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Review article

Roles of basic fibroblast growth factor, stem cells from dental pulp and apical papilla in the repair and regeneration of dental pulp and other tissues/organs

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Abstract Currently, the concept of regeneration and regenerative therapies are already being applied clinically to treat pulpal and periodontal diseases, as well as to repair and regenerate systemic organs and tissues. During wound healing, well-developed, functional vascular networks and revascularization are fundamental factors in restoring regenerative potential. Growth factors, stem cells, and scaffolds alone or in combination are reported to contribute to successful tissue repair and engineering via cell transplantation, cell homing or other technologies. Among the growth factors, basic fibroblast growth factor (bFGF) has been found to regulate the proliferation, stemness, migration, and differentiation of vascular and mineralized tissues into various cell types through the differential activation of FGF receptors (FGFRs) and downstream signaling pathways. In addition to growth factors, various dental stem cells

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are widely used for the regeneration of diseased or lost dental pulp and periodontal tissues, yielding promising results. Stem cells from the apical papilla (SCAPs) and dental pulp stem cells (DPSCs), with or without bFGF, have been shown to be crucial for angiogenesis/revascularization, neuronal growth, and the repair/regeneration of the pulpo-dentin complex, apexogenesis, and may potentially be used in the future to treat various systemic diseases such as myocardial infarction, diabetes, retinopathy, and others. Further studies are needed to optimize the use of bFGF and dental stem cells such as SCAPs and DPSCs by using cell transplantation, cell homing or other technologies for tissue and organ regeneration in experimental animal models and, eventually, in clinical patients in the future.

Introduction

Recently, the field of medical science has made significant progress due to advancements in techniques driven by the dedicated efforts of scientists and clinicians working to meet patients' expectations. Modern medicine now focuses not only on reducing mortality rates but also on preserving patients' self-care abilities and quality of life. How to repair, regenerate and replace the lost tissue and organ due to various diseases is a critical health and clinical treatment issue. Wound healing typically occurs in four key stages: hemostasis, inflammation, proliferation, and remodeling.[1] The success of tissue repair and regeneration depends on the efficiency of these processes, which in turn affects the effectiveness of clinical therapies. As a result, this area has inspired many scientists to investigate the crucial molecules, materials/scaffolds, cells and underlying mechanisms, with the belief that improving our understanding of the repair and regeneration processes could lead to better prognosis following treatment.[1,2] This is why regenerative medicine, which aims to regenerate oral tissues or other organs with normal function, plays a crucial role in advancing modern medical and dental practice. Regenerative therapies are generally categorized into cell-based and non-cell-based approaches, depending on whether exogenous cells are used (Fig. 1).[3,4] Studies have shown that cell-based therapies can enhance various cellular activities, such as proliferation and differentiation. However, challenges remain, including ethical concerns regarding the source and transplantation of exogenous stem cells, as well as the complexity of the application procedures.[4] Additionally, while stem cell transplantation may offer an alternative to conventional therapies, there is still insufficient clinical evidence to support its widespread viability.[5,6] The sources of autogenous tissues or stem cells for transplantation into the diseased sites are also limited and one major ethical concern. Therefore, more research is needed to advance clinical applications in the future. On the other hand, cell homing presents fewer challenges compared to cell transplantation. Since it does not require exogenous cells, it is a simpler technique with no ethical concerns. Endogenous cells, one of the sources used in cell homing, are recruited to the targeted site through the interaction of specific molecules. There is now ample evidence supporting the essential components of regenerative strategies. Their synergistic effects have been shown to enhance cellular abilities such as migration, differentiation, and proliferation.[4,5,7] In addition to stem cells and growth factors, the use of biocompatible scaffolds further contributes to the success of tissue engineering treatments by enabling the controlled release of key components.[8—10]

In regenerative strategies, revascularization refers to the process of inducing the formation of new vascular or capillary networks. Based on the principles of tissue healing, researchers have been inspired by the idea that enriched vascular networks are essential for supplying adequate nutrients and oxygen during the healing process. Studies have shown that revascularization is beneficial for a variety of conditions, including burns, post-surgical wounds, cardiac diseases, and retinal pathologies, all of which can benefit from regenerative approaches.[1,11—14] Additionally, this process may also enhance cellular capabilities in tissue engineering. In the context of endodontic regenerative strategies, pulp revascularization—a form of cell homing technique is already applied for treatment of non-vital teeth with an open apex and has been demonstrated to have positive effects in pulpal healing and regeneration.[5]

