REVIEW ARTICLE

Scaffold Materials and Growth Factors in Pulp-Dentin Complex Regeneration

Ayman Mandorah

Department of Restorative Dental Sciences, Faculty of Dentistry, Taif University, Taif, Saudi Arabia.

Abstract

Dental pulp is a highly specialized tissue that preserves teeth. Before a pulpectomy, it is crucial to preserve the dental pulp's capabilities using any remaining dental pulp to create a local restoration of the dentin-pulp complex. The goal of regenerative dentistry is to repair the pulp-dentin complex's capabilities that have been impaired by pulp damage and/or inflammation. A suitable scaffold is used in scaffold-based approaches, a regeneration strategy that mimics a biological environment and is thought to be essential for dental pulp regeneration. This review summarizes the current knowledge of the potential beneficial effects derived from the interaction of scaffold materials and growth factors in the dentin-pulp complex regeneration, as well as potential future developments in this exciting field.

Key words: Pulp-dentin complex, regenerative, scaffold

INTRODUCTION

Regenerative medicine is defined as a research field dedicated to the creation of living and functional tissues or organs for medical applications. In the field of dentistry, regeneration may be helpful in treating and mitigating diseases resulting from tooth loss, damage, or absence caused by trauma, cavities, periodontal disease, fractures, or genetic anomalies.[1] Regenerating the dentin-pulp complex and restoring its functions that have been hampered by pulp damage and/or inflammation is the long-term objective of pulp regeneration research. Dental pulp stem cells (DPSCs) have been identified as a promising cell source for pulp regeneration techniques since their isolation and characterization.[2]

The dentin-pulp complex (DPC), which is produced from the same source during embryogenesis and has related functions, is formed when dentin and pulp are combined.[3] In response to a bacterial provocation, like caries, or any physical insult, like cavity preparation or trauma, the pulp responds in three basic ways:[4] First, by reducing the dentinal permeability by intratubular deposition of sclerotic dentin or whitlockite crystals, thereby blocking the irritants; second, by the deposition of tertiary dentin, which can be reparative if formed by newly differentiated odontoblasts or reactionary if deposited by the pulpal immune response, which offers humoral and cellular challenges to invasive pathogens. Consequently, a DPC makes the tooth disease-free in an effort to maintain its biological and physical integrity.[5]

The pulp-dentin complex is represented by the pulp and dentine working together as an integrated functional unit. In the event of exposure, each component contributes to the healing of the dentin-pulp complex. The development of tertiary dentin, which differs from reactionary and reparative dentin, is the most prevalent and well-known aspect of pulp healing.[6] A dental biomaterial is applied directly over the exposed pulp in direct pulp capping (DPC), a vital pulp therapy (VPT) that is thought to be an effective and conservative treatment approach.[7]

For VPT and long-term oral health care to be successful, dental pulp vitality must be preserved. The dental pulp is necessary for sustaining tooth health, supplying vital nutrients, and healing wounds.[8] More intrusive treatment alternatives, such as root canal treatments, extractions, implants, or dentures, are required when pulp vitality is lost. These procedures can be expensive and time-consuming. To increase tooth longevity and reduce the need for intrusive

Address for correspondence:
Ayman Mandorah, Department of Restorative Dental Sciences, Faculty of Dentistry, Taif University, Taif, P.O. Box 11099, Taif 21944, Saudi Arabia.
E-mail: aomandorah@tu.edu.sa

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procedures, methods for preserving the health of all or part of the pulp are crucial.[9]

A range of techniques is used in VPT, from sealing the unexposed pulp to employing bioactive compounds to disinfect and stabilize the exposed pulp. The choice and effectiveness of pulp capping materials are critical to the success of VPT. Due to their high alkalinity and capacity to promote the production of mineralized tissue, traditional materials like calcium hydroxide (CH) have long been the mainstay of VPT. Notwithstanding these benefits, CH-based materials have important drawbacks that affect long-term clinical performance.[9]

To prevent reinfection, root canal therapy involves removing infected pulp tissue from the root canal system, cleaning it, and then filling and closing the canal.[10] In conventional root canal therapy, the disinfected root canals are filled with biocompatible materials. Pulp necrosis and apical disease in young permanent teeth have traditionally been treated with root canal therapy. However, this approach has a number of disadvantages, such as the tooth's vulnerability to fracture due to weak dentinal walls and the lack of ongoing root development. With the ability to overcome these constraints and encourage the restoration of functional pulpal tissue, tissue regeneration technology has become a viable substitute in recent years.[11]

