

Gene therapy and its applicability in Dentistry

Terapia gênica e sua aplicabilidade na Odontologia

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ABSTRACT

Objective: Explore scientific publications on the use of gene therapy in dentistry. **Methods:** A bibliographic survey was carried out with articles published in the last eleven years, available on online platforms that had the highest correlation to the proposed theme. **Results:** Since the 1960s, researchers have attempted to establish guidelines for treatments using gene therapy; however, it was only in the mid-1990s that their use in science was authorized. Gene therapy in dentistry has the ability to alter and improve genetically, through stem cells in dental tissues associated with recombinant viral vectors, therapeutic protocols against diseases that do not respond to conventional treatments. **Conclusion:** The perspectives of dentistry concerning this resource have been positive, mainly in the reestablishment and regeneration of tissues in pulp pathologies, periodontopathies, bone disorders, orofacial pain among others. It is known that this form of therapy still requires more research, however, in the near future, it may be a safe first option treatment in hospital and outpatient settings.

Indexing terms: Dental Care. Dentistry. Genetic therapy.

RESUMO

Objetivo: Explorar publicações científicas acerca do uso da terapia gênica na Odontologia. **Métodos:** Foi realizado um levantamento bibliográfico com artigos dos últimos dez anos disponíveis em plataformas online que continham maior correlação com o tema proposto. **Resultados:** Desde os anos 60 pesquisadores tentam estabelecer diretrizes para tratamentos com a terapia gênica, no entanto, somente em meados dos anos 90 o seu uso na ciência foi autorizado. A terapia gênica em odontologia tem a capacidade de alterar e melhorar geneticamente, através de células-tronco em tecidos dentais e sua associação a vetores virais recombinados, protocolos terapêuticos contra enfermidades que não tem resposta aos tratamentos convencionais. **Conclusão:** A perspectiva da odontologia diante deste recurso tem sido positiva, principalmente no reestabelecimento e regeneração de tecidos em patologias pulpares, periodopatias, distúrbios ósseos, dores orofaciais entre outros. Sabe-se que esta terapia ainda requer muitas pesquisas, entretanto em um futuro próximo poderá ser um tratamento de primeira escolha e de forma segura nos ambientes hospitalares e ambulatoriais.

Termos de indexação: Terapia genética. Odontologia. Assistência odontológica.

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INTRODUCTION

In 1850, austrian monk Gregor Mendel, in his experiments with peas, discovered and described genes and how they were arranged. In 1950, the double helix structure of the DNA was discovered by american biochemist James Watson and british biophysicist Francis Crick. Then, researchers discovered enzymes that separated the genes in a DNA molecule, uncovering the internal hereditary mechanism, which is extremely important in the world of science. Since then, medicine has benefited greatly from the discoveries in the area of genetics [1,2].

