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Future perspective of cytokine therapy as emerging regenerative periodontal techniques

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Abstract

Cytokine therapy using basic fibroblast growth factor (FGF-2) has attracted attention as a next-generation periodontal tissue regenerative therapy.

Various studies have been taking place for the characterization of FGF-2, the focus has been on the biologic effects of its use on periodontal tissues. Histochemical studies have been successfully carried out and clinical trials are underway since the last few years. The clinical trials taken place on animals as well as human models have shown that local application of FGF-2 creates a favorable environment for new tissue formation. Evidence of neo alveolar bone formation has been observed.

Apart from in vivo studies, various in vitro studies have shown FGF-2 to be beneficial to wound healing. The mechanism by which this takes place is described by various authors in their studies. The way FGF-2 maintains stems cells in an undifferentiated state and later promotes their proliferation during wound healing is an important observation.[1]

In a study where topical application of basic fibroblast growth factor (FGF-2; (bFGF) to alveolar bone defects was done in beagle dogs results indicated that a topical application of FGF-2 can enhance considerable periodontal regeneration [2,5]

Keywords: cytokine therapy, fibroblast growth factor-2 (FGF-2), regeneration, growth factors, tissue engineering

Introduction

Dental biofilm and plaque which forms adheres to the teeth and also the mucosa and gingiva. The accumulation of plaque gives rise eventually to chronic inflammation leading to progressive destruction of periodontal tissues that support the teeth. The treatment for periodontal disease involves removing the etiological factor mechanically with scaling and root planning. The bacterial biofilm together with the necrotic cementum is removed from the tooth surface. Appropriate application of this therapy eliminates periodontal tissue inflammation and stops the process of destruction. However, removing the cause of the disease does not regenerate the lost periodontal tissue to its original state [1]

The goal of periodontal therapy should be not only to arrest the progress of the disease but to eventually bring back the lost parts that is to regenerate the lost tissues wherever possible. Conventional surgical techniques have been time tested and have been proven effective in gaining access to the root of the teeth, accessing pockets and also creating a harmonious hard tissue architecture. But these techniques have hardly any effect on regenerating what was lost during the early phases of the disease.

Recently, surgical methods and material that have been able to bring back the functional components and regenerate them to the original levels have been carried out with success.

Studies of regenerative medicine for periodontal tissue have shown that tissue stem cells that make the regeneration of periodontal tissue possible are present in the tissue surrounding the tooth root, known as the periodontal ligament, even in adults.

The knowledge about the availability and use of fetal stem cells is widely known. But the sources of adult stem cells and their use in various regenerative procedures has been of great importance to make process in the field of stem cell regeneration. Stems cells of dental origin have shown great capacity to be regenerated. Some of the sources of dental origin stem cells are-

1. DPSCs
2. PDLSCs
3. SHEDs
4. SCAPs

Non-dental stem cells in adults are BMSCs, ASCs and ESCs.

Thus a thorough knowledge about them all is necessary for their judicious utilization in the field of Periodontology.

Growth factors are naturally occurring cells or their products that are present during cell division. They have a positive effect on wound healing and regeneration. Our body naturally activates the grown factors from the tissue adjacent to the site of destruction or injury to help with the process of healing and regeneration. These growth factors have been known to recruit and increase the proliferation of periodontal ligament fibroblasts. They also increase the synthesis of collagen which in turn gives boost to an increase in new PDL formation. The growth factors that may contribute to periodontal regeneration include platelet-derived growth factor, insulin-like growth factor, transforming growth factor-beta, fibro blast growth factors, poly peptide grown factors and bone morphogenetic proteins.

One of these growth factors is the fibroblast growth factor 2 which is from the huge fibroblast growth factors family containing 22 members designated from FGF-1 to FGF-23 (except FGF-15)

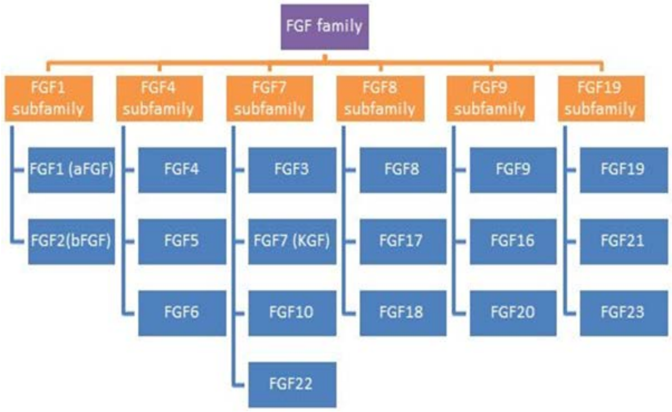

Figure 1:

Fibroblast growth factors have been proved in many animal and human studies to be extremely potent in inducing cell differentiation and proliferation especially FGF-2 which has shown to be a promising agent for wound healing and regeneration of periodontal tissues. FGF-2 induced a significant increment in the percentage of bone fill, bone mineral levels of the defect sites, length of the regenerated periodontal ligament, angiogenesis, connective tissue formation on the root surface, formation of dense fibers bound to the alveolar bone and newly synthesized cementum in teeth.

