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Review Article

Harnessing growth factors in endodontics

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Abstract

The primary objective of regenerative endodontic therapy is to re-establish the pulp-dentin complex in an immature permanent tooth with necrotic pulp that has been damaged by injury, inflammation and infection. The technique known as "cell homing," which effectively regenerates tissue at the site of tooth injury by attracting indigenous stem cells, is the foundation of this novel therapy. Many growth factors are involved in a complicated signalling network that controls this complex process. It is crucial to comprehend specific parts played by these growth factors throughout the regeneration and repair of dental tissue, such as orchestrating cell migration and differentiation. This review, summarizes the current understanding of the key growth factors, their involvement in dentin-pulp repair and regeneration and the challenges in completely regenerating the pulp-dentin complex.

Keywords: Signalling, Dentin-pulp regeneration, Growth factors.

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1. Introduction

Physical or microbiological trauma to the tooth pulp can result in pulp inflammation, which can subsequently lead to infection and necrosis. In these cases, non-surgical root canal treatment in teeth with mature apexes and apexification in teeth with immature apexes are the treatment options. However, as a result of these procedures teeth lose their sensitivity, vitality, and defence qualities.[1] In recent decades, the treatment protocol for non-vital permanent teeth with immature apex has changed towards new treatment methods, called Regenerative Endodontic Procedures. The ability to reinstate the vitality of injured tissue in the root canal and encourage maturation of root in a permanent non-vital tooth with open apex gives regenerative endodontic procedures an advantage over apexification procedures. Regenerative endodontic therapies integrate the principles of cellular biology, and tissue engineering and endodontics to treat inflamed and necrotic pulp. It makes use of three main components: Scaffolds, mesenchymal stem cells and growth factors (GFs).

1.1. Dental stem cells

Gronthos *et al*[2] discovered the stem cells in dental pulp in 2000. Due to their potential to create dentin-pulp complex, eventually they were referred to as dental pulp stem cells (DPSC). Several other stem cells were eventually discovered in oral cavity, including Stem Cells of the Apical Papilla (SCAP), Stem Cells of Human Exfoliated Deciduous teeth (SHED), and Periodontal Ligament Stem Cells (PDLSC).

DPSC are multipotent cells with the potential to differentiate into odontoblasts- like cells, osteoblasts, adipocytes, melanocytes and endothelial cells. They can form mineralized tissue and undergo neurogenesis.[3,4] In comparison to DPSCs, SHED have a greater osteoinductive activity and neurogenic potential *in vivo*.[5] In a co-culture with DPSCs, PDLSCs have shown upregulation of dentin sialoprotein and dentin sialophosphoprotein, however they can't induce mineralization.[6]

1.2. Growth factors (GFs)

For the recruitment, migration, proliferation and differentiation of dental stem cells, GFs are essential. By

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attaching to particular cell membrane receptors and starting complex intracellular signalling cascades, GFs affect the behaviour of individual cells. Cytokines are immunomodulatory proteins or polypeptides, involved in cell signalling. Cytokines and GFs are often used interchangeably due to their similar activities. GFs and cytokines have a local effect on target cells, unlike hormones which have systemic effects. They may act in endocrine, autocrine, paracrine manner. GFs have relatively low molecular weight, usually less than 25 kDa. They exhibit varying dose dependence and specificity with regard to cell they act upon. GFs regulate stem cell function by promoting proliferation, differentiation into several lineages, and stimulating them to secrete mineralized matrix. Their efficacy at very low doses, usually in the picogram range, is one of their defining characteristics.[7]

2. Mechanism of Action

Typically, a GF is produced by a signalling cell and recognized by a target cell by means of a surface receptor, which detects the signal and specifically responds to that GF. Tyrosine kinase domains can be found in the intracellular regions of receptors for several GFs. GFs transmit the extracellular signals by attaching to the specific receptors expressed on the target cell membrane, which initiates a series of intracellular signals, causing phosphorylation of certain protoplasmic molecules known as intracellular messengers. This leads to relaying of signals from the cell membrane inside the cell nucleus, which triggers the activation of transcription genes for a brief amount of time and the transcription of the gene into its mRNA and the ensuing synthesis of protein in the cell, leading to a response. (**Figure 1**)