Cell homing is a multistep process that recruits exogenous or endogenous stem cells to migrate toward the target site through the induction of various signaling molecules. Previous studies have shown that several angiogenesis-related molecules, including basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), early growth response factor-1 (Egr-1), platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and granulocyte colony-stimulating factor (G-CSF), play a beneficial role in the revascularization and tissue repair processes.[7,12,15,16] These molecules enhance the mobility, migration and differentiation of stem cells to injury sites, thereby supporting regenerative strategies in diabetes, myocardial, retinal, cutaneous, and dental pathologies.[12,13,17—19] Although there were many studies focused on dental pulp stem cells (DPSCs) applied on the regenerative application, it lacked for integrating the application of stem cells from apical papilla (SCAPs) and their association with bFGF for pulpo-dentin regeneratiion. In this review, we focus on the clinical applications of bFGF and

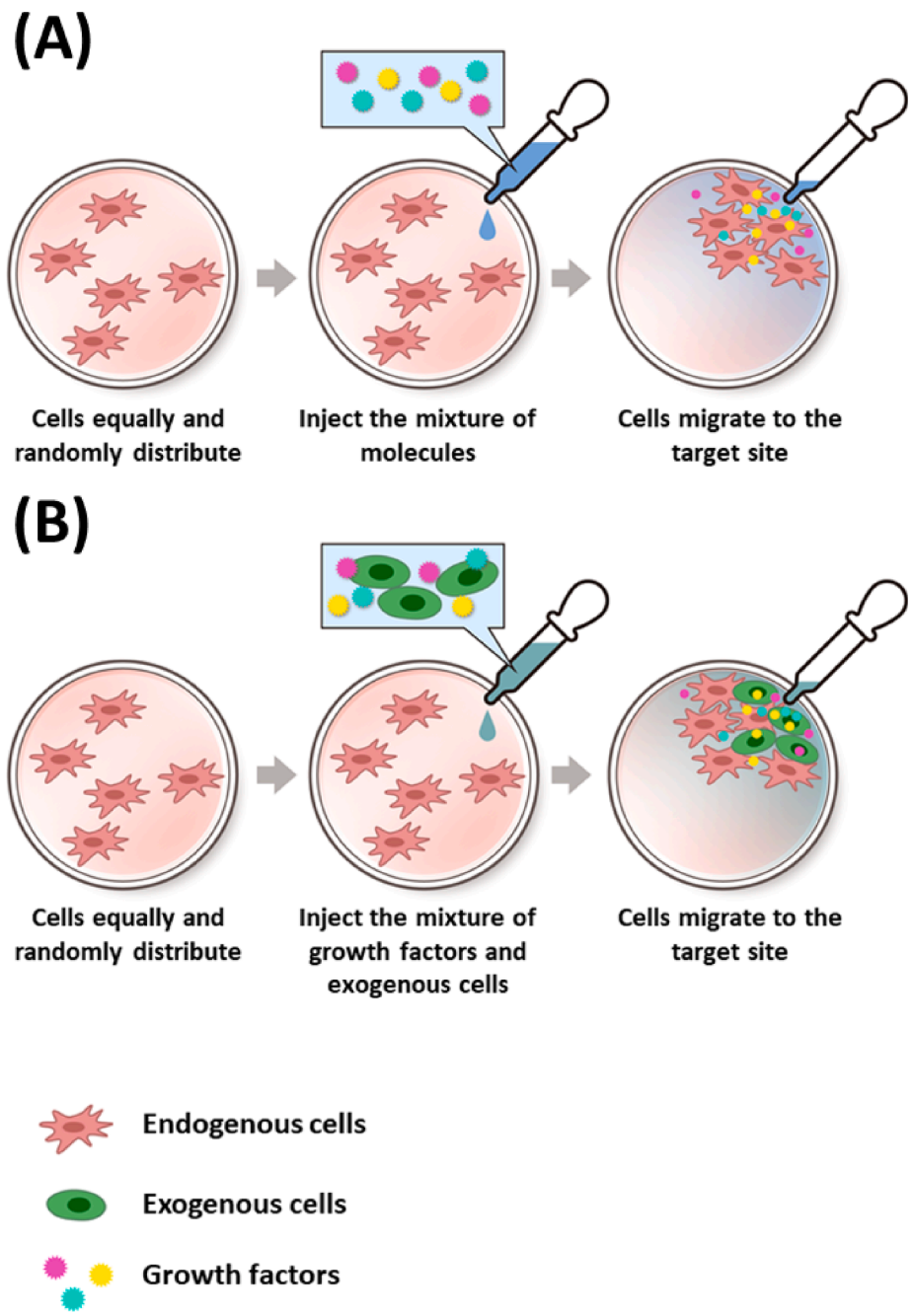

Figure 1 Cell homing and cell transplantation technologies for regenerative therapy. (A) Cell homing technique utilizes growth factors or other molecules to induce endogenous stem cells to proliferate and migrate to the diseased site, and then differentiate, repair and regenerate the lost tissues, (B) Cell transplantation is the placement (by injection or surgery) of exogenous cells with/without treatment by various growth factor to the diseased sites, to promote the endogenous cells to the target sites for tissue/organ regeneration.

SCAPs or HDPCs for vascular formation and tissue regeneration.

Fibroblast growth factors

Since 1973, human FGFs family members have been studied for their structures and specific mechanisms. It is known that the human FGF family consists of 22 members, which are divided into seven subfamilies. Among these, only the FGF19 subfamily belongs to the endocrine FGFs, with the Klotho protein acting as a cofactor for them. The other FGFs, classified as paracrine FGFs, exhibit a high affinity for heparin.[20,21] Researchers have found that the use of heparin or heparan sulfate proteoglycans (HSPGs) can provide a synergistic effect on pluripotent cellular responses when paracrine FGFs bind to their receptors.[10,20–22] This application has been shown to have positive effects on the local