This article describes the options of cytokine therapy using FGF2 as a possible option to promote periodontal regeneration.

What is Fibroblast growth factor-2?

FGF2, also known as basic fibroblast growth factor (bFGF)and FGF-β,is a growth factor and signaling protein encoded by the FGF2 gene[3,4]

It binds to and exerts effects via specific fibroblast growth factor receptor (FGFR) proteins, themselves a family of closely related molecules. Fibroblast growth factor protein was first purified in 1975; soon thereafter three variants were isolated: 'basic FGF' (FGF2); Heparin-binding growth factor-2; and Endothelial cell growth factor-2. Gene sequencing revealed that this group is the same FGF2 protein and is a member of the family of FGF proteins.

- Possibility of Cytokine therapy

Stem cells migrating to the site of treatment and inducing regeneration is the best and most acceptable way in the field of periodontal regeneration.

The process is done to cause differentiation of osteoblast and osteoclasts via different methods. This is where cytokine therapy comes into play. Application of cytokines activate the differentiation of various cells required for periodontal regeneration.

In the USA, a combination of platelet-derived growth factor (PDGF) and β-tricalcium phosphate (β-TCP) (β-TCP + 0.3 mg/mL PDGF) has been approved by the US Food and Drug Administration (FDA) to induce regeneration of periodontal tissue, which is marketed as GEM21S®. Cytokines are also applied in dentistry using a combination of bone morphogenic protein-2 (BMP-2) and bovine type I collagen, which has also been approved by the US FDA as a medical device used in alveolar ridge augmentation procedures and sinus elevation surgery. Thus, human recombinant cytokines are beginning to be applied in the field of dentistry. [1]

- Biological Functions of FGF2

The following are the biological functions of FGF-2 which facilitate regeneration of periodontal tissues-

1. Cell proliferation: cell proliferation of many cells have been observed, some of them are the Epithelial cells, endothelial cells and stem cells. Since FGF-2 promotes the proliferation of these cells, it can be used for periodontal regenerative procedures where cell proliferation is of utmost importance.

2. Cell migration: In multicellular organisms, cell migration plays a major role in growth and

development. Maintenance also requires cells to move from a particular location and in a specific direction. Migration of cells takes place by the process of chemotaxis. The cells migrate in response to certain signals. They often migrate to the site from where the signals are being transmitted. In an article by Holland EC, Varmus HE namely 'Basic fibroblast growth factor induces cell migration and proliferation after glia-specific gene transfer in mice', it showed that FGF-2 causes migration after the flia specific gene transfer.[13]

3. Cell differentiation: In multicellular organism's cell division takes place multiple time so that the undifferentiated and less specialized cells become more specialized. In developmental biology, cell differentiation plays a major role to change a single zygote to multiple specialized cell types with specific features and function. All types of FGF especially FGF-2 plays a major role in cell differentiation.

4. Angiogenesis: New blood vessels being formed from blood vessels that are already present is angiogenesis. Angiogenesis is a multistep process that begins with the degradation of the basement membrane by activated endothelial cells that migrate and proliferate, leading to the formation of solid endothelial cell sprouts into the stromal space. Next, vascular loops are formed and capillary tubes develop with the formation of tight junctions and deposition of new basement membrane. Angiogenesis has been known to be brought about by vascular endothelial growth factors (VEGF), angiopoietins, tumor necrosis factor- alpha (TNF-alpha), interleukins and chemokines etc. FGF-1 and FGF-2 are known to have angiogenic properties. They encourage angiogenesis by inducing promotion of endothelial cell proliferation and physical arrangement of the endothelial cells into tube shaped structures. Comparisons have been made between vascular endothelial growth factors (VEGF) or platelet derived growth factor (PDGF) and FGF-2 has proved to be more angiogenic

FGF2 inducing periodontal regeneration in periodontal tissue

Fibroblast growth factors (FGFs) are a group of proteins that promote fibroblast proliferation and were discovered in the brain and pituitary gland tissue. This family of proteins comprises FGF-1 to FGF-23.