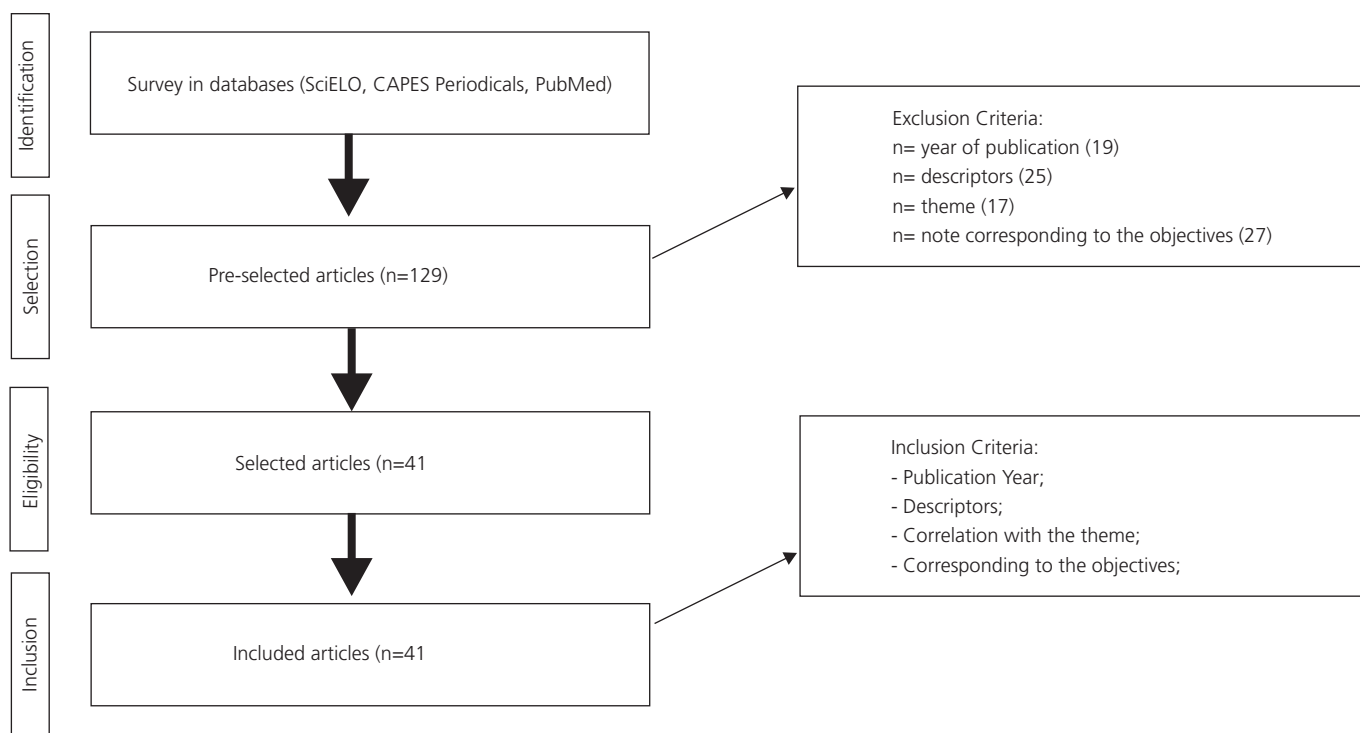
With the diversity of microorganisms and bacterial proliferation, it is difficult to control pathologies and homeostasis in the oral environment. Odontology has been employing technological resources in treatments through

gene therapy and recombinant DNA to repair the genome, manipulating and substituting defective genes for healthy genes and providing a certain relief of the symptoms or the cure of their ailment [3,4].

Since the 19th century, genetics has been evolving in a more pronounced way. With human genome sequencing, science has obtained information that helped in the processes of seeking human health. With the development of the researches, genetic engineering has evolved with greater capability to determine etiopathogenesis, the processes, the disorders caused by gene alterations, the genes responsible and the actions in modulations of metabolic defects for the prevention and treatment of the pathologies [1,5-7].

METHODS

Table 1. Flowchart with methodological data applied to research.



RESULTS

According to the selected publications, it was found that the use of gene therapy applied in several fields of odontology, aims to reestablish dentinary tissue,

restoring its functions and homeostasis. This therapy presented satisfactory results, when compared to current therapies, and as such, presents itself as a promissory form of treatment to pathologies, which do not respond successfully to conventional therapies.

Table 2. Applicability of the studies in Odontology.

Applicability of gene therapy in Odontology			
Author	Year of publication	Odontological field	Results of the studies
Ballantine et al. [1]	2017	Cariology	Verified the source of cellular differentiation and its potential regeneration of mineralized tissue in the control of caries.
Alkharobi et al. [8]	2018		
Madiyal et al. [9]	2018	Salivary glands	Modulation of the inflammatory processes and salivary fluid regulation.
Lai et al. [10]	2016		
Ferreira et al. [11]	2018		
Potdar & Jethmalani [12]	2015	Dentinary tissue regeneration	Accelerated differentiation of dentinary tissue from experiments with permanent teeth.
Sonoda et al. [13]	2018		
Atalayin et al. [14]	2016		
Kornman & Polverini [15]	2014		
Sharpe [16]	2016		
Pang et al. [17]	2016		
Aydin & Şahin [18]	2019		
Potdar & Jethmalani [12]	2015	Root tissue regeneration	Mesenchymal cell reprogramming and differentiation of pulpal tissue.
Akbar et al. [7]	2017		
Ledesma-Martínez et al. [19]	2016		
Sreedev et al. [20]	2017		
Volponi et al. [21]	2017		
Sharpe [16]	2016		
Anitua et al. [22]	2018		
Chen et al. [23]	2016	Periodontal diseases	Tissue differentiation with potential of autogenous source of periodontal ligaments.
Chen et al. [24]	2016		
Akbar et al. [7]	2017		
Kornman & Polverini [15]	2014		
Ledesma-Martínez et al. [19]	2016		
Volponi et al. [21]	2010		
Sharpe [16]	2016		
Aurrekoetxea et al. [25]	2015	Bone remodeling in Orthodontics and Implantodontics	Contributing to orofacial harmony and substituting metallic implants.
Vimalakshan et al. [3]	2018		
Madiyal et al. [9]	2018		
Padial-Molina et al. [26]	2015		
Enezei et al. [27]	2018		
Akbar et al. [7]	2017		
Ledesma-Martínez et al. [19]	2016		
Volponi et al. [21]	2010		
Sharpe [16]	2016		
Shanbhag et al. [28]	2016		
Aczél et al. [2]	2018	Orofacial pain	Controlling neural excitability with satisfactory response to orofacial analgesia.
Guedon et al. [29]	2015		
Shinoda [30]	2013		

