic, but also postnatal. As for "grown-up" stem cells, they exist in various tissues in the body, including bone marrow, blood vessels, liver, skin, adipose tissue and dental tissues. They are located in special niches, where their proliferation, migration and life expectancy are regulated. Postnatal stem cells are multipotent, they give rise to only one type of cell.

Dental stem cells represent a population of postnatal mesenchymal stem cells (MScs) capable of self-renewal and differentiation. Depending on the localization of MSc depots, they are subdivided into:

- Pulp stem cells;
- Stem cells of the apical papilla;
- Stem cells of extracted baby teeth;
- The precursor cells of the dental follicle;
- Periodontal ligament stem cells;
- MSCs derived from the alveolar process;
- Gum MScs;
- Progenitor cells (MScs aimed at differentiating only into specific types of cells) of the embryo.

Technological structure of tooth tissue engineering

Tissue engineering uses a tooth: 1) living cells; 2) materials imitating the extractant matrix (ECM) and 3) molecules inducing tissue regeneration.

Tissue engineering uses natural stem cells and induced pluripotent stem cells (iPSC). As a result of certain manipulations, these cells can acquire the phenotype required for tissue growth. For dental tissue engineering, the best source of the stem cells is the tooth itself, because tooth stem cells, unlike other stem cells, may have the ability to induce growth a tooth. Stem cells are extracted from the tooth pulp (DPSC), periodontal ligament (PDLSC), dental follicle (DFPC), papilla (SCAP) and milk teeth (SHED).

The use of stem cells in tissue engineering requires scaffold and growth factors. The ideal scaffold should support the attachment, migration, proliferation and spatial organization of cells.

In general, scaffold as a suitable matrix for tissue reconstruction should meet the following requirements:

1. Ease of use.
2. The presence of pores of a certain shape and size for cell diffusion, growth factors, nutrients and removal of vital products.
3. Ability to biodegradation, which occurs at a certain time without releasing toxins.
4. Biocompatibility with body tissues.
5. Low immunogenicity.
6. Ability to replace with regenerating tissue and vascularization.
7. Good physical and mechanical properties.

Interaction of the scaffold with cells and factors growth determines the success of tissue growth. Therefore, the scaffold obtained from ECM (ECM-Scaffold) is the best.

In addition to scaffold and stem cells, it is necessary to have a binding link that would regulate tissue growth. This may be the growth factors, certain genes and interfering RNAs.

Growth factors are peptide molecules that transmit signals for cell behavior control and interact with specific receptors on the cell surface. They provide the interrelation and interaction between cells and the extracellular matrix. Following cell damage, the secretion of growth factors triggering further processes of regeneration and angiogenesis begins. An example of the "work" of growth factors in a tooth can be called the formation of secondary and tertiary dentin, which occurs when the carious cavity is close to the tooth pulp or when there is increased tooth erasure. Among the key growth factors during tooth development are bone morphogenetic protein (BMP), platelet growth factor (PDGF) and fibroblast growth factor (FGF). They are primarily used in tooth tissue engineering. Both cells and nanoparticles, as well as the scaffold itself, can be used to deliver growth factors.

Basic methods of tooth tissue engineering

Cellular tissue recombination technologies

The cellular tissue recombination technology consists of 5 stages: 1) extraction of the tooth embryo; 2) extraction of epithelial and mesenchymal cells from the tooth embryo; 3) unification (recombination) of both cell pools and cultivation to reproduce epithelial-mesenchymal interactions of odontogenesis; 4) in vivo transfer of the cellular-tissue construct into the subrinal capsule or in vitro before the formation of the bioengineered tooth embryo; 5) transfer of the tooth embryo into the tooth well. Thanks to this method it was possible to obtain the equivalents of dental tissue and an entire tooth.

Cell layer technologies

Another effective tooth bioengineering technology, cell layer technology, has enabled understanding another important feature of odontogenesis. This feature is that inhalation of epithelial cells into mesenchymal cells triggers odontogenesis. It turned out that the layers of cells are well attached to the tissues and have a good survival rate after implantation. Cell layer technologies are successfully used for periodontal tissue engineering, tooth root regeneration and tissue repair Pulp and Odontblast layers.