Among these, FGF-2 induces the proliferation of a wide variety of cells, including fibroblasts, vascular endothelial cells, neuro ectodermal system cells, osteoblasts, chondrocytes, vascular smooth muscle cells, and epithelial cells. FGF-2 has attracted attention in the field of regenerative medicine because:(1) FGF-2 has potent angiogenesis-promoting action and (2) FGF-2 promotes the cellular proliferation of undifferentiated mesenchymal cells while retaining their pluripotency. An example of the clinical application of FGF-2 is as a therapeutic agent for intractable skin ulcers, such as decubital ulcers.

Mechanism of action of FGF-2 as described by Toshie Nagayasu-Tanaka et al on-beagle dogs in 2015 suggests the following

1. The fibroblastic cells derived from the bone marrow and PDL are accelerated and they produce new cells which help to form new tissues.
2. FGF-2 enhanced angiogenesis.
3. BMP-2 is known to cause osteoblastic differentiation and formation of new bone. FGF-2 is known to promote the expression of BMP-2. It proves to be very useful in the initial stages of periodontal regeneration.
4. Increases the presence by stimulating various fibroblastic cells like mesenchymal cells and promotes healing and angiogenesis.

5. As healing takes place, during 3rd to 7th day after application of FGF-2 its During subsequent healing processes, probably at 3–7 days after application, when FGF-2 activity disappears gradually at the administration site, the fibroblastic cells begin to differentiate into osteoblasts, cement oblasts, and PDL cells, inducing marked periodontal tissue regeneration.

6. FGF-2 shows visible and significant difference when used in periodontal regeneration. So based on many of the studies conducted by multiple authors the topical application of FGF-2 in periodontal defects helps to speed periodontal regeneration. [9]

Mechanism of induction of periodontal tissue regeneration with FGF-2. FGF-2 strongly promotes the migration and proliferation of immature human periodontal ligament (PDL) cells while retaining the cells' differentiation potential and increases the number of periodontal tissue stem cells at the site of periodontal tissue loss. Furthermore, FGF-2 promotes the production of angiogenesis and various extracellular matrices at the administration site, creating a suitable local environment for "periodontal tissue regeneration"

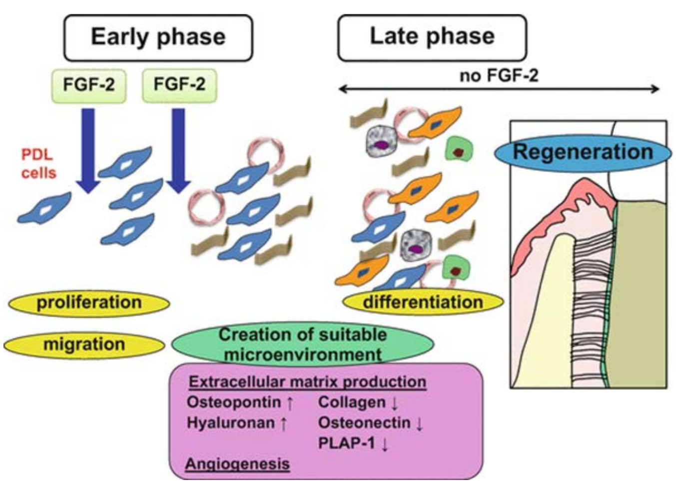

Figure 2:

Future trend of cytokine therapy using FGF2

The studies that have been carried out using FGF-2 have been using it as a drug only to check the efficacy and safety.

There have been no studies of using FGF2 with scaffolds for periodontal regeneration though some clinical studies are underway. Next step in the world of cytokine therapy would be to engineer a carrier that can make the use of FGF2 more efficient.

According to Anzai J et al in a study where The effects of concomitant use of fibroblast growth factor-2 (FGF-2) and beta-tricalcium phosphate (β-TCP) on periodontal regeneration were investigated in the beagle dog 1-wall periodontal defect model was studied it has beenq established that administration of 0.3 % FGF-2 with β-TCP increased bone mineral contents of the defect sites compared with β-TCP alone. This study also throws light on efficacious use of as an osteoconductive material for periodontal regeneration following severe destruction by progressive periodontitis. (10)

In human studies, by Kitamura, M et al. results strongly suggest that topical application of FGF-2 can be efficacious in the regeneration of human periodontal tissue with no adverse effects reported. (12)

If a new carrier for FGF-2 preparation is developed that can retain the space (space-making) at which the regeneration of periodontal tissue is expected, and with the appropriate formativeness and osteoconductive properties required by operators, the application of FGF-2 preparations is expected to be further broadened.