The objective of traditional root canal therapy is to totally obturate the root canal system and eradicate the infection. Due to the thin dentinal walls and intricate root canal anatomy, it can be particularly difficult to achieve a full seal in young teeth with open apices.[12] Regenerative endodontic procedures (REPs), on the other hand, seek to utilize the body's innate capacity to produce functioning pulpal tissue.[4] This method usually entails cleaning the root canal system, adding a scaffold, and promoting the recruitment and development of stem cells (SCs).[11]

The importance of periapical bacterial disinfection in dental pulp regenerative cell treatment is highlighted by the fact that complete disinfection of the periapical tissue is essential for effective pulp regeneration in apical periodontitis. In addition, the application of tissue engineering techniques in root canal therapy, including SCs, scaffolds, growth factors (GFs), and gene therapy, shows promise in reliably restoring a crucial support structure within necrotic root canal areas. To restore normal function, the idea behind pulp regeneration through regenerative dental pulp therapy is to replace injured dental pulp tissue with healthy tissue.[13,14]

While traditional root canal treatment focuses on effective cleaning and obturation of the root canal system, regenerative endodontics offers a more biological approach by promoting tissue regeneration within the root canal. For successful results, both methods stress the significance of thorough cleansing, disinfection, and root canal system shape.[11]

AIM OF THIS REVIEW

The aim of this review was to evaluate the role of scaffolds and GFs in pulp-dentin regeneration.

BASICS OF PULP-DENTIN REGENERATION

Like general tissue engineering, pulp tissue engineering that aims to regenerate the pulp-dentin complex also needs three key components: SCs, scaffolds, and GFs. It is hypothesized that the presence of resident SCs of the apical papilla and microenvironmental stimuli affects the tissues' or organs' capacity to regenerate.[15]

Stem/progenitor cells

SCs are essential components of contemporary tissue engineering that aim for regeneration, particularly in cases when the damage is too severe for self-regeneration or cell-free methods. Similar to the broad idea of tissue engineering concepts that employ cell-based therapies, cell-based pulp regeneration necessitates the delivery of a cell source into the host in order for tissue to regenerate to its original or nearly original form. The regeneration of a pulpodentinal complex and the advancement of the conversion of lab research into clinical applications are two promising uses of SCs.[16]

Scaffolds

Biomaterials serve as carriers of cell transplantation, giving DPSCs a three-dimensional environment in which to grow and metabolize. In addition, biomaterials with appropriate bioactive cues may produce a favorable milieu that enhances DPSCs' capacity for self-renewal and multipotentiality, hence fostering tissue regeneration. Nowadays, pulp regeneration makes extensive use of scaffold materials, both synthetic and natural.[17]

Scaffolds serve as a stable habitat for signaling molecules and SCs. An ideal scaffold for regenerative endodontics should distribute cells that contain growth hormones and be biodegradable. Diverse scaffold materials, including synthetic and natural polymers, are being investigated and reported with differing outcomes.[15]

GFs

Strong GFs can speed up the regenerative process, even though SCs' multi-potent qualities can encourage pulp regeneration. GFs are essential for stimulating pulp regeneration because they facilitate the mobilization and engraftment of exogenously transplanted SCs to recipient tissues, speed up the recruitment of endogenous

SCs to the injured sites, and enhance their regenerative function.[18] Research has demonstrated that a variety of GFs, either by themselves or in combination, can cause a wide range of biological effects in DPSCs, including migration, proliferation, and differentiation, all of which are critical for pulp regeneration.[19]

SCs

In Regenerative endodontic therapies, SCs are necessary for dental pulp regeneration due to their unique properties. Due to their plasticity, they can develop into odontoblast-like cells, which are necessary for the formation of a functional pulp-dentin complex in necrotic pulp. In bioreactors, SCs from tissues such as bone marrow or dental pulp are grown and differentiated under carefully monitored conditions before being added to biodegradable scaffolds. By giving the damaged pulp structural support, these scaffolds promote tissue regeneration.[20,21]