healing of the spinal cord, cardiovascular system, bones, skin, and pulp.[20—22] Studies have also demonstrated that FGFs are responsible for various biological functions, including mitogenesis, embryonic development, cell motility, differentiation, angiogenesis, and wound repair and regeneration.[10,23] Based on this knowledge, clinicians have attempted to apply FGF-related treatments to aid in the healing of burns and ulcers.[22] Each subfamily of FGFs is involved in specific mechanisms. For example, acidic fibroblast growth factor (aFGF) and bFGF (basic fibroblast growth factor) have been shown to induce angiogenesis in endothelial cells.[10] Various signaling pathways are activated through the interaction between FGFs and their specific receptors, enhancing the biological functions both *in vitro* and *in vivo*.[24] Some potential applications of various FGF-related treatments for mucositis, periodontal regeneration and wound healing are summarized in Table 1.[25—31] The role of bFGF in the dental pulp development, repair, and regeneration has been suggested via influence on cell proliferation, differentiation, angiogenesis, neural differentiation, dentoalveolar mineralization.[32,33] However the effects of other type of FGFs on dental pulp repair and regeneration are limited and awaits further investigation.

Fibroblast growth factor receptors and their expression in healthy and diseased dental pulp and other tissues

There are four transmembrane tyrosine kinase receptors in the fibroblast growth factor receptor (FGFR) family: FGFR1, FGFR2, FGFR3, and FGFR4. Each FGFR consists of an extracellular ligand-binding domain, a transmembrane region, and an intracellular tyrosine kinase domain. The extracellular domain is composed of three immunoglobulin (Ig) domains (D1—D3), with FGFs binding primarily to the D2—D3 region. This binding induces FGFR dimerization and subsequent transphosphorylation of the intracellular domain.[34] It is well established that FGFR binding on various cell types can modulate specific cellular responses.[10] Additionally, the relationship between the increased expression of FGFRs and various diseases such as breast cancer, lung cancer, gastroesophageal cancer, bladder cancer, and hepatocellular carcinoma has been reported.[35—39] As noted above, numerous studies have investigated the regulation of FGFRs as a potential therapeutic approach for these diseases. In the oral cavity, FGFR1, 2, 3 and 4 are found to be differentially expressed in developmental tooth root, human DPSCs and SCAP with associated activation of transforming growth factor-β-activated kinase 1 (TAK1), extracellular signal-regulated kinase kinase (MEK)/extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (MAPK), but inhibition of phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt) signaling.[40—44]

