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Role of Angiogenesis in Endodontics: Contributions of Stem Cells and Proangiogenic and Antiangiogenic Factors to Dental Pulp Regeneration

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Abstract

Introduction—Dental pulp regeneration is a part of regenerative endodontics, which includes isolation, propagation, and re-transplantation of stem cells inside the prepared root canal space. The formation of new blood vessels through angiogenesis is mandatory to increase the survival rate of re-transplanted tissues. Angiogenesis is defined as the formation of new blood vessels from preexisting capillaries, which has great importance in pulp regeneration and homeostasis. Here the contribution of human dental pulp stem cells and proangiogenic and antiangiogenic factors to angiogenesis process and regeneration of dental pulp is reviewed.

Methods—A search was performed on the role of angiogenesis in dental pulp regeneration from January 2005 through April 2014. The recent aspects of the relationship between angiogenesis, human dental pulp stem cells, and proangiogenic and antiangiogenic factors in regeneration of dental pulp were assessed.

Results—Many studies have indicated an intimate relationship between angiogenesis and dental pulp regeneration. The contribution of stem cells and mechanical and chemical factors to dental pulp regeneration has been previously discussed.

Conclusions—Angiogenesis is an indispensable process during dental pulp regeneration. The survival of inflamed vital pulp and engineered transplanted pulp tissue are closely linked to the

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process of angiogenesis at sites of application. However, the detailed regulatory mechanisms involved in initiation and progression of angiogenesis in pulp tissue require investigation.

Keywords

Angiogenesis; proangiogenic and antiangiogenic factors; pulp regeneration; pulp stem cells

In blood vessel formation, the terms *vasculogenesis* and *angiogenesis* have been distinctively discussed. Vasculogenesis is defined as the formation of the primary vascular plexus from preexisting vascular precursor cells in the embryo (1). However, angiogenesis is the formation of new blood vessel from preexisting capillaries (1) and is responsible for the majority of the blood vessels formed during physiological and pathologic conditions (2, 3). Angiogenesis is initiated as a result of insufficient oxygen and nutrient supply and is regulated by tightly balanced production of numerous stimulatory and inhibitory chemobiological molecules such as growth factors, cytokines, matrix metalloproteinases (MMPs), endogenous angiogenesis inhibitors, transcription factors, adhesion molecules, and also components of the extracellular matrix (ECM) (4–8). The therapeutic modulation of angiogenesis process includes antiangiogenic therapies for fighting against malignancies (9–13) and proangiogenic therapies in repairing cardiovascular diseases and wound healing disorders by new blood vessels supplying blood to damaged tissues (9, 10, 14).

Human dental pulp is a highly vascularized tissue, which because of its vascular network and progenitor or postnatal dental pulp stem cells (DPSCs) has an impressive naturally inherent regenerative capacity (15–17). Dental pulp regeneration is part of the regenerative endodontic concept, which provides replacements for damaged tooth structures including pulp-dentin complex (18). It is a field in regenerative medicine and a branch of tissue engineering, which uses stem cells, biochemical factors, and engineering materials to replace lost or impaired biological tissues (19, 20). After isolation, the tissue-engineered stem cells are propagated in special medium and transplanted inside the prepared root canal space to develop into new pulp tissue (18). The success of tissue engineering depends on oxygen and nutrient transport to the implanted cells. If blood supply cannot be established rapidly, necrosis of the transplant will occur (21). This rule is also applicable to dental pulp regeneration, where angiogenesis is a key to both the development and regeneration of the dentin-pulp complex (17, 22). Angiogenesis establishes the blood supply and brings the oxygen, nutrition, and prevascular stem cells for regeneration (23).

Here we discuss an overview of the role of angiogenesis in dental pulp regeneration and the proangiogenic or antiangiogenic factors involved. The main aspects pursued in this review include the following:

1. The evaluation of the current state and the research trend regarding the role of angiogenesis in regenerative endodontics from January 2005 through April 2014.
2. The determination of the elements or components, such as the stem cells or proangiogenic or antiangiogenic factors, that are involved directly in the

angiogenesis process in dental pulp regeneration and the field of regenerative endodontics.

3. The clarification of strong and weak points regarding the angiogenesis events in dental pulp regeneration to introduce the present challenges and complexities in regenerative endodontic procedures that should be taken into consideration in research studies. Regarding the current state, in the conclusion section for each evaluated heading, the current state and research trends have been introduced and also the weak points or challenges are addressed to aid future studies to target these points.