In addition, SCs' capacity for self-renewal guarantees a steady supply of undifferentiated cells for pulp regeneration. For tissue repair and bioengineered pulp therapies, DPSCs exhibit strong self-renewal, which is controlled by important factors such as transforming GF beta (TGF-β), bone morphogenetic protein (BMPs), and fibroblast GFs (FGFs).[22] Furthermore, DPSCs' multipotency enables them to differentiate into a variety of cell types, including fibroblasts, endothelial cells, and odontoblasts, all of which are necessary for reconstructing the pulp-dentin complex and reestablishing critical processes, including immunological defense and sensory perception. SCs are positioned as a key component of endodontic therapies in the future due to their special mix of restorative powers.[21]

For the pulp-dentin complex to successfully regenerate, selecting the appropriate cell source is essential. Due to their better integration with preexisting tissues and lower risk of immunological rejection, autologous cells, which are taken from a patient's own tissues, such as bone marrow or dental pulp, are greatly desired. These cells are perfect for guaranteeing a more consistent regenerative result and encouraging the restoration of complete pulp functionality.[23]

SCAFFOLD MATERIALS

The scaffold facilitates cell adhesion, infiltration, differentiation, and proliferation by acting as a three-dimensional milieu that is essential for SC activities. In addition, it uses GFs to modify the metabolism of SCs. It makes it easier for nutrients and oxygen to be absorbed throughout the regeneration process. For dentin-pulp complicated restoration, a wide variety of scaffolds are currently available. However, the long list of requirements makes it difficult to choose the perfect material [Table 1].[24]

Safety, non-toxicity (with regard to degradation products), biocompatibility, low immunogenicity, microporosity, and the capacity to stimulate cell proliferation while being degradable (performing its purpose momentarily before being replaced by freshly produced tissue) are all requirements for the scaffold. Both natural (such as chitosan, alginate, hyaluronic acid [HA], and gelatin) and synthetic (like ceramics and composites) materials are used as scaffolds in regenerative endodontics. Scaffolds that work well with combination techniques incorporating different materials are especially favored.[24,25]

Ideal requirements of a scaffold

a) A high porosity and an adequate pore size are necessary to facilitate cell seeding and diffusion throughout the whole structure of both cells and nutrient
b) It should enable efficient waste, oxygen, and nutrient transportation
c) Biodegradability is important, as scaffolds need to be absorbed by the surrounding tissues without the requirement of surgical removal
d) The rate of tissue synthesis must match the rate of breakdown
e) Biocompatibility is required
f) It should possess sufficient mechanical and physical strength.[26]

Types of scaffolds

Natural scaffolds

Naturally derived materials such as collagen, fibrin, gelatine, chitosan, HA, alginate, and peptide-based scaffolds have been studied as scaffolds for pulp regeneration because they are highly biocompatible, biomimetic, easily accessible, affordable, and simple to fabricate into hydrogels. This is because blood clots induced in pulp revascularization may be among the earliest natural substances to develop.[17]

Collagen

Collagen Type I makes up about 90% of the organic materials in dentin and the periodontal ligament. Collagen's triple helix shape gives it strength, and it maintains its strength and flexibility at various organizational levels. In addition to providing structural support, collagen has components that draw integrins, which aid in cell adhesion to the matrix and initiate critical cellular processes for tissue creation and repair.[27]

Collagen has the following benefits: It is biocompatible, biodegradable, has a strong tensile strength, mimics the natural extracellular matrix of dentin, has high alkaline phosphatase activity, permits the creation of both soft and hard tissues, and creates a trap for osteoinductive elements. Collagen can be crosslinked with chemicals to increase its strength or change the rate at which it degrades. It can also

Table 1: Characteristics of stem cells and their application in pulp regeneration[18]

Stem cells	Advantages	Disadvantages
DPSCs	• Tissue specificity • Potent capacity for vascular formation • Easy accessibility	• Available pulp tissue is reduced under pathological conditions
SHEDs	• Tissue specificity • Higher proliferative activity • Lower immunogenicity • Osteoinductive capacity • Higher neurogenic differentiation capacity	• Deficient in the specific formation of the ECM
PDLSCs	• Potent capacity for differentiation into cementoblasts and osteoblasts • Prone to form directionally arranged fibers	• Low cell numbers in original cultures • Low neurogenic differentiation capacity
DFPCs	• Participate in the regeneration of cementum and periodontal ligament	• Low cell numbers in original cultures • Isolation difficulty • Prone to differentiate into specific periodontal lineages
SCAPs	• Strong osteogenic and angiogenic differentiation potential • Anti-inflammation function • Dynamic secretome • Prone to differentiate into primary odontoblasts rather than reparative dentin	• Low cell numbers in original cultures • Difficult to isolate and distinguish from PDLSCs, DFPCs and HERS
HERS	• Participate in tooth root and periodontium formation	• Low cell numbers in original cultures • A lack of appropriate culture methods
BMSCs	• Participate in the formation of osteoid tissue and pericyte-supported capillaries	• Low neurogenic differentiation capacity • Invasive surgical procedures required to obtain cells
ADSCs	• Abundance • Ease of harvest and processing	• Weak odontogenic and angiogenic differentiation potential