Basic fibroblast growth factor

Among the FGF family, bFGF has been shown to induce various biological activities, including cell migration and differentiation. Notably, it acts as a key regulator of angiogenesis *in vivo*.[23,32] In the context of tissue engineering, bFGF has demonstrated an aggregating effect on stem cells from various origins, including bone marrow mesenchymal stromal cells (BMMSCs), adipose tissue-derived mesenchymal stem cells (ADMSCs), SCAPs, DPSCs, and stem cells from human exfoliated deciduous teeth (SHED).[9,45—47]

As a paracrine FGF, bFGF interacts with heparin/heparan sulfate (HS), a property that may help protect it from enzymatic degradation.[21,46] Studies have reported that bFGF can promote revascularization both directly and indirectly through the paracrine effects of mesenchymal stem cells. Additionally, it has been found to enhance the effects of follicle-stimulating hormone, parathyroid hormone, Egr-1, and breviscapine treatment.[14,16,48,49] In the dental pulp, bFGF was shown to stimulate proliferation, but inhibited alkaline phosphatase activity possibly via MEK/ERK signaling.[41] bFGF also stimulated the neuronal differentiation, angiogenesis, dentoalveolar mineralization, tooth root formation by regulation the activities of DPSCs and other types of cells.[33,40,50,51]

Table 1 The potential use of various FGFs in clinical treatment.

Medicine/components	FGF types	Functions
Palifermin	FGF7	For improving the radiotherapy- or chemotherapy-related oral mucositis.[22,25]
Repifermin	FGF10	For preventing the mucositis after autologous hematopoietic stem cell transplantation.[26]
FGF2	FGF2	For enhancing the healing process of chronic tympanic membrane perforation.[27] For benefiting burns or chronic ulcers healing.[2,28—30] For the periodontal regeneration of replanted avulsed teeth.[31]
FGF19	FGF19	For regulating systemic molecules including glucose, phosphate, and bile acid.[22]
Proangiogenic growth factors (FGF2, VEGF, and PDGF)	Growth factor mixture	For inducing revascularization and healing in diabetic wounds.[12]

VEGF: vascular endothelial growth factor, PDGF: platelet-derived growth factor.

Dental stem cells

There are many stem cell sources from teeth and surrounding tissues. One of them is DPSCs which are originated from dental pulp and show gene expressions of CD271, CD166, CD146, CD106, CD105, CD90, CD73, CD59, CD49, CD44, CD29, CD13, CD10, CD9. They showed higher expression of NANOG and SOX2 than periodontal ligament stem cells (PDLSCs), and SCAPs are suspected with highly proliferative potential compared with DPSCs. Both of them showed the ability of differentiation into adipocytes and odontoblasts, however, several studies have indicated that SCAPs are considered to have a higher mineralization potential.[52] Besides, compared with DPSCs and PDLSCs, an *in vivo* study described that SCAPs had the greater ability for mineral tissue formation.[53] According to the origin, SCAPs are believed to play a key role on the pulpal revascularization.[5,54] DPSCs under the effect of bFGF showed evident angiogenic and neurogenic differentiation.[55] The comparative summary of DPSCs and SCAPs shown in Table 2.

Potential roles of basic fibroblast growth factor, dental pulp stem cells and stem cells from apical papilla in treatment of cardiac, retinal, cartilaginous, tracheal pathologies, and diabetes

In cardiac diseases, tissue engineering for myocardial infarction has been under development for years, with revascularization at the transplantation site playing a crucial role in achieving a satisfactory prognosis. Restoring a mature and abundant vascular system remains a key objective in regenerative healing. Studies have shown that vascular growth factors, such as bFGF, when attached to a biocompatible scaffold, enhance angiogenesis.[8] Additionally, systemic injection of bFGF has been found to improve cardiac function when used in conjunction with human pluripotent stem cell (hPSC)-derived cardiovascular progenitor cells (CPCs) as a regenerative treatment.[17] Accordingly, photobiomodulation by low level laser was shown to stimulate bFGF, VEGF-A, VEGF-C, VEGF-D, bone morphogenetic protein-9 (BMP-9) and VEGF receptors' expression and capillary-like vascular structure formation in DPSCs.[56]

