

Vascular Endothelial Growth Factor and Its Relationship With the Dental Pulp

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Abstract

The dental pulp is a loose connective tissue located within rigid dentinal walls. Therefore, when subjected to a stimulus, the pulpal tissue has little expansion capacity. The defense mechanisms of this tissue include the formation of tertiary dentin as well as the production of signaling molecules that help in the repair. The dentin matrix is rich in growth factors (GFs) that, when diluted and diffused into the pulp tissue, aid the healing process of the dentinopulpal complex. The angiogenic GFs participate in this event. Vascular endothelial growth factor (VEGF), a potent mitogen for endothelial cells, promotes endothelial cell survival and angiogenesis. Among its receptors, VEGFR-2 seems to be the most intimately associated with mitogenic activities, cell migration, vascular permeability, and survival of endothelial cells. This literature review addresses the cell-signaling process that occurs in response to a pulp stimulus up to its transduction in the target cell, describing the VEGF, as well as its characteristics and receptors. The reported studies have correlated the expression of VEGF and its potential functions that may have an impact on several dental specialties, thus indicating that further clinical investigations should be conducted in order to translate the results obtained until this moment primarily in laboratory experiments. (*J Endod* 2007;33:524–530)

Key Words

Dental pulp, growth factor, vascular endothelial growth factor, vascular endothelial growth factor receptors

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Dentistry has advanced remarkably as a science, and studies in the field of cell and molecular biology have given an important contribution by showing the phenomena that occur at the cellular level and elucidating the behavior of cells against different stimuli. The chemical messengers and signals and the protein macromolecules that compose the extracellular matrix (ECM) act as cellular ligands allowing the exchange of information between the cells. The ligand binds to specific sites on the cell membrane surface, which are the receptors. Activated by the binding to the ligand molecule, the receptors trigger intracytoplasmatic-signaling cascades that will stimulate or inhibit the transcription of a certain gene. Among the chemical signaling molecules are the growth factors (GFs). The GFs are synthesized by most cells and, when bound to specific receptors, will guide the behavior of the target cell. The vascular endothelial growth factor (VEGF) is considered the most important GF controlling the vascular responses in the body. It is a mitogen for endothelial cells, and its expression is related to the phenomenon of angiogenesis. This literature review addresses the cell-signaling process that occurs in response to a pulp stimulus up to its transduction in the target cell, describing the VEGF, its characteristics, and receptors. The findings of studies associating this GF with the dental pulp are also discussed.

Dental Pulp

The dental pulp is a specialized loose connective tissue, containing cells, fibers, ground substance, blood vessels, and nerve endings. It is enclosed within rigid dentin walls (1) and forms with the dentin an embryologic and functional entity known as the dentinopulpal complex. The pulp tissue has several functions including initiation, formation, protection, nutrition, repair, and promotion of tooth vitality. Histologically, four distinct zones can be distinguished in the pulp tissue: the odontoblastic zone at the pulp periphery, a cell-free zone beneath the odontoblasts, a cell-rich zone in the area of pulpal tissue, and the pulp core where there are major vessels and nerves (2).

Although fibroblasts are the most predominant cell type in the dental pulp, other cell types can be observed as well such as odontoblasts, blood cells, Schwann cells, endothelial cells, and undifferentiated mesenchymal cells. Additionally, during inflammatory episodes, cells involved in the immune response, such as macrophages, mast cells, antigen-presenting cells, and plasma proteins may also be found (2).

The collagen and reticular fibers are part of the ECM of the human dental pulp and play an important role in tissue support. Type I collagen is the main fiber component, but types III (3, 4), V, and VI (5) also represent a significant part of pulpal ECM.

The pulp cellular and fibrillar elements are surrounded by a gelatinous ground substance that has great water content and contain numerous glycosaminoglycans, glycoproteins, and proteoglycans. This gelatinous substance acts as a barrier against bacterial invasion, consisting of a nonspecific defense element (3). In addition, the cells are constantly interacting with the ECM. The ECM, in turn, has a wide functional significance, forming a substrate that provides the adequate conditions for growth and differentiation of the cells from the various tissues (4).