3. Growth Factor Delivery

In conventional experimental studies GFs were directly applied in culture medium. However, direct application has various drawbacks, including low retention of GFs, due to which high concentration of GFs must be administered for a specific biological effect, potential toxicity of excessive GF concentration on cells, half-life of free GFs and a challenge of maintaining optimum GF concentration during the course of the therapy. Several polymeric and inorganic material based controlled GF releasing systems have been developed to overcome these drawbacks (**Figure 2**). These are following:

1. Polymers: They offer various advantages such as: prevent GF from degradation by their encapsulation; provide localized and sustained release of GFs guaranteeing the release of critical concentrations of GFs throughout tissue regeneration and potential to offer structural support which allows tissue ingrowth during tissue regeneration.[8] These are designed from biodegradable and biocompatible natural or synthetic polymers, for dentin-pulp tissue engineering.[9]
   a. Natural polymers: Biopolymeric materials like collagen, alginate, chitosan and hyaluronic acid have been employed in dentin-pulp tissue engineering,[10,11,12,13] due to the presence of favorable qualities like biocompatibility and biodegradability. Hyaluronic acid (HA) is a naturally occurring polysaccharide which is chief component of extracellular matrix of epithelial and connective tissue. It degrades quickly *in vivo* but has poor mechanical strength.[14] Alginate is a naturally occurring polysaccharide, which can serve as appropriate matrix for tissue regeneration to occur. Chitosan is a N-deacetylation product of chitin. It is antimicrobial, biocompatible, biodegradable to non-toxic byproducts. Several drawbacks of natural polymers still remain such as, variability in different batches, possible immunogenicity, sterilization induced inactivation of GFs, and manufacturing expenses.[15]
   b. Synthetic polymers: These were developed due to their easy processing and the capacity to precisely modify their physical, chemical and mechanical properties as needed for various applications. Available as solid scaffolds, nano-particles or hydrogels, depending upon the mechanical and degradative qualities and the method of administration for specific application. Hydrogels can be used as injectable matrices, while solid scaffolds require more invasive delivery. Synthetic hydrogels are water-soluble polymers that are cross-linked, which swell in the presence of water to form a gel; examples are poly (vinyl alcohol) and poly (ethylene glycol), Poly(lactide-co-glycolide).
2. Inorganic materials: They have a high compressive strength and are biodegradable, however they don't have intrinsic mechanisms for the regulated release of GFs. Thus, GF encapsulation or chemical conjugation to the material surface is done; examples calcium/ phosphate materials, glass ceramics, bioactive glass and hydroxyapatite.

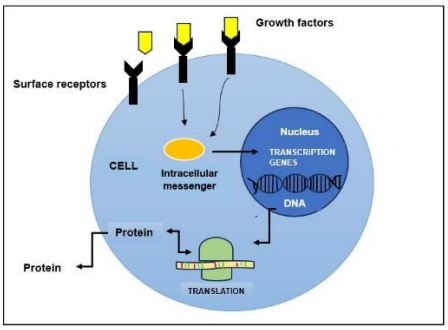

Figure 1: Transmission of the extracellular signals into the cell, via growth factors leading to activation of transcription genes, formation of mRNA, translation and formation of proteins, inducing a response.

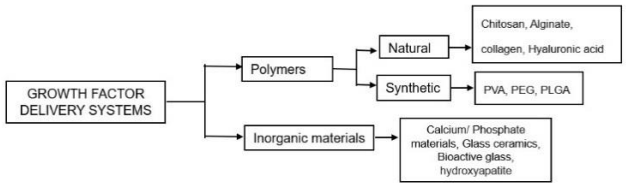

Figure 2: Different types of growth factor delivery systems.

4. Important Growth Factors

GFs support a number of processes involved in dentin-pulp repair and regeneration, including cell migration, cell proliferation and differentiation and angiogenesis. Following are the key GFs for tissue regeneration:

4.1. Transforming growth factor-β

It is a multifunctional growth factor, which is a representative of a large family of GFs with diverse activities. The term "multifunctional" suggests that TGF-β can either increase cell proliferation and growth or inhibit it, or have numerous other actions. TGF-β1 regulates cell proliferation, differentiation and reparative dentinogenesis, contributing to tooth development and repair. It promotes the formation of extracellular matrix and also induces odontoblast differentiation process both *in vitro* and *in vivo*.[16] TGF-β1 and TGF-β2 promote collagen matrix production in pulp fibroblasts. TGF-β1 was found to enhance the production of type I collagen in the odontoblastic/subodontoblastic zone, in tooth slices.[17] TGF-β inhibits the synthesis of proteolytic enzymes that break down matrix proteins while activating gene transcription to increase the synthesis and secretion of matrix proteins.