DPSCs: Dental pulp stem cells, SHEDs: Stem cells from human exfoliated deciduous teeth, PDLSCs: Periodontal ligament stem cells, DFPCs: Dental follicle precursor, SCAPs: Stem cells from the apical papilla, HERS: Hertwig's epithelial root sheath, BMSCs: Stem cells from bone marrow, ADSCs: Adipose tissue stem cell, ECM: Extracellular matrix

be processed into a number of shapes, including porous sponges, gels, and sheets.[26] However, compared to tooth mineralized tissues, endogenous collagen scaffolds have limited force resistance and rapid enzyme reactivity. Due to this, their application is restricted, such as when the alveolar bone is regenerating or when teeth's periodontal tissues are being supported.[28]

Fibrin

Thrombin's enzymatic action polymerizes the plasma protein fibrinogen to form fibrin, a naturally occurring biomaterial. When it comes to biocompatibility, cost, cell adherence, and immunological reaction, it is superior to the majority of synthetic polymers and collagen gels. When obtained from autologous sources, fibrin exhibits no unwanted immunogenic responses. In addition, fibrin hydrogels can be molded into certain three-dimensional geometries and are injectable and repeatable.[17]

Since the mid-1990s, platelet-rich plasma (PRP) therapy has been utilized in oral and dental surgery. It is a new technology in sports medicine. The patient-derived fibrin (platelet-rich fibrin [PRF]) scaffold, which is based on PRP technology, functions as a biodegradable and autologous delivery system in recent times. As part of guided tissue regeneration operations in periodontics and oral surgery, PRP/PRF was widely employed in conjunction with collagen membranes to regenerate alveolar bone and the periodontal ligament. It has been demonstrated that PRP therapy effectively accelerates the healing process.[29]

Chitosn

Chitosan, a biopolymer derived from chitin, has emerged as a promising material in the field of regenerative endodontics due to its favorable biological properties. It is appropriate for dental applications since it is non-toxic, biodegradable, and has good biocompatibility. In addition, the natural antibacterial qualities of chitosan can aid in lowering the bacterial load in the root canal system, improving the outcome of regeneration treatments. Numerous studies have shown that it can encourage cellular adhesion and proliferation, suggesting that it could be used as a scaffold material in pulp regeneration.[30]

Chitosan has several benefits, including non-toxicity, easy bioabsorption, antibacterial action, gel-forming capacity, increased alkaline phosphatase activity, and fibroblast and odontoblastic proliferation. Its hydrophilic quality promotes cell adhesion and proliferation, and it is a porous scaffold

that can be shaped into any shape. Its weakness and uneven behavior with implanted cells, the difficulty of precisely controlling the size of the hydrogel holes, and the potential for toxicity from chemical changes to the chitosan structure are its drawbacks.[26]

HA

An essential part of the extracellular matrix in the dentine niche is HA, a glycosaminoglycan. In the dentine niche's microbiological environment, extracellular matrix proteins are crucial for controlling SC development and homeostasis. Every stage of regeneration, including extracellular matrix repair, cell migration, proliferation, and differentiation, is known to benefit from HA at varied molecular weights.[31]

HA and scaffolds derived from it offer numerous advantages, including biocompatibility, biodegradability, non-immunogenicity, non-thrombogenicity, and hydrophilicity. The main purpose of the scaffold in cell-free regenerative endodontic therapy (CF-RET) is to extract endogenous SCs from the periapical tissue. HA stimulates the migration of SCs from the apical papillae (SCAPs) into the root canal area by interacting with their membrane receptor CD44. SCAP differentiation and mineralization are encouraged by growing them in hydrogels based on HA.[24]