DISCUSSION

The perspective of Gene Therapy

Since the 1960s, researchers have attempted to create protocols for the usage of gene therapies, however only in 1990 the FDA (Food and Drug Administration) authorized the first protocol. In this protocol, two patients with primary immunodeficiency were submitted to genetic treatment and one of them was cured. Gene therapy is defined as the capability of genetic altering and bettering in the face of monogenic diseases, when conventional treatments are not able to obtain success. Genetic intervention can provide good results in the regeneration of damaged tissues, with beneficial physiopathological alterations to the patient. The clonal genetic cells of the oral epithelium are capable of differentiating in ameloblasts and dental structures of bioengineering. When prepared in mesenchymal dental tissues, they can be used as regulating mechanisms of genetic expression associated with amelogenin and ameloblastin proteins [4,6,19,31-34].

The role of vectors

Vectors are codified viruses with the potential to enter cells and perform a carrier function, transporting nucleic acids DNA and RNA. This causes subsequent modifications in the usual expression of the host cell. Among the most studied vectors is the retrovirus from the family Lentivirus. Nowadays, it is among the most used, precisely because of its low chance to provide contraindications [7,35,36].

Applicability in Odontology

In 2006, the International Society For Cellular Therapy defined and authorized criteria on multipotent cells and their molecular processes in odontology. Stem cells offer regenerating potential in various tissues, with the ability to reestablish enamel, dentin, periodontal ligaments, pulp, dental papilla, periosteum, periapical follicles, salivary glands, bones and nerves. This granted bioengineering a field of activity and development to work with patients who have craniofacial alterations that require tissue regeneration due to trauma or pathologies. Thus, various branches of odontology can benefit from this technology [5,7,15,16,19,21,34,36-38].

Genetics X Kariology

Dental caries are chronic, multifactorial diseases, caused by the formation of bacterial biofilm in susceptible teeth and is considered a public health concern. With the advent of the genome sequencing of the *Streptococcus mutans* bacterium, it is possible to analyse the functionality, influence and interaction in the formation of caries. When affected by caries, the dentinal tissues act in defense of their dental pulp, stimulating the formation of a hard mineralized tissue, in other words, a reactionary dentin, difficulting the destruction of the vascularised subjacent pulpar tissue. Studies try to analyse if, when stimulated by these pluri and multipotent cells, the odontoblasts can be sources of differentiation with potential for regeneration of the mineralised tissues [1,8].

Correction of the salivary secretory glands

Deficiency in the salivary secretory glands implicate in oral morbidities such as caries, gingivitis and periodontal diseases. People with autoimmune conditions such as Sjogren's Syndrome or who went through head and neck radiotherapy have their oral homeostasis compromised due to hyposalivation. Researches and treatments through genetic transcription showed beneficial modulatory effects, treating inflammatory processes and regulating the fluids of the secretory glands. Thus, high expectations guide the reestablishment of the oral homeostasis resulting from use of these new technologies [9,10,11].

The use of molecular biology in the regeneration of Dentinary Tissues

For there to be regeneration of a specific type of tissue, a triad of stem cells, molecular induction for the tissue proliferation and a support structure is necessary. Researches were made using stem cells and it was discovered that stem cells from dental elements are much more potent, being able to differentiate into several types of craniofacial tissues. According to studies performed in permanent third molars, signs of induction and tissue proliferation could be observed. In a certain amount of time, these cells differentiate into others of odontoblastic tissue, that have similar morphology to the formation of dentin. The stem cells from the permanent teeth had their

differentiation more accelerated than those of primary teeth, due to being more mature [12-16].