4.2. Bone morphognetic proteins (BMP)

BMPs are multi-functional growth factors. They are constituents of the transforming growth factor β superfamily, except for BMP-1. BMPs are essential in guiding chondrogenesis and osteogenesis during embryonic development. BMP-2, -4, -5, -6, -7 and -9 have highest osteogenic potential. BMP-4 and BMP-5 are expressed during ameloblastic differentiation, while during odontoblastic differentiation BMP-2,-4,-6,-7 are expressed.[18] BMPs have shown potential as effective agents for induction of a mineralized barrier in pulp, when used in pulp capping procedures.[19]

4.3. Platelet derived growth factor (PDGF)

PDGF family includes five polypeptides: PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD. Capillary endothelial cells contain PDGF receptors that have been shown to have an angiogenic effect. Capillaries produce PDGF-B chain, which recruit pericytes that are necessary to promote the structural integrity of the vessels.[20] PDGFs promote cell proliferation and dentin matrix protein production, but suppresses the action of alkaline phosphatase in dental pulp cells *in vitro*.[21]

4.3. Insulin like growth factor (IGF)

IGFs control proliferation and differentiation in several different types of cells. IGF-1 reduces apoptosis in cells and enhances their proliferation rates. IGF-1 have significant impact on the potential of dental MSCs to differentiate, inducing odontogenic and osteogenic differentiation of DPSC, PDLSCs and SCAPs *in vivo*.[22,23]

4.4. Fibroblast growth factor (FGF)

FGFs induce cell proliferation in a multitude of cell types, including endothelial cells, epithelial cells and mesenchymal stem cells. It is essential for regulation of bone development and differentiation. Furthermore, bFGF stimulates tissue repair, increases tissue regeneration, participates in neurogenesis, and serves as an angiogenic factor.

FGF-8 is a strong chemoattractant which induces mesencephalic neural crest cells to migrate. It prevents mineralization and encourages neural differentiation of DPSCs.[24] Angiogenesis is facilitated by FGF-1 and FGF-2, which causes endothelial cells to proliferate and physically arrange into structures resembling tubes. Compared to VEGF or PDGF, FGF-1 and FGF-2 are more formidable in inducing angiogenesis.[25]

4.5. Vascular endothelial growth factor (VEGF)

In three-dimensional *in vitro* models, confluent microvascular endothelial cells are observed to infiltrate collagen gels and form capillary-like structures in response to VEGF, which is known to trigger angiogenesis.[26] VEGF is essential for survival of endothelial cells.[27] VEGF has the ability to induce vascular permeability, demonstrating its important role in inflammation.

5. Growth Factors in Repair and Regeneration

5.1. Dentin-pulp complex repair

Tertiary dentin matrices are secreted at the sites of dental injury, via reactionary and reparative dentinogenesis. These matrices create Dentin Bridge over the exposed pulp or strengthen the dentin barrier between injured dentin and the underlying unexposed pulp. To replace the cells that perished as a result of the injury, the initial phase involves recruiting stem cells for later differentiation into odontoblast-like cells. TGF-β family, is chemotactic for mesenchymal stem cells. Primary signalling role of GFs is the initiation of cytodifferentiation of odontoblast-like cells from stem cells. The capacity of TGF-β1 and BMP-7 to stimulate reactionary dentinogenesis in unexposed pulps via odontoblasts in cultured tooth slices has been demonstrated. Release of matrix-bound GFs from the dentin during either an injurious or restorative process, potentially act as a signal for pulp stem cells to differentiate into odontoblast-like cells. Following differentiation, the deposition of the reparative dentin matrix and dentin bridge formation, requires incitement of the secretory action of the odontoblast-like cells. In the future,

biomaterials containing GFs can be developed as pulp capping agents to repair dentin-pulp complex. A study by Imura *et al*, applied a combination of HAP nanoparticle powder and FGF, which led to pulp tissue regeneration and creation of a dentinal bridge with countless dentinal tubules, as evidenced by histologic and radiologic findings.[28]

5.2. Dentin-pulp complex regeneration

Regenerative endodontics have three treatment outcomes: clinical signs and symptoms resolve; further apical closure occurs and neural regeneration occurs.