Materials and Methods

Purpose of Review

The present review was conducted to evaluate the role of angiogenesis in dental pulp regeneration. Specifically, the potential effects of cell-related factors such as the contribution of stem cells and the proangiogenic and antiangiogenic factors in dental pulp regeneration were reviewed through the literature.

Inclusion and Exclusion Criteria

The inclusion criteria considered all articles including review studies, *in vitro* or *in vivo* studies, and case reports in peer-reviewed journals published in English from January 2005 through April 2014 that evaluated the cellular and elemental factors that are directly related to angiogenesis process in dental pulp regeneration. The studies that investigated the effects of angiogenic factors in regenerative endodontic procedures were included, whereas other investigations that did not address these criteria were excluded.

Search Methodology

The search methodology used in this review article included electronic searches that were done in the PubMed database by using key words mentioned in the MeSH headings regarding the role of angiogenesis in the dental pulp regeneration and the stimulatory or inhibitory factors in pulpal angiogenesis process.

Search Strategy

In the electronic search of scientific papers in the PubMed database the following key words were used in combination with angiogenesis: dental pulp regeneration, dental pulp stem cells, orthodontic forces, proangiogenic growth factors such as vascular endothelial growth factor, fibroblast growth factor, platelet-derived growth factor, angiopoietins, matrix metalloproteinase, stem cell factor, and antiangiogenic growth factors. A number of full-text articles and the reference lists of the relevant articles were also evaluated to supplement the search. The evaluation of the eligibility and finding of relevant data was done independently by 2 reviewers. A third reviewer was selected for resolving of any disagreements met during evaluation processes.

Dental Pulp Regeneration

Contributions of DPSCs and Angiogenesis—In stem cell biology, which is a part of tissue regenerative procedures, the highly potential stem cells, which are provided from vital tissues, are propagated and used for treatment of different pathologic conditions. Among different sources for stem cells such as umbilical cord blood, bone marrow, peripheral blood, and adipose tissue, the most common sources of stem cells used in this field are the mesenchymal stem cells isolated from bone marrow (BM-MSCs) (24, 25). In addition, DPSCs are introduced as another source for tissue regeneration procedures (18, 24, 25). DPSCs are postnatal, multipotent stem cells with similarities and some limitations to BM-MSCs (18, 26). Several authors have also reported some advantages in clinical usage of DPSCs including lower mortality rate, less legal or ethical issues, easy access from extracted teeth, and cryopreservation without losing their multi-differentiation potential (24–28).

Sieveking and Ng (29) found 2 distinct roles for stem cells such as BM-MSCs. They may act in a paracrine fashion through expression of proangiogenic factors. Alternatively, they may differentiate into endothelial cells and directly participate in neoangiogenesis. The activity of human dental pulp cells in secretion of proangiogenic factors has been well-documented by many authors (30–35). Bronckaers et al (30) demonstrated that human dental pulp stem cells (hDPSCs) are able to induce angiogenesis in a paracrine fashion through expression of a wide range of angiogenic factors including vascular endothelial growth factor (VEGF) and monocyte cheomtactic protein-1 (MCP-1). Furthermore, hDPSCs can stimulate the migration of endothelial cells through activation of the PI3K/AKT and MEK/ERK signaling pathways *in vitro*. Other authors have also shown that DPSCs are able to secrete a variety of proangiogenic factors including VEGF, fibroblast growth factor 2 (FGF-2), platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1), MMP-9, and transforming growth factor beta (TGF-β) and promote the migration and tubulogenesis activity of endothelial cells (22, 31–35) (Fig. 1).

Concerning the endothelial differentiation potential of hDPSCs, several investigators have indicated that in the presence of specialized differentiation medium, hDPSCs can express some of the endothelial cell markers including CD31, CD105, CD34, and von Willebrand factor *in vitro* (36–38). Janebodin et al (39) indicated that DPSCs can resemble perivascular supporting cells and induce more mature blood vessels when co-cultured with endothelial cells.