Synthetic scaffolds

In addition to natural scaffolds, a number of synthetic polymers have been developed, including polyglycolic acid, poly(d,l-lactide-co-glycolide), polylactic acid, poly(l-lactic) acid, polycaprolactone, and polyethylene glycol (PEG). Various inorganic materials, including calcium phosphates such as hydroxyapatite (HA) and beta-tricalcium phosphate, as well as silica glass–phosphate combinations, have been used as scaffold materials in regenerative therapies. Because synthetic scaffolds are non-toxic, biodegradable, and easily manipulable in terms of mechanical rigidity and breakdown rate, they have been extensively researched as scaffolds with potential for tooth regeneration.[32,33]

Due to their adjustable characteristics, biocompatibility, and ease of manufacture, synthetic polymers are frequently used in regenerative dentistry. These materials provide a regulated structure for cellular adhesion and growth and are commonly employed as scaffolds to facilitate tissue regeneration. Their capacity to distribute bioactive compounds, biodegradability, and adjustable mechanical strength are important features.[34] Notwithstanding their benefits, it is still difficult to match the mechanical characteristics of natural oral tissues and achieve appropriate integration. Their breakdown products may also be hazardous. Consequently, thorough examinations of cytotoxicity need to offer a preliminary assessment *in vitro*.[35]

Bioactive scaffolds

The development of novel bioactive materials that can enhance molecule release and encourage tissue regeneration and healing has become a major focus of recent research in the fields of dental materials and endodontics. The biological activity of a device or medication is known as bioactivity, and it is mostly related to the type of biomolecules and chemical compounds that are included and have the potential to be released into the surrounding tissue.[36]

Hydrogels

For dental pulp regeneration, hydrogels made of synthetic and natural polymers are suitable materials. Their water content ensures consistent viscosity and elasticity. PEG developed for direct pulp capping. Maleate Citrate hydrogel is an injectable drug delivery vehicle that demonstrated intriguing results with appropriate cell viability and control of the included CH.[37] Compared to traditional inert materials, the use of bioactive endodontic hydrogels in root canal therapy has a number of benefits. First of all, an endodontic hydrogel, a bio-inspired hydrogel like a fibrin-based hydrogel, will be able to encourage the production of a dentin-pulp-like complex, which is a sign of a healing process. Second, the hydrogel's bioactive ingredients are readily released to produce an environment that is conducive to tissue regeneration.[36]

Nanofibrous scaffolds

Nanofibrous scaffolds, which are becoming increasingly common in the RET, can improve adhesion, allow cells to manifest more normal 3D morphologies when compared with smooth materials, solid films, and tissue culture polymers. The diameter of a nanofibrous scaffold ranges from 1 to 100 nm, which is comparable to the size of collagen. In addition, its enormous surface area, which is inversely correlated with diameter, promotes cellular migration and adhesion. In addition, the nanofibers' pores are appropriate for cell attachment and penetration. It has been demonstrated that cells grown on extremely porous nanofibrous meshes enhance cellular adhesion and proliferate. Due to their enormous surface area, interconnected porosity akin to the extracellular matrix (ECM), and nanoscale fiber, nanofibrous scaffolds become an excellent material for RET.[38]

Injectable scaffolds

Injectable polymerizable hydrogel

These hydrogels are mostly made of biocompatible polymers that can be injected as a liquid into the root canal, where they will polymerize *in situ* to produce a scaffold that resembles gel. The root canal system has a complex morphology, and it is challenging to incorporate the scaffolds in the form of sheets and blocks. This scaffold can create a three-dimensional structure that promotes cell growth, proliferation, and differentiation by filling in the canal's uneven voids. The capacity of injectable hydrogels to transport bioactive substances, such as GFs or antibiotics, straight to the site of tissue injury is one of its major benefits. In addition, hydrogels' mechanical strength and rate of degradation can be modified to meet the unique needs of the regenerative

process, guaranteeing that the scaffold offers continuous support during tissue recovery.[39,40]

PRF

The second-generation platelet concentrate, PRF, is a reservoir of several GFs for regeneration and has a supraphysiological concentration of platelets when compared to whole blood. According to recent cell tests, PRF can enhance the migration, proliferation, or differentiation of gingival fibroblasts, periodontal ligament fibroblasts, and SCAPs. The high penetration ability of injectable PRF (i-PRF) suggests that it may be an ideal material for pulp regeneration, as i-PRF could be easily injected into root canals and completely fill the voids.[41]

The injectable scaffold has a number of advantages over the pre-formed scaffold, such as: (1) It is performed in a minimally invasive manner, which reduces the risk of infection and improves comfort; (2) It can easily fill any irregularly shaped defects; and (3) It overcomes the challenges of cell seeding and adhesion, as well as the delivery of bioactive molecules, because these factors can be simply mixed with the material solution before being injected *in situ*. An injectable scaffold is preferable to a pre-formed one, given the size, shape, and intricate structure of dental and craniofacial tissues.[42]