Pulp Injury

The intensity and duration of tooth injury, either from carious or traumatic origin, has considerable implications on the subsequent pulp response. In mild pulp injuries,

such as those caused by superficial carious lesions, the odontoblasts and other pulp cells may survive and become stimulated to secrete a reactive tertiary dentin matrix. However, more severe pulp injuries, such as those caused by deep carious lesions, may damage the odontoblasts and pulp cells underneath the lesion. These cells are often replaced by a new cell line similar to the odontoblasts, which will secrete a reparative tertiary dentin layer. In case of pulp exposure, this reparative dentin may lead to the formation of a dentin bridge that will contribute to pulp tissue healing. Even though the results from both types of injury are quite similar with respect to the deposition of a tertiary dentin matrix at the pulp-dentin interface, there are remarkable differences in the ongoing biologic events. The reactive dentin requires only the stimulation of the existing odontoblastic cells, whereas the reparative dentin requires the recruitment of pulp progenitor cells and their differentiation into odontoblast-like cells for further dentin matrix secretion. Both of these events require cell signaling for their start (6).

Cell Signaling and GFs

Typically, a special type of molecule is produced by one cell (i.e., the signaling cell) and detected by another (i.e., the target cell) by means of a protein receptor, which recognizes the signal and specifically responds to the signaling molecule. The protein receptor is the first step in a series of signaling transduction events in the target cell in which the incoming extracellular signal is converted into intracellular signals that guide the cell behavior (7–9) (Fig. 1).

Studies relating to the cell-signaling mechanisms during tooth development have been of paramount importance to underscore the events involved in dentin repair. The molecular signal to induce odontoblast differentiation and the subsequent stimulation for secretion of dentin matrix by these cells is a class of molecules called GFs. The GF are small protein cells with bioactive effects on several cell activities and

behaviors, including cell division, differentiation, and migration. They are found throughout the body and are responsible for the regulation of most cellular events (6).

During the carious process, the acids released from bacterial biofilm diffuse through the dental tissues and dissolve the enamel and dentin matrix. The dentin matrix has biologically active molecules that have the capacity of influencing the cell events in the dentinopulpal complex, when released during caries-induced demineralization (10). For example, the angiogenic GFs sequestered in the dentin matrix will be released during caries-induced demineralization and might contribute to the repair process together with the other sequestered cytokines (11). There are specific receptors for each GF on the cell surface. Bound to the receptor, the GF triggers an intracellular signaling cascade that will have an effect on cell behavior and function (12).

Most cell-surface receptors are associated with the ion channels, G protein, or enzymes. The nature of the intracellular signal triggered when the signaling molecule binds to the receptor will depend on the type of target cell and on the association that occurred. Enzyme-bound receptors became known because of their function in the responses to GFs. Most of these factors act as local mediators and are only required at very low concentrations. Responses to them are characteristically slow and require several intracellular transduction steps, which, in the end, will lead to changes in gene expression. The largest class of receptors associated with enzymes is the one whose cytoplasmic domain works as a receptor tyrosine kinase (RTK), phosphorylating lateral tyrosine chains into selected intracellular proteins. Such an RTK class includes most GF receptors (7–9) (Fig. 2).

Several GFs start and regulate the angiogenesis and might have either positive or negative regulatory effects (13–21) (Table 1). They may act either directly to regulate the endothelial cell function or indirectly to regulate the expression of other GFs by different cell types (22).

Cell communication may occur in an endocrine, paracrine, or autocrine fashion. In the first one, the hormones are released to the extracellular space, enter the blood capillaries, and are spread over the body, acting remotely on the target cell. In the paracrine fashion, the chemical signs act close to the secretion site, affecting cell types other than those that originated the sign. In the autocrine fashion, the chemical signs act on the secretion site, affecting the same cell type as the one that emitted the sign (7–9) (Fig. 3).