The dental pulp stem cells of exfoliated teeth (SHED) are capable of differentiating into endothelial-like cells (40, 41). Bento et al (41) indicated that VEGF/MEK1/ERK signaling pathway is a key regulator of the endothelial differentiation of DPSCs. Liu et al (42) showed that the inhibition of miR-424 might assist the dental pulp regeneration process. Kim et al (43) reported that a sudden increase in SIRT1 gene expression can up-regulate the angiogenic markers such as VEGF, FGF-2, and endothelial cell adhesion molecules such as vascular endothelial cadherin and platelet endothelial cell adhesion molecule-1. Dissanayaka et al (44) reported that the direct co-culture of DPSCs and endothelial cells can enhance the expression of angiogenic phenotype *in vitro*. Nakashima and Iohara (45) found that CD31(−)/CD146(−) or CD105(+) cell types isolated from dental pulp, in the presence of

stromal cell–derived factor-1, can produce pulp tissue including vascular and neuronal structure in 14 days, formation of dentin in 35 days, and impose trophic action on endothelial cells. Other cells of pulp tissue seem to have remarkable effects on angiogenesis process. Tran-Hung et al (22) co-cultured dental pulp fibroblasts with human umbilical vein endothelial cells and indicated that fibroblasts can induce angiogenesis through secretion of FGF-2 and VEGF (Table 1).

Proangiogenic and Antiangiogenic Factors

Mechanical Stimulation—Muscle contractions promote angiogenesis through enhanced production of nitric oxide from vasodilated blood vessels (9). Higher capillary shear stress also increases the expression of VEGF and angiogenesis in skeletal muscles (46). Derringer et al (47,48) detected an increase in the number of microvessels in pulp tissue of orthodontically moved teeth that was due to the elevation of the angiogenic growth factors. They later used a combination of 5 neutralizing antibodies against VEGF, FGF-2, PDGF, epidermal growth factor (EGF), and TGF-β to assess the angiogenesis process in human dental pulp of orthodontically moved teeth (49). They observed a significant decrease in angiogenesis of pulp tissue of subjected teeth (49,50). Grünheid et al (51) studied the dental pulp cellular responses to orthodontic forces induced by elastic bands for 1–168 hours and reported a series of responses including macrophage invasion, cell proliferation, and angiogenesis during experimental monitoring. In 2007 Derringer and Linden (52)demonstrated the release of proangiogenic growth factor, EGF, in human dental pulp of orthodontically moved teeth. Thus, mechanical alteration in tooth has a significant impact on local angiogenesis and tissue regeneration.

Biochemical Stimulation—The biochemical stimulation of angiogenesis is related to the production of proangiogenic and antiangiogenic factors including growth factors. The growth factors such as bone morphogenetic proteins have an impeccable role in tissue engineering (53). The DPSCs can secrete proangiogenic factors such as VEGF, FGF-2, PDGF, MMP-9, IGF-1, TGF-β, interleukin-8, and MCP-1 (30). Roberts-Clark and Smith (54) acclaimed that dentin matrix can act as a reservoir for these angiogenic growth factors, and after any injury to pulp-dentin complex, these substances are released to promote angiogenesis in regenerating pulp tissue (Table 1). However, the molecular and cellular mechanisms involved remain poorly understood.

VEGF—VEGF is one of the major proangiogenic growth factors with many regulatory impacts on neuronal and vascular cell function such as survival, proliferation, migration, and sprouting of capillary vessels at the secreted sites (55–57). After binding to their respective receptors on the cell surface, VEGF and FGF can activate intrinsic tyrosine kinases and initiate signaling cascades that impact angiogenesis events (58). Three growth factors including VEGF, FGF, and angiopoietin-2 are mostly expressed as a result of hypoxia occurring in ischemic tissues or rigidly growing tumorigenic tissues (59). The exposure of hDPSCs and human dental pulp fibroblasts to hypoxic conditions resulted in an increase in the level of transcription factor hypoxia-inducible factor-1alpha and VEGF in pulp cells; however, the FGF level was not responsive to hypoxia (33) (Fig. 1*A*).

Among all proangiogenic factors, VEGF is the most essential factor for differentiation of vascular system (60). VEGF was shown to be a potent mitogen for endothelial cells, which can promote their proliferation and migration (61). The treatment of dental pulp tissue with 0–50 ng/mL recombinant human VEGF or recombinant human FGF-2 for 7 days resulted in increased number of microvessels and neovascularization (62). VEGF-A is a member of VEGF family that is more extensively studied (63). Other VEGF family members include VEGF-B, -C, and -D, which are also expressed in the dental pulp tissue and have autocrine and paracrine effects during angiogenesis (63).