GFs

GFs control endogenous or transplanted cells during dental pulp-dentin regeneration. They are proteins or polypeptides that attach to particular receptors on the surface of target cells (such as BMP receptors) and influence a variety of cellular processes, such as the migration, proliferation, differentiation, and apoptosis of all dental pulp cells, including stem/progenitor cells. Pulp regeneration depends on bioactive cues that attract the right cells (TGFs β1, β3 for odontoblast differentiation and activation of dentin matrix).[26]

GFs such as platelet-derived GF (PDGF), TGF, BMPs, vascular endothelial GF (VEGF), FGF, and insulin-like GF can regulate and coordinate these repair and regeneration processes. They promote the growth of odontoblast-like cells, which are essential for the creation of dentin, by influencing the proliferation and differentiation of SCs. GFs can be strategically used in REPs to increase tissue performance, hasten healing, and guarantee long-term success in restoring tooth vitality [Figure 1].[26,43]

TGF-β

The TGF-β family comprises a group of diverse GFs, including TGF-β, BMPs, growth and differentiation factors, Anti-Mullerian hormone, activin, and nodal. The approximately 390 amino acids that make up TGF-β are mostly secreted by

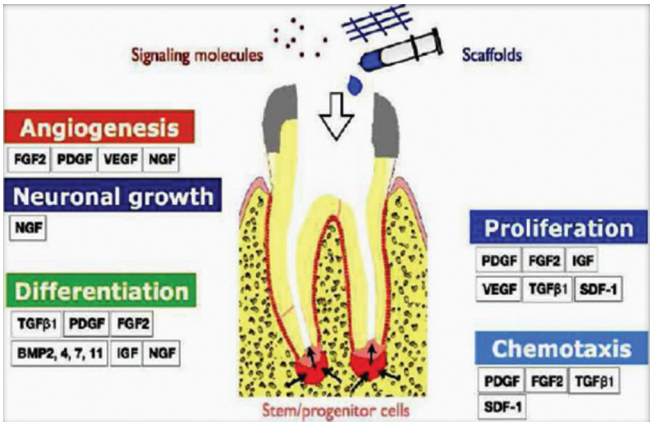

Figure 1: Effects of growth factors on dental stem/progenitor cells[43]

platelets, macrophages, and bone. The active C-terminal 112-amino acid version of this inactive polypeptide is produced by proteolytic cleavage. TGF-β's active form forms 25 kD homodimers through dimerization. Human dentin contains the three isoforms of TGF-β1, TGF-β2, and TGF-β3 that are seen in mammals.[44] The most significant GF is TGF-β1, which is essential for odontoblast maturation and mineral embedment and increases the creation of collagen by fibroblasts in the dental pulp.[45] Inactive TGF β-1 is integrated into the dentin matrix during dentin development. When the dentin demineralizes, this latent form may be liberated. Extreme pH exposure, heat application, ultrasonic treatment, integrin binding, ionizing radiation, proteolytic enzymes, and the use of chelating agents like ethylenediaminetetraacetic acid are some of the techniques that can be used to activate TGF β-1.[46]

BMPs

BMPs belong to the TGF-β family. They play a variety of roles in osteogenesis, vasculogenesis, and development. BMPs control the specialization of different cell types and play important roles in embryonic development. Numerous human disorders are linked to the deregulation of BMP activity at different phases of signal transduction. It is not unexpected that BMPs play a part in the development of tumors and regulate the many stages of cancer growth. However, their precise roles are still unclear, and the results have been mixed.[47]

VEGF

VEGF is a heparin-binding protein that is important for angiogenesis and has a particular affinity for endothelial cells.[27] VEGF stimulates neo-vascularization in the injured area by promoting endothelial cell proliferation and increased survival. VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placenta GF are all members of the VEGF family.[28] The most flexible of these isoforms is VEGF-A. VEGF-A,

also referred to as vascular permeability factor, binds to two tyrosine kinase receptors, VEGFR1 and VEGFR2, to enhance cell migration, proliferation, vasodilatation, and vascular permeability.[44]