Stem cells in the treatment of periodontal diseases

Periodontal diseases are pathologies with a chronic inflammatory origin, which cause alterations to the supporting tissues, damaging the periodont. It is a great challenge to establish a new formation of periodontal ligaments, but studies indicate that the cells in the periodontal ligaments are progenitor cells, and, when stimulated, have regenerative and multipotential capacities. The ligament cells which were stimulated by gene therapy were isolated and cultivated with the intention to analyse their capabilities. Layers of stem cells designed to facilitate the cell implantation along an anchorage of fibril and acellular cement presented results of cellular differentiation into osteoblasts, cementoblasts, adipocytes and fibroblasts. In vivo studies demonstrated tissue regeneration, proving periodontal ligaments can be an autogenous source of great importance to assist in the regeneration of periodontal diseases [7,15,16,19,21,23,24].

On the regeneration of root tissues

Injuries caused by pathologies on the root tissues have been a major concern in odontology. Studies into the reprogramming of mesenchymal cells and transduction with retroviruses show great efficiency in the reproduction and differentiation of pulpar tissues. These cells were put inside a root canal system along with biological modulators and with the induction of blood clotting, which signaled the formation of a cellular matrix, similar to the pulp, with vascularization and mineralised tissues such as dentin. There is still a substantial discussion to be had concerning this technology and the real possibility of reestablishing a necrotic pulpar tissue. More researches and analysis are necessary to confirm the indications until it is applied in clinical practice [7,12,16,19,20,21].

Gene therapy in bone remodeling, Implantodontics and Orthodontics

Researches with tissue engineering and genetic therapy have been of major importance in concern to the treatment of morbidities and bone repair needs caused by

trauma, pathologies and orthodontic movement needs. The cells that differentiate into osteoblasts and osteoclasts act inhibiting the mechanism of bone resorption. Thus, studies have assisted in the aesthetic and functional reestablishment in the area of bone remodeling. Treatments using recombinant human protein to fill alveoli post tooth extraction for the increasing of the alveolar ridge, and for the repair of bone resorption are more promising than traditional grafting (allograft, xenograft and aloplast). The gene BMP2, which is located in the chromosome 20p12, after transcription, forms a homodimeric protein with subunits of 114 amino acids, performing a regulatory and hematopoietic development function, with the differentiation of osteoblast, chondroblast, mineralization and bone remodeling cells. The continuity of these studies is still imperative due to the lack of consensus regarding the amount of protein necessary for the production of tissue, which can cause troubling changes, such as soft tissue edema, but the success of the technique with the assistance of genetic therapy is proven in the face of research. The cells from apical papilla from unerupted third molars are known as stems and differentiate into odontoblasts and adipocytes, and, along with stem cells are able to form a biological root to reestablish the orofacial harmony with an implant. These cells are similar to embryonic cells and would substitute a metal implant [3,7,9,16,19,21,25,26].

Gene therapy in the treatment of orofacial pain

Orofacial pains are reported as acute or chronic and are responsible for changes in the quality of life of the individual, being considered a public health problem. Studies with gene therapy have assisted in the process of gene recombination. Molecules and enzymes are responsible for carrying anti-inflammatory cytokines mediated by transferences with vectors to specific regions of neurotransmitters in the central nervous system, controlling impulses and influxes related to neural excitability, which causes hyperalgesia. This study indicates that, in a short time span, there will be a satisfactory answer related to prolonged orofacial analgesia [2,28,29].

CONCLUSION

The research on stem cells and genetic engineering, especially those using viral vectors are considerable, which

assures the possibility of new alternatives for treatments and cure in the face of the need of reestablishment of oral health. It is known that more studies are still needed for gene therapy to be considered a first option treatment. However, with the analysis of all possible risks and benefits, it is possible to expect a promising future for the advance of these new gene technologies. Gene therapy is already a reality and odontology longs for its satisfactory results.

Collaborators

R Batista, C Arruda, Y Tavares, T Freitas and T Araújo, data acquisition, writing and evaluation of the article. A Ramos, article evaluation and guidance.

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