Bronckaers et al (30) and others reported a very high amount of VEGF secretion by hDPSCs in dental pulp (22,32–35). Bento et al (41) introduced a key role for VEGF in differentiation of pulp stem cells into endothelial cells. The dental fibroblasts can also enhance angiogenesis by secretion of FGF-2 and VEGF (22). Güven et al (64) introduced an alternative pathway known as cyclooxygenase-2–dependent pathway for expression of VEGF protein in dental pulp. Other adjunct treatments might affect the secretion of VEGF protein. Scheven et al (65) used low-power ultrasound (30 kHz) on the odontoblast-like cells and suggested that ultrasound has an autocrine effect that can enhance the dentin repair by increasing the production of main VEGF-A isoforms including VEGF-120, VEGF-164, and to a lower amount VEGF-188. Thus, VEGF is a key regulator of angiogenesis in the pulp tissue whose alterations may have significant impact on maintenance and regulation of pulp tissue and tooth integrity (Table 1).

FGF—The FGF family members are mostly single-chain polypeptides with 2 prototypes and 22 members (12). The first prototype FGF-1, also known as acidic FGF, is the most important in the FGF family because it has the widest range of action and the capability of binding to all 7 FGF-receptor subtypes (12). FGF-1 can stimulate the proliferation and differentiation of all cell types required for blood vessel formation including endothelial cells (66–68). The other prototype FGF family member is FGF-2, also known as basic FGF, which is less potent than FGF-1and more potent than VEGF or PDGF. This prototype can enhance the proliferation of endothelial cells and also their organization into capillary-like network *in vitro* (66–68).

FGF proangiogenic factors are also well-discussed in the dental pulp regeneration processes (22, 30, 43). However, the majority of these studies were focused on the secretion and the function of FGF-2 molecule. As previously mentioned, FGF-2 can be produced by hDPSCs along with other proangiogenic factors (30) (Fig. 1*A*). This important growth factor is also produced by dental pulp fibroblasts (22). Kim et al (43) reported that a transient expression of SIRT1 gene can up-regulate the proangiogenic markers like FGF-2. Takeuchi et al (69) indicated that FGF-2, similar to granulocyte-colony stimulating factor, has wide effects on cell proliferation and migration during angiogenesis process. Li and Sae-Lim (70) demonstrated that FGF-1 applied on a collagen matrix carrier could induce the dental hard tissue formation like the dentin produced by $Ca(OH)_2$ (Table 1).

PDGF—PDGF is a dimeric glycoprotein that is composed of 2 A (−AA) or 2 B (BB) chains or a combination of A and B (AB) and has the potential to induce cell proliferation (71). Keck et al (72) demonstrated that VEGF and PDGF-B share significant homology. Although

both have mitogenic activity, they have different target cells and activities during angiogenesis events. The distinctive action of PDGF has also been mentioned by Matsuoka and Grotendorst (73). Generally, production of PDGF-BB by endothelial cells promotes the proliferation and migration of perivascular supporting cells to newly forming blood vessels. The interactions of perivascular supporting cells with endothelial cells through both paracrine and autocrine mechanisms are essential for stability and functionality of blood vessels.

The hDPSCs express this growth factor as well (22, 30,33–35) (Fig. 1*A*). Roberts-Clark and Smith demonstrated that the dentin matrix contains a higher amount of PDGF than other growth factors including VEGF and FGF-2 (54). Tran-Hung et al (32) showed that after dental pulp injury, production of PDGF-AB by endothelial cells is critical for recruitment of perivascular supporting cells to newly forming vessels and stabilization and maturation of these vessels.

Angiopoietins—The angiopoietins (Ang) are group of proteins with remarkable role in angiogenesis and lymphangiogenesis (74). Angiopoietins have 2 major forms including Ang-1 and Ang-2, which interact with Tie-1 and Tie-2 receptors on endothelial cells (74). Dental fibroblasts express Ang-2 along with other growth factors such as VEGF, FGF-2, PDGF, angiogenin, and EGF (22,75). El Karim et al (75) reported that different types of neuropeptides including calcitonin gene-related peptide, neuropeptide Y, substance P, and vasoactive intestinal polypeptide can modify the expression of mentioned angiogenic growth factors secreted from pulp fibroblasts. These factors play a critical role in initiation and stabilization of angiogenesis through competitive interactions with Tie-2 receptor (75). However, little is known about Tie-1 activity and functions during angiogenesis.