FGFs

Growth molecules called FGFs are crucial for the growth, repair, and regeneration of teeth. Basic FGF (bFGF) is the FGF family that has been studied in dentistry the most.[48] The mechanism of action states that bFGF binds to the cell membrane's tyrosine kinase FGF receptors 1–4. Cell migration, proliferation, and differentiation are initiated by a series of intracellular signaling pathways, including the RAS-MAPK, PI3K-AKT, PLCγ, and JAK/STAT signaling pathways, which are triggered when bFGF attaches to its receptors. These results raise the possibility that bFGF regulates particular biological processes in tooth pulp regeneration and repair via various intracellular signaling pathways.[49]

PDGF

PDGF is the major serum polypeptide GF; it is stored in platelets and is released during blood clotting. PDGF promotes wound healing in soft tissues and mediates regular tissue repair processes. GFs, such as PDGF-BB, have been demonstrated in animal studies and human trials to promote periodontal tissue regeneration. Therefore, PDGF-BB has been licensed by the Food and Drug Administration for use in periodontal therapy for gingival recessions, furcation lesions, and intrabony abnormalities. PDGF is a powerful mitogen for mesenchymal cells, including fibroblasts, PDL cells, and alveolar bone cells, and a powerful chemoattractant for neutrophils, monocytes/macrophages, and fibroblasts. In addition, PDGF-BB increases these cells' production of collagenase and type I collagen.[50]

INTERACTION BETWEEN SCs, BIOMATERIALS, AND THE REGENERATIVE MILIEU

The spatial arrangement of the SC niche usually includes anatomical and functional interactions that contribute to the specification of the cell's fate and the preservation of its stemness potential.[51] These interactions, which involve both cellular and acellular components, are reciprocal and dynamic. The following are essential components of the physiological milieu:

a) Cellular counterparts, such as immune/inflammatory cells, perivascular and endothelial cells, and mesenchymal and stromal support cells
b) Extracellular matrices, such as adhesion and signaling receptors
c) Soluble factors, such as GFs, chemokines, and hormones.[52]

When SCs are transplanted without a scaffold or supporting elements, endogenous niche-directed therapies may be used to increase support. On the other hand, a controllable method to replicate the physiological SC niche is the transplanting of cells, scaffold, and factors, all three of the previously described pillars of regeneration. When creating *ex vivo* transplants that closely resemble their native environment, it is crucial to take into account the cellular actors and chemical signals that make up SC niches under various physiological and pathological situations. The enlarged cells' actions to support tissue regeneration *in vivo* can be predicted by the proper interaction between them and their *ex vivo*-created habitat.[52]

It is to be noticed that because SCs are self-renewable and can develop into several tissue lineages, they are a crucial part of tissue engineering and cell-homing processes. DPSCs, SCAPs, human periodontal ligament SCs (PDLSCs), and centrally residing SC populations like human bone marrow stromal SCs and hematopoietic SCs may all play a significant role in revitalization procedures. GFs released from dentin, other cells, or scaffold materials, as well as GFs produced by SCs themselves, can alter their behavior.[53]

CLINICAL APPLICATIONS

REPs

A necrotic pulp and irreversible pulpitis operation debrides tissues from the root canal, disinfects the root canal, and instruments the periapical tissues through the open root apical foramen to promote bleeding into the canal to revascularize it. In addition to incorporating a scaffold or biological process into the root canal to encourage the development of important tissue, which will sustain the mineral deposition to fortify dentine and expand the roots of immature teeth.[54]

SC transplantation, cell homing, and REPs are currently the main approaches used in regenerative endodontics. While only REPs have been extensively used in clinical practice, SCs transplantation has been shown to successfully repair pulp tissue in clinical settings. REPs is a biologically based method that uses the idea of tissue engineering to replace damaged structures, such as dentin and pulp-dentin complex cells, with the goal of not only healing apical lesions and resolving symptoms but also maintaining root development and strengthening dentinal tissues to prevent future root fracture. Regenerating a functional pulp-dentin complex, immunological competency, and normal nociception are the ultimate objectives.[55]

Revascularization

The pulp revascularization method involves using a file to induce bleeding from the apical papilla after the root canal

has been cleaned with a mixture of CH and antibiotics. This allows a blood clot to develop inside the root canal. In the end, this mechanism completes root development by facilitating the migration of SCs capable of differentiating and producing dentin. The periapical tissue contains a high number of SCs that can differentiate into multiple cell types, including osteo/odontogenic, neurogenic, and other lineages, including chondrocytes and even adipocytes.[56]