The term 'revascularization' was introduced by Iwaya *et al*.[29] As tissues regenerated in the root canal space included both hard and soft tissues in addition to blood vessels, later, instead of revascularization, revitalization was suggested.[30]

It was Iwaya *et al.* that introduced the concept of revascularization in a clinical setting to treat immature non-vital permanent teeth. Their idea was derived from the studies on the revascularization of immature reimplanted and auto-transplanted dog's teeth, as well the application of a combination of antibiotics, ciprofloxacin and metronidazole for root canal disinfection. Through their treatment, the clinical indicator of apical periodontitis was eliminated, the walls of root canal thickened, and the apical closure of the immature roots occurred.[29]

In addition to forming similar structure as the natural dental pulp, the optimal pulp regeneration procedure should also bring back the pulp's functionality. The following conditions should be met by functional dental pulp: new dentin should be deposited at a regular pace and density and it should resemble that of natural dental pulp, vascularity and nerve distribution.

5.3. Role of GFs in nerve regeneration

Several GFs promote nerve growth in regenerated pulp such as NGF, BDGF, bFGF, IGF, GDNF, EGF etc. A viable method for achieving effective pulp regeneration is to use GFs and chemokines to enhance the regeneration of pulp-like tissue and nerves.

Li and Wang administered a mixture of PDGF-BB, NGF, and BDNF, in teeth during root canal treatment and then implanted them in rats' dorsum subcutaneously. They discovered the creation of vascular pulp-like tissue with positive S-100 signals, which show that nerve fibers have recovered.[31] Kim *et al*. employed collagen gel to transfer a range of GFs, including FGF, into human teeth and then transplanted them into rats and discovered nascent pulp-like tissue undergoing blood vessels and nerve regeneration.[32]

6. Endogenous Source of GFS

6.1. Dentin matrix

Dentin matrix is a reservoir of GFs and a variety of GFs are embedded in the dentin matrix during tooth development. The release of these GFs is essential to facilitate the regenerative process after caries, dental trauma, or during revitalization procedures. A study by Ivica A *et al*. found that TGF-β1 is deposited in peritubular dentin with larger concentrations near the dental pulp, gradually decreasing near the periphery and it was found in both young mature roots and immature roots.[33] The regenerative process can be enhanced by the release of GFs with the use of ethylenediaminetetraacetic acid (EDTA), calcium hydroxide, mineral trioxide aggregate (MTA), dental adhesives, ultrasonic activation and epigenetic modulators.[34,35,36,37,38,39] Irrigation with 17% EDTA releases TGF-β from the dentin matrix. When it comes to eliminating the inorganic constituent of the smear layer and decalcifying dentin, citric acid is just as efficient as EDTA. Hristov *et al.* stated that 10% citric acid and 17% EDTA have no statistically significant difference when it comes to the effect on the vitality of SCAPs, therefore 10% citric acid can be used in conjunction with 1.5% NaOCl.[40] according to Chae *et al.* 10% citric acid is more biocompatible and effective in releasing TGF-β1 *in vitro* than EDTA.[41]

6.2. Blood clot

When intra-canal bleeding is induced, stem cells and GFs are released into the root canal space to promote pulp regeneration, and blood clot is formed that act as a scaffold. Because platelet concentrates (PRP, PRF) are high in GFs and may improve regeneration capacity, they have also been employed as a scaffold in place of blood clots. An important feature of Platelet concentrates is the persistent release of GFs for at least 7 days at the application site.