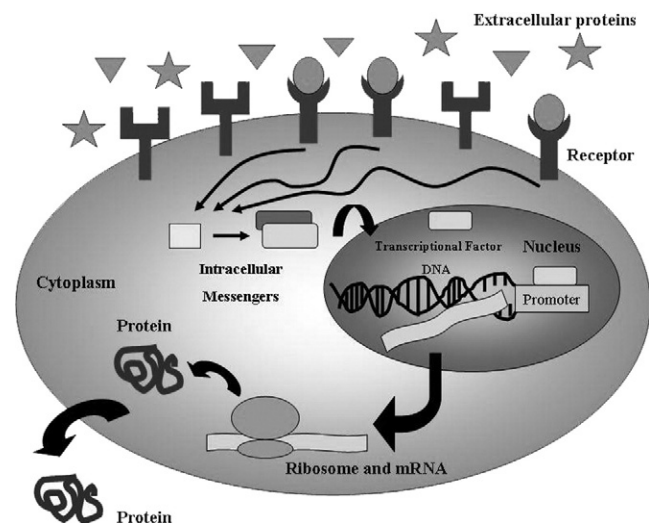


Figure 1. Transmission of the extracellular matrix signs into the cell and induction of protein synthesis. The extracellular matrix signals are often transmitted by growth factors, cytokines, and chemokines, which bind to the specific receptors present on the target cell membrane. These receptors are proteins that allow for the binding of specific signaling molecules. Thereafter, a series of intracellular signs is triggered, possibly leading to a phosphorylation process of cytoplasmic molecules called intracellular messengers. These molecules transmit signals from the cell membrane into the cell nucleus, activating the expression of one or several genes for a limited time. The extracellular signals may activate the transcription factor, a molecule that adheres specifically to a gene promoter, activating the gene transcription into its mRNA and the consequent protein synthesis.

Angiogenesis

Blood vessels may originate from two distinct processes: vasculogenesis and angiogenesis. In vasculogenesis, endothelial cell differentiation occurs from mesodermal precursor cells (angioblasts), whereas, in angiogenesis, new vessels are formed from preexisting vessels. Vasculogenesis occurs during the embryonic development and leads to the formation of the primary vascular plexus. These endothelial canals are further developed, forming a more complex system and ramifying into larger and smaller vessels. New capillary vessels are then formed through angiogenesis by the division of the original vessels (23).

Angiogenesis is part of an important natural process essential to a large number of physiologic (embryonic development, ovulation, and wound repair) and pathologic (arthritis, diabetic retinopathy, and tumors) processes. In many important diseases, the body loses control over angiogenesis, resulting in an excessive blood vessel development, as observed in retinopathy of prematurity, cancer, and psoriasis (24, 25).

Numerous angiogenic inducers have been identified, including the basic fibroblast growth factor (bFGF), transforming growth factor (TGF)- α , TGF- β , platelet-derived growth factor (PDGF), and tumor