Percutaneous trans-myocardial revascularization (PTMR) and trans-myocardial revascularization (TMR) have also been shown to promote angiogenesis within the channel remnants they create.[57] Research indicates that the combination of TMR with vascular growth factors—including VEGF, bFGF, and insulin-like growth factor-1 (IGF-1)—enhances both transplanted cell survival and left ventricular (LV) function in laboratory animal models. As a result, while TMR alone contributes to revascularization, the addition of vascular growth factor therapy significantly amplifies angiogenic effects.[58] Furthermore, trans-myocardial drilling revascularization combined with heparinized bFGF-incorporated degradable stent implantation (TMDRSI) has demonstrated notable benefits for acute myocardial infarction, including enhanced cell proliferation, survival, myocardial remodeling, and LV function. Moreover, this approach, when combined with BMMSCs transplantation, further improves myocardial regeneration.[11,59] Munarin et al. reported that regenerative engineering therapy utilizing VEGF and bFGF accelerated angiogenesis in a three-dimensional (3D) model.[60] This marked a significant breakthrough, transitioning from traditional two-dimensional models to a more physiologically relevant 3D perspective. Intriguingly miR4732-3p mimic treatment and extracellular vesicles from human DPSCs showed cytoprotective of cardiomyocytes and preserved cardiac functions against ischemic insult, decrease infarct and cardiac inflammation in infarct nude rats.[61,62] Intramyocardial injection of DPSCs into infarct nude rats significantly induced angiogenesis, decreased infarct size, and improve ventricular functions.[63] Moreover, DPSCs was found to attenuate the D-galactose-induced cardiac aging in experimental

Table 2 Comparison of the characteristics of DPSCs and SCAPs.[52–55]

	DPSCs	SCAPs
Origin	Dental pulp	Apical papilla
Surface MSC markers	CD271, CD166, CD146, CD106, CD105, CD90, CD73, CD59, CD49, CD44, CD29, CD13, CD10, and CD9; but not CD133, CD117, CD45, CD34, CD31, CD24, CD19, or CD14	CD166, CD146, CD106, CD105, CD90, CD73, CD61, CD56, CD51, CD44, CD29, CD24, and CD13; but not CD150, CD117, CD45, CD34, CD18, or CD14
Proliferation potential	Lower	Higher
Tissue formation	Higher ability of vascular formation	Higher mineralization potential
Differentiation potential	- Odontogenesis - Adipogenesis - Myogenesis	*in vitro* study showed) - Odontogenesis - Adipogenesis - Neurogenesis - Osteoblastic cells.
bFGF application	- Promote the proliferation - Enhance the tendency to angiogenic and neurogenic differentiation	- Promote the proliferation - There is not enough evidence indicating that bFGF can induce the specific differentiation pathways on SCAPs.

MSC: mesenchymal stem cells, bFGF: basic fibroblast growth factor.

rats.[64] All these results support the important role of bFGF and stem cells from dental pulp and other sources for treatment of myocardial diseases. However, further studies are needed to know the possible use of SCAPs and substantiate these findings and optimize their clinical application.

In retinal, cartilaginous, tracheal pathologies and diabetes, tissue regeneration is closely linked to revascularization. In retinal pathologies such as retinopathy of prematurity (ROP), pathological neovascularization can lead to blindness. Studies have shown that treatment with an appropriate dose of VEGF or bFGF gene therapy can protect astrocytes and enhance physiological revascularization.[13] Autologous DPSCs from extracted 3rd molar was further found to improve the corneal endothelial cell production and avoid corneal transplantation.[65] Both human DPSCs and SCAPs or their extracellular vesicles are found to provide retinal ganglion cell neuroprotection, promote retina cells formation, as well as retina and optic nerve injury regeneration with expression of biomarkers' gene of retina epithelial cells and retina progenitor cells such as Retina and anterior neural fold homeobox (RAX), PAX6, LIM homeobox 2 (LHX2), SIX homeobox3 (SIX3), Zonula occludens-1 (ZO-1), Retina pigment epithelium specific 65-kD protein (RPE65), Bestrophin-1 (BEST1), Cellular retinaldehyde binding protein (CRALBP), and Melanocyte inducing transcription factor (MITF). This can be derived from the paracrine effect or cell replacement by human DPSCs and SCAPs for treatment of retina diseases.[66–69] In addition, applying these growth factors to the auricular perichondrium has been shown to induce angiogenesis. Furthermore, experiments using angiogenic inhibitors have suggested a potential relationship between revascularization and cell/tissue regeneration.[70] In tracheal healing, topical administration of fibrin glue enriched with bFGF improves the viability of de-vascularized trachea autograft than no treatment, suggesting the possible importance of bFGF to enhance vascular networks formation.[71]