MMPs—MMPs are a group of important enzymes in angiogenesis. These biological molecules have a key role in degradation of the ECM of vessel walls, allowing the migration of endothelial cells (76) (Fig. 1). In 2009 Zheng et al (77) showed a significant increase in the level of MMP-3 and MMP-9 produced by either endothelial cells or endothelial progenitor cells in response to dental pulp injury. Muromachi et al (78) indicated that the amount of MMP-3 was increased after pulpotomy, which can induce the production of connective tissue growth factor/CCN family 2 (CTGF/CCN2) independent of the MMP-3 protease function. MMP-3 can dependently act on dynamin-related endocytosis and affects migration of pulp cells (78). In 2013 Ozeki et al (79) acclaimed that the proinflammatory cytokines including interleukin-1β, tumor necrosis factor-α, and interferon-γ can induce the production of MMP-3, increase cell proliferation, and present antiapoptosis effects on odontoblast-like cells derived from embryonic stem cells.

Stem Cell Factor—Stem cell factor (SCF) is a chemokine that is fast acting and plays a key role in hematopoiesis during embryonic period (80). It was shown that SCF is one of the important factors related to the migration of stem cells through the endothelium to be recruited in required site. In the process of recruitment of stem cells, the first step is the homing or navigation of these cells to the required site for repopulation and differentiation (81). Pan et al (82) evaluated the effect of this proangiogenic factor in regeneration of dental pulp and showed that high amounts of SCF can be found in sub-odontoblastic layer of Höhl

in dental pulp (Fig. 1*A*). They reported that SCF has the potential to induce cell homing, angiogenesis, and tissue remodeling effects at applied sites (82).

Other Biochemical Substances—Limjeerajarus et al (83) showed that iloprost, a PGI2 analogue, can increase the expression of VEGF, FGF-2, and PDGF growth factors in pulp tissue (84). Simvastatin (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor) is a chemical substance from the statin family that can enhance angiogenesis and endothelial cell functions (85) and stimulate new bone formation. Min et al (86) assessed the effect of simvastatin on hDPSCs and found that after exposure to simvastatin, pulp stem cells can express odontogenic and angiogenic markers. Kim et al (87) used hinokitiol, a natural iron-chelating agent, on dental pulp cells and reported an increase in production of hypoxia-inducible factor-1alpha and VEGF in pulp cells and promotion of their angiogenic potential.

L-mimosine (prolyl hydroxylase inhibitor) can increase the expression of VEGF in applied tooth slices (88). Kajiya et al (89) acclaimed that LL-37 peptide can induce the migration of the human pulp cells and promote pulp-dentin complex regeneration. Izumi et al (90) localized metallothionein, a cysteine-rich protein, in dental pulp after injury and suggested that metallothionein is closely related to the angiogenesis events and proliferation of differentiated odontoblast cells during the healing process.

Biochemical Inhibitors—Bronckaers et al (30) reported that DPSCs can produce antiangiogenic factors including endostatin, IGFBP3, uPA, TIMP-1, and PAI-1. Roberts-Clark and Smith (54) indicated that the dentin matrix components in low concentrations have proangiogenic impact, whereas in high concentrations they have inhibitory effects on angiogenesis events of dental pulp. Hyperglycemia that is due to negative influence on immune system function can interfere with inflammatory phase including microvascular problems leading to chronic periodontal disease (91–94). Garber et al (95) reported no complete dentin bridge formation under pulp-capping material in diabetic rats. Hyperglycemia can also drastically affect inflammatory condition of dental pulp tissue and interfere with cellular proliferation and angiogenesis, which jeopardizes the pulp tissue healing. There is now a large family of endogenous inhibitors of angiogenesis whose function in tooth development and regeneration needs evaluation. These include thrombospondin-1 and thrombospondin-2, whose expression plays a significant role in vascular homeostasis and pathologic neovascularization. Another important physiologic antiangiogenic agent is platelet factor 4. Fragments of platelet factor 4 are effective inhibitors of angiogenesis process and are useful agents for therapeutic purposes (96). However, the antiangiogenic role of these agents on angiogenesis events of dental pulp tissue has yet to be discussed in studies.