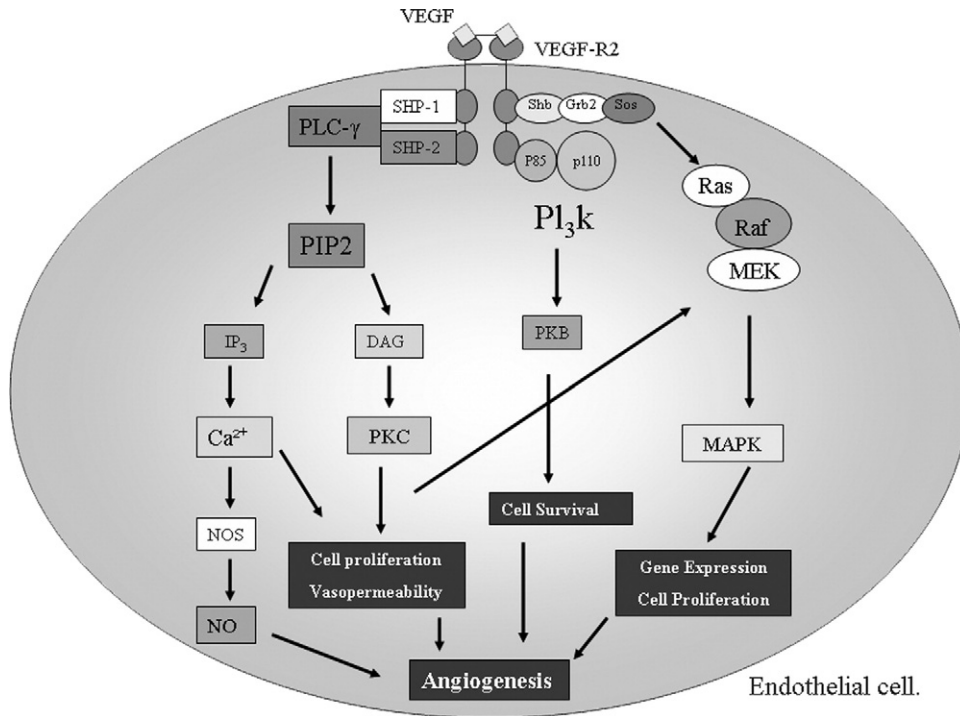


Figure 2. Signaling pathways activated by VEGF. Upon ligand binding, the receptor tyrosines are phosphorylated, allowing the receptor to associate with and activate a range of signaling molecules, including phosphatidylinositol 3-kinase (PI3K), Shc, Grb2, and the phosphatases SHP-1 and SHP-2. VEGF receptor activation can induce activation of the MAPK cascade via Raf stimulation leading to gene expression and cell proliferation, activation of PI3K leading to PKB activation and cell survival, activation of PLC-g leading to cell proliferation, vasopermeability, and angiogenesis. (Courtesy of © Sigma-Aldrich—Adapted with permission).

necrosis factor- α (TNF- α). Among these, VEGF is considered by many a master regulatory molecule for angiogenesis-related processes (26).

VEGF

Senger et al. (27) described the partial purification from a guinea pig hepatocarcinoma cell line of a protein that promoted an increase in vascular permeability. According to the authors, this protein, designated as vascular permeability factor, could be a specific mediator of the hyperpermeability of tumor blood vessels and be involved in the formation of tumor-associated ascites (26). Ferrara and Henzel (28) isolated an endothelial cell-specific mitogen from cultured bovine pituitary follicular cells. Because this protein presented growth-promoting activity only when associated with vascular endothelial cells, it was a so-called VEGF. In view of this, some authors decided to investigate the complementary DNA sequences encoding VEGF and vascular permeability factor. Some activities, such as endothelial cell mitogenesis and vascular permeability induction, were found to be mediated by both factors (29, 30).

The VEGF is originally a basic 45-kDa heparin-binding glycoprotein (28). The VEGF family currently includes six known members:

VEGF-A, B, C, D, E, and PDGF. VEGF-A and VEGF-B are intimately related to angiogenic phenomena. The alternative messenger RNA (mRNA) splicing of a single gene involving eight exons codifies a large number of VEGF isoforms (30), with polypeptide subunits containing 121, 145, 165, 189, and 206 amino acids (25). Among the five presented isoforms, VEGF₁₆₅ is the most abundantly found (31). The ECM of cells expressing VEGF₁₈₉ or VEGF₂₀₆ helps the endothelial cell growth. In contrast, VEGF is biochemically undetectable in the ECM of cells expressing VEGF₁₂₁ and VEGF₁₆₅. Nevertheless, ECM derived from cells expressing VEGF₁₆₅ is able to stimulate the endothelial cell growth, although less effectively. A possible explanation for this may be the fact of VEGF₁₆₅ being more powerful than the other isoforms (32).

Vascular endothelial growth factor proteins may become available for the endothelial cells by at least two different mechanisms: either by alternative splicing, originating diffused proteins like VEGF₁₂₁ and VEGF₁₆₅, or by protease activation and longer isoform cleavage (26). This GF is a key regulatory factor of vascular permeability and angiogenesis (33) (Table 2).