Additionally, the results of animal experiments suggest that if the 0.3 % FGF-2 preparation is used concurrently during dental implant surgery, the healing time to achieve osseointegration will be shortened and robust integration will be achieved; further verification of these concepts is required in the future. (11)

Delivery systems for FGF-2

FGF-2 have the potential to bring about regeneration of a wide spectrum of tissues like skin, blood vessels, muscles, bone, tooth, nerve tissue etc due to their biological functions and roles. In various in vivo studies it has been observed that FGF-2 loses its biological functional activity mainly due to enzymatic degradation and diffusional loss. So for optimal results a large dose of FGF-2 is required for prolonged periods.

To make up for this shortcoming, FDF-2 encapsulated with or adsorbed to a certain material is advisable. A large amount of materials both natural and synthetic have been studied in vitro and in vivo as carriers for FGF-2.

Scaffolds for FGF2

Beta tricalcium phosphate(β-TCP)

Study done on dogs for intrabony defects by Yosei Ol et al in 2009 combined effect of β-tricalcium phosphate and basic fibroblast growth factor. The study suggested that FGF-2 used with this scaffold accelerated and enhanced cementogenesis and osteogenesis.[14]

A similar study was done where the safety of beta tricalcium phosphate was evaluated and was found to fulfil all safety protocols. It was also proven to be effective in periodontal regenerative treatment.

Collagen based scaffold

In a study done on rats, by Kobayashi et al in 2010, FGF2 was used with a collagen gel sponge composite scaffold to evaluate if it stimulates bone augmentation.

Study on Beagel dogs by K. Okawa et al in 2016 fabricated a regenerative scaffold comprising type I collagen and beta-tricalcium phosphate (β-TCP) nanoparticles. If the collagen scaffold is coated with beta tricalcium phosphate then the property of collagen is enhanced. This combination has been effective in the field of tissue engineering.[15]

Poly lactic-co-glycolic acid (PLGA)

Poly galactic co- glycolic acid used along with plasmid DNA encoding fibroblast growth factor-2 was studied by Liming Jiang et al in 2020 in a clinical study. It was known to produce periodontal ligament regeneration. The results were studied in vitro. Hence use of poly lactic co glycolic acid in regenerative therapy as a scaffold for FGF-2 should be extensively studied.[16]

Silk

A silk scaffold loaded with growth factors like FGF-2 and Vascular endothelial grown factor was tested to find ability of the pre adipose cells to grow and differentiate. A study done by Henning Haken et al in the year 2016, Silk was claimed to be a possible and promising biomaterial for scaffold formation.[17]

Bioactive glass nanospheres (MBNs)

The novel method was used In a study done by Min Sil Kang in the year 2015 to use a nanofibrous scaffold as a therapeutic device to carry growth factors. The Mesoporous form of bioactive glass nanospheres was used as a nanocarrier for long term delivery of FGF18, FGF-18 is an osteogenic enhancer.

After this end eavour modified form a core–shell structure of a biopolymer fiber made of polyethylene oxide/polycaprolactone was introduced to load FGF2. The conclusion discusses the use of MNVs as a safe and effective platform for the delivery of FGF-2. This method should se studied and utilized in periodontal regenerative field for optimisation of the effects of cytokine therapy. [18]

Water bourne polyurethane (WPU)

Waterbourne polyurethane are fibrous membranes that when used as scaffold can be used for GTR and GBR procedures in periodontology.

Chi Zang et al in 2021 by the method of emulsion electrospinning loaded the WPU membrane with FGF-2. The result of his study should regeneration of periodontal tissue because of the vascularization of the biomimetic GBR membrane.[19]

Conclusion

The field of periodontology is unique in a way that allows us to use a variety of materials and methods to bring about varied results.

It is considered that the amount of regeneration is directly proportional to the amount of tissue lost and the degree of periodontal destruction.

One of the emerging branch in the field of periodontal regeneration is the use of FGF-2. Studies on Cytokine therapy regarding its effects, safety and feasibility should be done so that this treatment option is used on a large scale wherever indicated for regenerative periodontics therapy by combining optimal conditions with cytokines, stem cells, and scaffolding materials.

A major challenge to find an optimal scaffold for delivering FGF2 should be overcome with vigorous research. In the near future, we hope to establish patient-specific periodontal tissue regenerative procedures using cytokine therapy.

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