It has been proposed that the blood clot serves as a scaffold to help SCs migrate and engraft. Mineral trioxide aggregate or other bioactive endodontic cements are used to seal the blood clot inside the root canal. Nevertheless, the regeneration of an ordered pulp tissue that contains blood vessels and neurons is not equivalent to the development of this blood clot. A histological analysis using hematoxylin and eosin staining shows the absence of odontoblasts and the presence of connective tissue, fibroblasts, and blood vessels with few lymphocytes.[57]

At present, the origin of the cells involved can be used to widely differentiate the regeneration treatments that target the pulp-dentin complex. These approaches are now separated into two categories: CF-RET and cell-based RET (CB-RET). The goal of CB-RET is to directly repopulate the pulp space and achieve full tissue regeneration by transplanting SCs from the host (autologous) or donors (allogeneic) into the root canal after *ex vivo* growth. Notwithstanding its potential benefits, this strategy has a number of drawbacks, such as erratic cell availability, contamination risk, immunological rejection, high expenses, and regulatory obstacles related to *ex vivo* cell manipulation.[16,57]

Apexogenesis

Apexogenesis, a VPT, is a crucial treatment option for preserving the vitality of immature permanent teeth affected by caries or trauma. Promoting the root and apex's continuous development is the aim of apexogenesis, which enables a better prediction.[58] The process of apexogenesis involves removing the inflammatory pulp and applying CH to the pulp tissue that is still healthy. The coronal part of the pulp is traditionally removed using this technique. However, the specific clinical scenario must dictate how much tissue is removed. It is challenging to gauge the degree of inflammation, but only the inflammatory tissue is removed. Several medical professionals have discovered that the inflammation was restricted to a portion of the 2–3 mm coronary after the pulp was mechanically exposed and left untreated for about 160 h. As a result, superficial pulpotomy, also referred to as Cvek was developed, removing only the pulp's outermost layer.[59]

CHALLENGES AND FUTURE DIRECTIONS IN RETs

Regenerating nerve and vascular structures within the dental pulp presents a number of difficulties for RETs. Due to the pulp's complicated milieu and the neural components' restricted capacity for regeneration, nerve tissue regeneration is intrinsically complex. The exact differentiation of SCs into neurons and the alignment of new nerve fibers with existing ones are still major obstacles to the functional integration of newly generated brain circuits.[60]

The restoration of a strong blood supply, which is necessary for the survival and functionality of regenerated pulp tissue, is another crucial obstacle. Hypoxia, nutritional shortages, and impaired cell survival and differentiation can result from inadequate vascularization in designed tissues.[32] It has been demonstrated that adding angiogenic factors to scaffolds, such as VEGF and angiopoietin, can encourage the development and maturation of blood vessels. In addition, scaffolds with pre-designed vascular channels can be created using bioprinting technologies. These scaffolds can then be seeded with endothelial cells to create functioning vascular networks. Because mesenchymal stem cell (MSCs) can develop into vascular cells and promote endothelial growth, they also have the potential to improve vascularization.[61,62]

Future studies should concentrate on biomaterials that actively promote vascular growth and stabilization in addition to mimicking the ECM structure. The effectiveness of vascularized pulp regeneration may be increased by combining bioprinting with angiogenic agents and investigating MSC-based methods further. Commercialization and regulatory approval are major obstacles to the clinical translation of RETs, in addition to biological and technical difficulties. One of the main obstacles preventing the broad use and accessibility of regenerative therapies is the high cost of cell separation, scaffold construction, and GF manufacturing.[63,64]

CONCLUSION

Using the revascularization approach, pulp-dentin regeneration based on tissue engineering was carried out in a clinical setting. This procedure is acknowledged as a paradigm change from the previously employed technique of material restoration. It has recently been taken into consideration as a therapy option for both immature and mature teeth. Nonetheless, there is widespread agreement that the pulp-dentin complex is less likely to be the final tissue acquired by REPs than bone-like tissue combined with connective tissue. The terminology "pulp-dentin regeneration," "pulpal repair," and "wound healing" has generated dispute. One method for producing ectopic mineralized tissue creation is revascularization, which is based on the cell-homing strategy. It also exposed the drawbacks, such as the imbalance between total disinfection and stem/progenitor cell viability and the unpredictable nature of bleeding induction. However, in addition to the clinical benefits of encouraging root formation, it is clear that pulp-dentin regeneration offers

biological benefits such as tooth homeostasis, an improved immune system, and a functional pulp-dentin complex.

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