Vascular endothelial growth factor has a significant homology with PDGF-B and another VEGF family member, namely placenta growth

TABLE 1. Factors that upregulate and downregulate VEGF expression

Factors	Up- or Down regulation	Authors
Bacterial LPS and LTA	Upregulate	Botero et al. (13), Telles et al. (14)
Interleukin 1 beta	Upregulate	Konishi et al. (15)
IGF-I	Upregulate	Akeno et al. (16)
Ginsenoside-Rg1	Upregulate	Leung et al. (17)
ERRP (EGF receptor-related protein)	Downregulate	Rishi et al. (18)
PTEN (Phosphatase and tensin homolog deleted on chromosome 10)	Downregulate	Lee et al. (19)
HSulf-1	Downregulate	Narita et al. (20)
Chondromodulin-I	Downregulate	Yoshioka et al. (21)

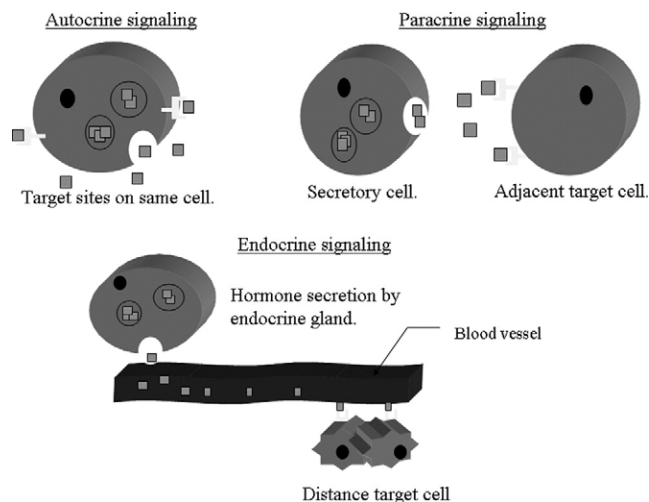


Figure 3. Release of growth factors. Cell communication may occur in an autocrine, paracrine, or endocrine fashion. In the autocrine fashion, the chemical signs act on the secretion site, affecting the same cell type as the one that emitted the molecular signal. In the paracrine fashion, the chemical signals act close to the secretion site, affecting cell types other than those that originated the signal. In the endocrine fashion, the hormones are released to the extracellular space, enter the blood capillaries and are spread over the body, acting remotely on the target cell.

factor (PIGF). PIGF can form dimers with VEGF, and, although it has little or no direct mitogenic or permeability enhancing activity, PIGF is able to potentiate significantly the activity of low VEGF concentrations (25). Despite being structurally related and mitogenic, PDGF and VEGF act on different target cells and present different biologic properties (29).

VEGF and Its Receptors

VEGF receptors are expressed on vascular endothelial cell surfaces. They are RTK and are present in three forms: fms-like tyrosine-kinase-1 (Flt-1) or VEGFR-1, fetal liver kinase-1 (Flk-1), kinase domain region (KDR) or VEGFR-2, and fms-like tyrosine-kinase-4 (Flt-4) or VEGFR-3 (34). They also interact with a coreceptor family, the neuropilins, which present the VEGF to its receptor, increasing the effectiveness of the signal transduction cascade (35, 36). There is strong evidence that these receptors possess different signal transduction properties and probably mediate different functions because of their distinct affinity to VEGF (31, 35, 37). This has posed many difficulties in clarifying their individual contribution in VEGF signaling (35) (Table 3).

VEGFR-1 was the first RTK identified a decade ago, and there were several unanswered questions regarding the functions of this molecule

TABLE 2. VEGF functions on endothelial cells

Function	Mechanism
Proliferation	Activation of mitogen-activated protein kinases
Permeability	Vesicovascular organelles; endothelial fenestrations; opening of junctions between adjacent endothelial cells
Invasion	Induction of metalloproteinases uPA, uPAR, TTPA
Migration	Activation of FAK, p38, nitric oxide
Survival	Induction of PI3K/Akt, Bcl2, A1, survivin, XIAP, or FAK; inhibition of caspases
Activation	Upregulation of integrin expression; alteration of cell cytoskeleton

(38, 39). Roberts et al. (40) reported that, in the absence of VEGFR-1, more ligand would be available to bind VEGFR-2 and the first step of signal transduction, RTK phosphorylation, would be upregulated. This upregulation, in turn, would lead to increased signaling through all of the numerous pathways that are activated by VEGFR-2 signal transduction, including proliferation, survival, migration, and permeability. These authors showed that negative modulation of VEGFR-1 influences VEGFR-2 signaling, interfering with the tyrosine phosphorylation level.