In the context of islet transplantation for diabetic patients, a major challenge is the lack of islet vascularization due to impaired extracellular matrix (ECM) proteins.[72–74] Recombinant collagen combined with bFGF has been shown to promote angiogenesis and mimic the environment necessary for ECM secretion.[73] Research has demonstrated that bFGF-induced revascularization is a fundamental mechanism of tissue regeneration. Moreover, human DPSCs can differentiate to insulin producing islet cells, and are shown to be effective for treatment when transplanted into diabetic rats.[75,76] Similarly, SCAPs are also found to differentiate into pancreatic β-islet cells as indicated by expression of C-peptide, glucagon and insulin.[77] So HDPCs and SCAPs can be potentially used for treatment of diabetes However, many underlying mechanisms remain to be fully elucidated.

Role of basic fibroblast growth factor and dental pulp stem cells in revascularization

The proliferation of human DPSCs is induced by various concentrations of exogenous bFGF.[55] And *in vitro* study demonstrated that bFGF induces a cell homing effect in DPSCs, comparable to that elicited by granulocyte colony-stimulating factor (G-CSF). It was suggested that bFGF plays a significant role in the migration of endogenous progenitor cells toward sites of regeneration.[5] Under the action of bFGF, DPSCs showed direct endothelial differentiation. Apart from direct endothelial differentiation, stem cells promote vascularization through a paracrine regulatory relationship by secreting angiogenic factors, which indirectly stimulate endothelial cell activity. However, there is insufficient evidence to demonstrate the exogenous bFGF having the direct influence on the secretion of angiogenic factors by DPSCs or SCAPs.[78] This point can be further addressed in the future.

Role of basic fibroblast growth factor and stem cells from apical papilla in pulpal revascularization and regeneration

Two critical factors for the success of endodontic treatment are complete disinfection and the healing process. Several pulp capping materials, such as calcium hydroxide and mineral trioxide aggregate (MTA), are used for treating pulp pathologies. However, their role in pulp regeneration is limited.[45] The goal of regenerative endodontics is to induce pulp- and dentin-like tissues to restore the pulp vitality.[7] Although cell-based therapy for open apices has enhanced regeneration, greater cell-homing effects and a clearer understanding of the therapeutic limits regarding defect size are necessary to achieve satisfactory prognoses.[4] Among these factors, an abundant vascular network serves as a cornerstone for successful regeneration, as it delivers essential nutrients and growth factors required for cell proliferation and differentiation.

Currently, pulp revascularization is primarily applied to immature teeth, as their sufficiently large apical foramen provides the necessary vascular network for regeneration.[7,79] In contrast, mature teeth with closed apices face challenges in dental tissue regeneration due to limited nutrient, oxygen, and growth factor supply through vascularization. A systematic review indicated that stem cell transplantation may enhance pulp regeneration; however, the number of studies conducted has been limited and possibly lacks standardization.[6] Autotransplantation of minced dental pulp tissues from third molars of 6 patients to the instrumented, disinfected and blood filled mature permanent teeth showed partial success with 3 cases showing root canal calcification and 1 case showing pulpal sensitivity.[80] In 51 permanent teeth with pulp necrosis and apical periodontitis, inducing blood clot methods or application platelet-rich fibrin (PRF) were used for regenerative endodontics with an overall success rate of 76.5 % and recovery of pulpal sensitivity in 17.6–41.2 % of teeth.[81] In 32 patients with non-vital anterior teeth, after mechanical debridement, either PRF placement, or 3 weeks of Ca(OH)2 medication followed by PRF placement into root canals showed partial clinical success.[82] While recently regenerative endodontic procedures was reported to offer an alternative treatment for necrotic mature teeth with promising results, more standardized therapeutic protocols are required for further confirmation.[83]