Conclusions

Angiogenesis is an undeniable process during whole dental pulp regeneration. The survival of engineered and transplanted pulp tissue is closely related to formation of new blood vessels at applied sites. The role of angiogenesis in vital pulp therapies is also of utmost importance in this field. The neovascularization induced by hDPSCs, side population cells, and dental pulp fibroblasts in inflamed pulp tissue can promote the healing process of

injured tissue. The contribution of DPSCs to angiogenesis has been more evaluated in paracrine secretion of a wide range of angiogenic factors. These cells have perivascular supporting cell topography and function and can promote the migration and tubulogenesis of endothelial cells. Although there is limited evidence regarding the direct differentiation of DPSCs to endothelial cells, the direct differentiation of DPSCs to endothelial cells is absolutely required for dental pulp regeneration procedures in closed apex teeth. The need for direct differentiation of hDPSCs to endothelial cells can be more complex and difficult to achieve where the pulp tissue transplantation is performed in dental canals prepared in matured teeth. In this situation, the closed apex is the major concern for formation of anastomosis between newly formed vessels in the transplanted tissue and periapical vascular network.

Mechanical stimulations by orthodontic forces appear to have positive effect on angiogenesis process. This positive effect is due to the increased expression of several growth factors such as VEGF, FGF2, PDGF, EGF, and TGF-β in dental pulp tissue. However, the exact mechanisms and the cells involved are not clearly defined and may be unique to dental pulp cells. The impact of chemical stimulation and inhibition of angiogenesis events is through the expression of many growth factors, which are well-discussed by others. However, these growth factors act as a double-edged sword in reality. It is clear that angiogenesis events are tightly orchestrated and regulated by several intrinsic and extrinsic factors. Hence, the imposed extrinsic chemical stimulatory or inhibitory factors should be used firmly under control of clinicians. We still lack detailed knowledge of the regulatory angiogenesis events in the dental pulp and balanced usage of growth factors. In future studies, cautious and controllable manipulation of growth factors should be treated as an important goal to establish a practical, functional, and nonhazardous regenerated pulp tissue with regulated and controlled neovascularization process at desired sites.

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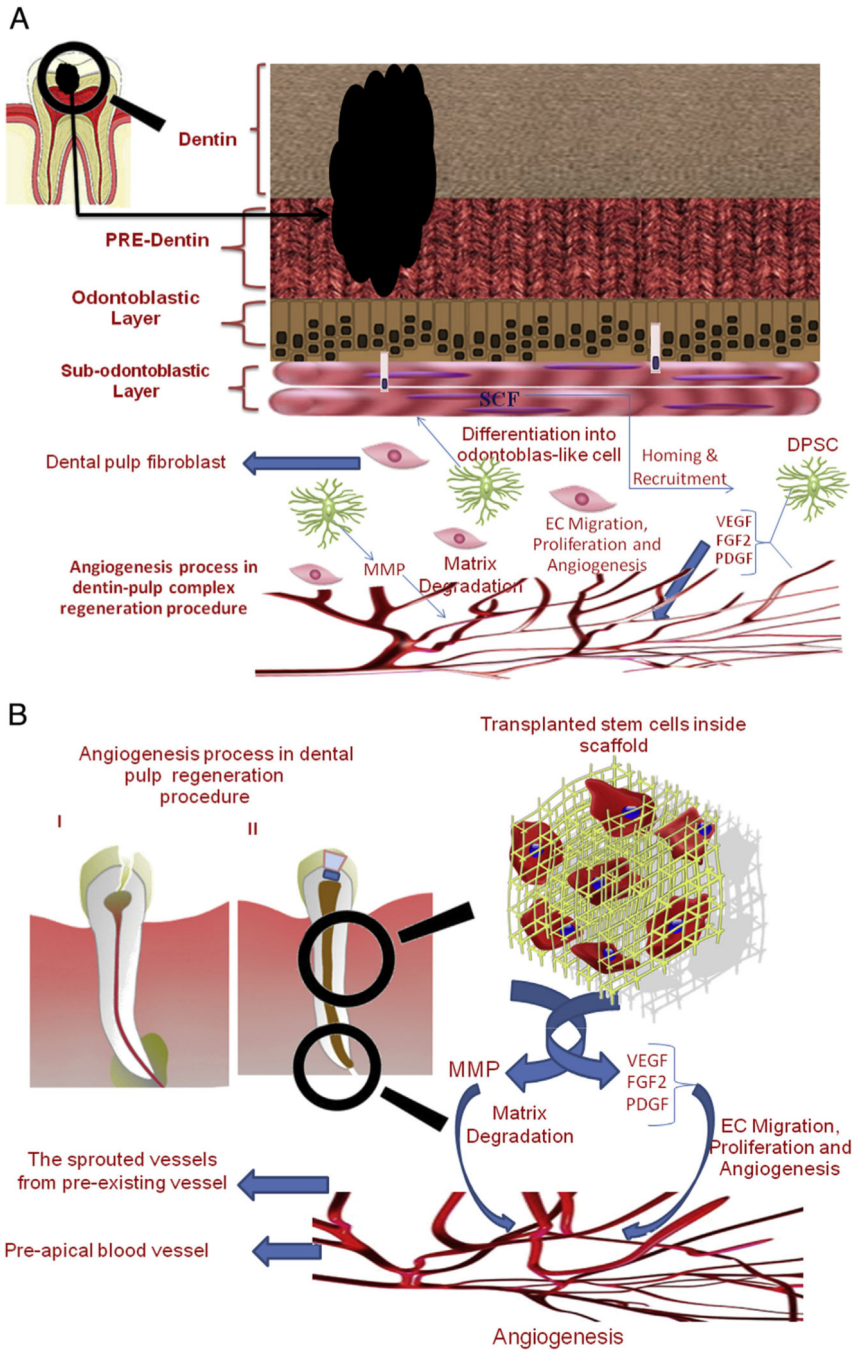