Compared with VEGFR-1, VEGFR-2 has less affinity to VEGF, even though it presents a greater signaling activity. The mitogenic activity in endothelial cells is mediated mainly by VEGFR-2, which determinates its proliferation. Additionally, it mediates the cell migration and vascular permeability in response to VEGF, whereas VEGFR-1 has a weak or undetectable response (31, 36, 37, 41–43).

VEGF and Dental Pulp

The dental pulp is a low-compliance tissue enclosed within rigid dentin walls (44). Some specific situations require an increase in vascular density. However, excessive blood vessel development can be deleterious and lead to irreversible pulp pathology because the pulp tissue has limitations for release of internal pressure (45). The most common cause of pulpitis is the presence of cariogenic bacteria and their byproducts (46). VEGF gene expression by human pulp fibroblasts was induced by black-pigmented bacteroides (*Pseudomonas endodontalis*, *Pseudomonas gingivalis*, and *Pseudomonas intermedia*) that may be involved in developing pulpal inflammation through the stimulation of VEGF production (47). Inflamed tissues enhance the expression of inflammatory mediators. Chu et al. (48) reported that proinflammatory cytokines can induce VEGF mRNA gene expression in human pulp and gingival fibroblasts, which may partially contribute to the destruction of pulpal and periapical tissues through the expansion of the vascular network coincident to progression of the inflammation.

Efforts have been made to investigate and relate the influence of lipopolysaccharides (LPS) produced by gram-negative bacteria and the lipoteichoic acid (LTA) produced by gram-positive bacteria on VEGF expression (13, 14). In the presence of sucrose, caries-related gram-positive bacteria produce large amounts of LTA (49), an amphiphilic molecule anchored to the bacterial cell wall and associated with inflammation (50). Gram-negative bacteria have also been found in teeth with dentin caries and symptoms of reversible pulpitis (51, 52) as well as in teeth with deep caries and/or pulp exposure and symptoms of irreversible pulpitis (53). In contrast to the LTA found in gram-positive bacteria, the cell wall of gram-negative bacteria contains LPS. LPS hydrophobic component (lipid A) determines the endotoxin properties of this molecule, such as toxicity, pyrogenicity, and macrophage and complement activation (54).

It has already been established that *Escherichia coli* and *P intermedia* LPS induce mRNA VEGF expression (55). It has also been verified that the inhibitor of the activator protein-1 (AP-1) transcription factor inhibits VEGF induction by *E coli* LPS and that the increase in VEGF production by LPS requires the synthesis of new proteins (55). In their study with pulp cell culture, Botero et al. (13) found that odontoblast-like cells and macrophages upregulated VEGF expression in response to LPS stimulus. However, this was not observed for undifferentiated pulp cells and fibroblasts. Therefore, they concluded that the ability to respond to LPS stimuli and thereby increase VEGF expression is not a general response for every cell type but rather a specific response for certain cells.

Using pulp cell culture, Telles et al. (14) found that the release of LTA induced VEGF upregulation in macrophages, odontoblast-like cells, and undifferentiated pulp cells. These observations suggest that the LTA

TABLE 3. Specificity of the receptors to the VEGF ligand and their biologic effects

VEGF Family Members	Receptor	Function
VEGF-A	VEGFR-1, VEGFR-2, neuropilin-1	Angiogenesis, vascular maintenance
VEGF-B	VEGFR-1	Not established
VEGF-C	VEGFR-2, VEGFR-3	Lymphangiogenesis
VEGF-D	VEGFR-2, VEGFR-3	Lymphangiogenesis
VEGF-E	VEGFR-2	Angiogenesis
PlGF	VEGFR-1, neuropilin-1	Angiogenesis and inflammation

produced by gram-positive bacteria might have a direct role in the increase of neovascularization observed in infectious sites. However, LTA did not induce VEGF expression in fibroblasts. In addition, these authors (14) believe that VEGF regulation in these cells is primarily posttranscriptional because mRNA VEGF expression remained constant under LTA stimulus.