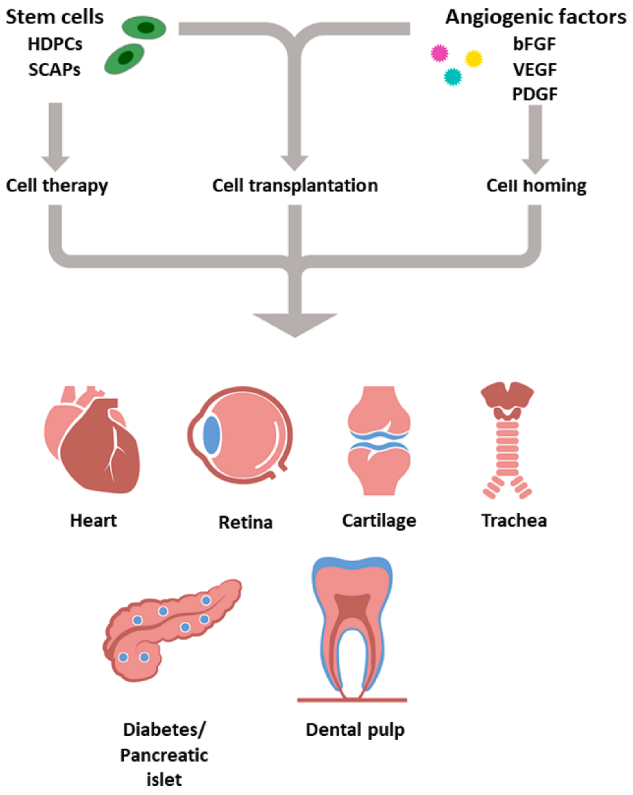

Figure 2 Human dental pulp cells (HDPCs), stem cells of apical papilla (SCAPs), basic fibroblast growth factor (bFGF) or other growth factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) alone or in combination can be used to promote regeneration for tissues/organs such as dental root, heart, retina, pancreas, cartilage, and more others via cell transplantation, cell homing and other techniques.

Various studies have demonstrated that bFGF induces revascularization by preserving endothelial cell survival and stimulating cell migration, proliferation, differentiation, and the secretion of vascular factors, including VEGF and hepatocyte growth factor (HGF), in a concentration- and time-dependent manner. SCAPs are also shown to differentiate into neuronal-like cells, which is important for pulpal regeneration.[84] Given the promising results of cell-based regeneration in medical science, researchers have explored the use of dental-derived tissues as a more accessible source for cell therapy. Studies have shown that bFGF enhances stem cell expression, and preserves the pericyte-like characteristics of DPSCs, thereby promoting angiogenesis and maintaining vessel-like structures.[45,85] bFGF was found to stimulate the growth, with increased expression of cyclin B1, cdc2, and tissue inhibitor of metalloproteinase-1 (TIMP-1) of SCAPs via associated MEK/ERK signaling.[41] bFGF also stimulates plasminogen activator inhibitor-1 (PAI-1), urokinase plasminogen activator receptor (uPAR), but decrease uPA to regulate matrix turnover in SCAPs.[42] Additionally, bFGF-loaded biocompatible scaffolds have demonstrated the ability to modulate odontogenic-related protein expression in human dental pulp cells, thereby enhancing regenerative potential.[45]

While cell-based therapy has shown strong regenerative potential, cell homing is emerging as a novel and more clinically feasible approach in regenerative endodontics. Kim et al. provided evidence for the regenerative potential of cell homing by utilizing basal cytokines in combination with PDGF, VEGF, or bFGF.[15] Studies have suggested that a mixture of growth factors can effectively recruit endogenous stem cells; however, minimizing the number of cytokines used should be considered.[15] Further research is necessary to establish the clinical feasibility of growth factors and cell homing strategies for future regenerative strategy.

Conclusions

DPSCs, SCAPs, bFGF or other growth factors alone or in combination can be potentially used to induce revascularization and regeneration for dental root and other systemic organs such as heart, retina, pancreas, cartilage, and more others via cell transplantation, cell homing and other techniques (Fig. 2). The application of bFGF and stem cells are shown to have promising results in enhancing the proliferation, migration, angiogenesis, and differentiation for regeneration of dental pulp and other tissues both *in vitro* and *in vivo*. However, their clinical applications—whether through cell transplantation or cell homing—remain inadequately understood. Further studies are needed to elucidate whether bFGF can induce vascular cell differentiation and angiogenesis of HDPCs and SCAPs and the associated signaling mechanisms. How to optimize cell transplantation delivery systems, develop more effective cell homing strategies and clinically apply bFGF and dental stem cells in conjunction with various biomaterials or other growth

factors for tissue/organ regeneration can be further explored. Whether similar clinical revascularization procedures with induction of blood clot formation, application of PRF or various growth factors with scaffolds can be used to stimulate pulpo-dentin regeneration in necrotic pulp of mature teeth with closed root apex should be further addressed in the future.

Declaration of competing interest

All authors declare there are no conflict of interest for this submission.

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