Figure 1.

Schematic presentation of angiogenesis process in regenerative endodontic procedures: (*A*) the dentin-pulp complex regenerative process including the contributions of DPSCs and growth factors contribution in the angiogenesis process occurring through this regenerative process; (*B*) the dental pulp regeneration procedure performed inside a prepared root canal by transplanting a tissue-engineered scaffold including stem cells, which secret the necessary growth factors for sprouting angiogenesis.

TABLE 1

Angiogenic Factors Involved in Dental Pulp Regeneration

Type of element	Angiogenic effects	Mechanisms of action
DPSCs	Proangiogenic and antiangiogenic	1. Expression of proangiogenic factors such as VEGF, FGF-2, PDGF, IGF-1, MMP-9, TGF-β, and MCP-1
		2. Differentiation into endothelial-like cells
		3. Promoting endothelial cell migration by PI3K/AKT and MEK/ERK
		Expression of antiangiogenic factors such as endostatin, IGFBP3, uPA, TIMP-1, and PAI-1
SHED	Proangiogenic	Differentiating into endothelial-like cells through the VEGF/MEK1/ERK signaling pathway
Dental pulp fibroblasts	Proangiogenic	Inducing the secretion of FGF-2 and VEGF
Orthodontic movements	Proangiogenic	Expression of proangiogenic factors such as VEGF, FGF-2, PDGF, EGF, and TGF-β
Dentin matrix components	Proangiogenic and antiangiogenic	In low concentrations act as a reservoir of proangiogenic factors
		In high concentrations act as antiangiogenic agent due to unknown mechanism
VEGF	Proangiogenic	1. Proliferation and migration of endothelial cells and maturation of sprouted capillary vessels
		2. Activation of intrinsic tyrosine kinases
		3. Differentiation of DPSCs into endothelial cells
FGF (FGF-1 and FGF-2)	Proangiogenic	Proliferation and migration of endothelial cells
PDGF	Proangiogenic	Proliferation and migration of perivascular supporting cells
Angiopoietins (Ang-1 and Ang-2)	Proangiogenic	Initiating and stabilization of angiogenesis through competitive interactions with Tie-2 receptor
MMP	Proangiogenic	Degradation of ECM of vessel walls allowing migration of endothelial cells
SCF	Proangiogenic	Homing or navigation of stem cells
Iloprost	Proangiogenic	Expression of VEGF, FGF-2, and PDGF
Simvastatin	Proangiogenic	1. Enhancing the endothelial cell functions
		2. Stimulation of DPSCs to express odontogenic and angiogenic markers
Hinokitiol	Proangiogenic	Production of hypoxia-inducible factor-1alpha and VEGF in pulp cells
L-mimosine	Proangiogenic	Expression of VEGF
LL-37 peptide	Proangiogenic	Migration of human pulp cells
Metallothionein	Proangiogenic	Enhancement of angiogenesis events and proliferation of differentiated odontoblast cells
Hyperglycemia	Antiangiogenic	Interfering with immune system cells function and inhibiting cellular proliferation