Cellular compartmentalization technology

Every stage of tooth development has a clear compartmentalization of epithelial and of mesenchymal cells. These stages were even called in the form of compartments of cells: "kidney", "cap" and "bell." This method reproduced the compartments of cells on early stages of odontogenesis. When using this method at the 1st stage, as well as in the methods of cellular tissue recombination and cellular layers, isolated epithelial and mesenchymal cells from the rudiments of the teeth. Further, in contrast to these methods, the two types of cells were not mixed and layered in layers, but were introduced into the collagen drop so that the mesenchymal the cell pool surrounded the epithelial one, imitating the compartmentalization of these cells at the stage of "cap" of the natural development of the tooth. Bioengineered rudiments of teeth, obtained by this method were placed in a sub-reinal the capsule and they formed complete teeth. Later, it turned out that the length of contact between compartments of epithelial and mesenchymal cells predetermines the crown width and the number of tubercles on the teeth.

Production technologies of bioengineered dental complexes

Another fruitful idea in the field of solving the issues of tooth integration with the recipient's tissues to first grow a bioengineering complex containing a mature tooth, periodontal ligaments, and alveolar bone, and then transfer the complex into a well in the jaw. The tooth complex transferred to the well has been integrated with bone, preserving the periodontal ligaments, and forming contact with the opposite tooth.

Problems in the translation of the tooth's tissue engineering into dentistry

Transferring or, in other words, broadcasting experimental developments in dental tissue engineering to a dental clinic is constrained by the lack of answers to several important questions.

1. Which cell type to choose?

In the experiment, the use of embryonic cells has led to good but caused many problems: the difficulty of obtaining autologous cells and the risk of tumor formation. Therefore, researchers have paid attention to autologous adult stem cells. Dental epithelial cells are in the Malasse network on the roots, but their fence is very complicated. Dental mesenchymal stem cells are found in the adult tooth. They are suitable for the regeneration of tooth tissues, but not for the growth of an entire tooth, because they do not have odontogenic potential. iPSC can increase the chances of translations of bioengineering of the tooth to the clinic, because they can be differentiated into epithelial and mesenchymal cells. Another source of cells for growing a tooth may be obtained by reprogramming the cell phenotype. For example, bypassing the iPSC stage, pancreatic cells were reprogrammed into β-cells. Probably, the cells of the mouth mucosa could be reprogrammed into dental cells in a similar way.

2. What technology to use.

Whether tissue should be grown in vitro or in situ is a complicated question. Conditions in vitro are more controllable. However, normal tissue formation requires a natural microenvironment, which is difficult to ensure in vitro. The existing technologies cannot yet reliably control the shape, color and number of growing teeth. This problem can be partially solved by first growing roots and then adding an artificial crown.

3. How to ensure the formation of supporting tissues, blood supply and innervation of the bioengineering product.

Paradont plays a key role in the attachment of the tooth, and blood supply and innervation play a key role in the regeneration and functioning of the tooth. For this reason, the bioengineered tooth needs to stimulate the formation of structures in order to transmit tissue engineering to the clinic paradontium, revascularization and reinnervation.

4. How to ensure that the bioengineered tooth develops within a clinically acceptable period of time.

It takes a long time to grow a human tooth, which makes it problematic to use such teeth as an alternative to implants. This problem can be solved by developing a way to accelerate the formation of human bioengineered teeth.

5. Will the transplanted bioengineered tissue grow in line with the growth of surrounding natural tissues and how it will change over time the properties of the transplanted tissue? There is evidence that through 20-30 years of age, this tissue can initiate tumor growth.

Conclusion

There are many reasons to believe that tissue engineering technology will help to produce the entire tooth complex, which consists of a single tooth and a periodontal tooth, and will largely replace the existing methods of teeth prosthetics. It is also important that teeth developed in tissue dentistry can help the development of other organ regeneration technologies and have an influence on all regenerative medicine.

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