Several approaches have been explored to harness the regenerative potential of GFs for dentin-pulp regeneration, including:

1. Cell-based concept: Using tissue engineering concept, research in animal models, has demonstrated that it is possible to regenerate pulp-like tissue following stem cell transplantation in dentin discs, tooth slices and even complete tooth roots.[42,43] However, these investigations were carried out in a sterile environment as opposed to root canals in clinical setting, which will be infected. In a study by Srisuwan *et al*, DPSCs were combined with a FGF and BMP-4 mixture and transferred into a tissue engineering chamber, where the new generated tissue was found comprising blood vessels and DSPP- positive matrix.[44] Many obstacles need to be addressed in clinical practice, including accessibility and isolation of autologous stem cells, their storage and culture, handling and contamination of stem cells. Other problems include facilities that adhere to good manufacturing practices, government regulations and the clinician's expertise.
2. Cell homing concept: Recruitment of stem cells from their environment is a crucial step for regeneration and targeted tissue healing following damage. GFs and cytokines derived from dentin matrix, help in

recruitment of stem cells during tissue damage. The recruitment of endogenous SCs by signalling "mobilization" components to the site of injury to promote repair is known as cell homing. Compared with the cell-based strategy, this method is more clinically translatable because it does not require cell isolation and culture and Government approvals for use of GFs. In this strategy endodontic access and minimum instrumentation is done followed by disinfection with chlorhexidine, and a finally irrigation is done with 17% EDTA, which stimulates the discharge of GFs from dentin, which in turn improves stem cells chemotaxis from the apical region. Additionally, the stem cells that are migrating inwards will also release GFs. The intra-canal medicament; calcium hydroxide placed in the first visit, will also aid these processes by inducing the continued release of GFs from dentin. The calcium hydroxide medicament is removed with prolonged irrigation with EDTA. Mechanical agitation in the periapical area invokes bleeding into the canal to brings in cells, and introduces GFs from the developing blood-clot in the root canal space. When MTA is placed in contact with the blood clot, it induces GFs release for a longer time and augments the ongoing regenerative processes. At this stage, accumulation of various potent GFs occurs, derived from both dentin and cells which aid in the regeneration process.[45]

GFs released from dentin matrix have varied impact on the stem cells,[46,47,48] including:

Chemotaxis: interleukin-8, TGF β-1
Angiogenesis: VEGF
Neurogenesis: NGF
Cell proliferation: FGF-2, IGF-1
Cell differentiation: IGF-1, BMP-2, BMP-4, TGF-β1

One of the important factors to consider is the apical foramen size before inducing bleeding in the root canal. If the size of apical foramen is too small, it will affect both stem cell migration and neovascularization. Dental traumatology studies indicate that the replanted teeth require an apical foramen size of at least 1.1 mm[49] or 1.5 mm[50] for adequate revascularization. However, in revascularization studies cell homing and neovascularization has been observed with an apical size of even 0.8 mm [51] or 0.32 mm.[52]

7. Future Directions

In the future, tissue engineering techniques applied in more controlled clinical settings may prove more successful in creating tissues that resemble the original pulp and dentin. Therapies utilizing autologous stem cells in conjunction with specially designed scaffolds and the timely and sequential release of the appropriate GFs will be the foundation of such treatments. Biocompatible materials infused with GFs for use in root canal obturation and sealing can be developed. These materials may accelerate tissue repair, reduce the risk of microbial invasion and improve the overall success of endodontic treatment.

Several regenerative processes of dental stem cells are associated with pulp regeneration and a single signalling pathway cannot be modified to meet the requirements of structural and functional pulp regeneration. Combining various GFs that target different signalling pathways may be a more practical strategy in pulp regeneration. Further researches should focus on maintaining the safe, consistent, and manageable effects of signalling modulation when applied clinically.

8. Conclusion

GFs have a pivotal function in coordinating the intricate mechanisms underlying dentin-pulp regeneration, providing opportunities for the developing advanced regenerative endodontic treatments. Dental tissue engineering techniques are still in their infancy, despite improvements in our comprehension of the molecular mechanisms underlying tooth morphogenesis and regeneration. Resolving issues related to safety, effectiveness, and clinical translation is crucial in order to fully utilize GFs-based methods.

9. Significance

1. This review covers the fundamental information on growth factors and their mechanism of action for tissue engineering procedures.
2. It provides information on biological and synthetic matrices and biomaterials for dentin-pulp regeneration.
3. It provides practitioners with valuable understanding of the challenges faced during successful regenerative procedures and significance of maintaining or restoring tooth vitality.

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11. Conflict of Interest

None.

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