The VEGF produced by the human pulp cells acts directly on them in an autocrine way and promotes chemotaxis and cell proliferation and/or differentiation. This action is mediated by VEGFR-2 and partly by signaling of AP-1 transcription factor by means of the c-fos protein, although both receptors (VEFR-1 and VEGFR-2) are present in the pulp cells (56). The presence of a coreceptor on the cell surface is required for signal transmission of LTA and LPS molecules. Toll-like receptor-4 has been identified as the necessary coreceptor to transmit the LPS signal (57–59). Conversely, toll-like receptor-2 may be a signaling component of a cellular LTA receptor (60).

To investigate the effect of the degree of adhesive resin polymerization on the induction of apoptosis, mouse odontoblast-like cells, undifferentiated pulp cells, and macrophages were exposed to unpolymerized, partially polymerized, or polymerized single bond adhesive system (3M/ESPE, St Paul, MN). It was observed that nearly 100% of the previously mentioned cells were apoptotic after a 12-hour exposure to unpolymerized single bond, whereas the untreated controls showed less than 10% apoptotic cells. Exposure to partially polymerized single bond–induced apoptosis in approximately 40% to 50% of the undifferentiated pulp cells and odontoblast-like cells after 12 hours, whereas exposure to adhesive resin polymerized for 40 seconds did not induce apoptosis of these cells. Macrophages seemed to be more susceptible to apoptosis upon exposure to partially polymerized or polymerized adhesive resin than the other studied cells (61). In another study, the same authors (62) investigated the effect of single bond adhesive system (3M) and one of its hydrophilic monomers, 2-hydroxyethyl methacrylate (HEMA), in VEGF expression by pulp cells, using the same cell types of the previous study plus gingival fibroblasts. VEGF expression was up-regulated in odontoblast-like cells and macrophages, while it remained unchanged in undifferentiated pulp cells and fibroblasts. Additionally, VEGF expression mediated by single bond or HEMA was not accompanied by remarkable changes on cell morphology that could have been detected at the light-microscopy level. The increase in VEGF expression may possibly explain pulp neovascularization observed in response to the application of adhesive resins at site of direct pulp exposure.

Roberts-Clark and Smith (11) isolated soluble and insoluble matrix fractions from human dentin and quantified the angiogenic GFs (including VEGF) by the enzyme-linked immunosorbent assay method, which were found in both types of matrixes. Therefore, dentin matrix contains angiogenic GFs and their release after injury might contribute significantly to the overall reparative response of the dentinopulpal complex.

Artese et al. (63) used immunohistochemistry to assess VEGF and factor VIII expression in pulp cells in normal healthy pulps and in cases of irreversible pulpitis. A statistically larger number of microvessels in the healthy pulps compared with irreversibly affected pulps were re-

ported. This could be explained by failure of the vascular function in the pulp tissue and blood flow reduction in the presence of an irreversible pathology.

The presence and distribution of VEGF in periapical granulomas with or without proliferating epithelium and periapical cysts have been assessed by immunohistochemistry (64). An immunopositive reaction for VEGF was observed in all periapical lesions, although with some differences in cell immunolabeling, which correlated to the lesions' stages of development. In periapical granulomas without epithelium, almost all inflammatory infiltrate presented strong reactivity. In periapical granulomas that had rests of Malassez, the inflammatory cells presented a moderate staining, whereas all epithelial cells were stained by VEGF. In the radicular cysts, all epithelial layers were immunopositive, whereas no inflammatory cell presented immunolabeling in these specimens.

The use of neutralizing antibodies (anti-h VEGF, FGF2, PDGF, TGF- β , and epidermal growth factor) allowed investigating the presence of a combination of five angiogenic GF diffusible in the human dental pulp during application of orthodontic force. The neutralizing antibodies significantly reduced the number of microvessels in the evaluated cell cultures, thereby indicating that this GF combination is released during orthodontic movement (65). Derringer and Linden (66) assessed the angiogenic pulp response both individually and by means of different combinations. Likewise, neutralizing antibodies (anti-h VEGF, FGF2, PDGF, and TGF- β) were used, and a significant decrease of pulp microvessels was observed; the increase of combinations tended to accentuate this decrease.

Kaku et al. (67) investigated whether recombinant human VEGF (rhVEGF) stimulated osteoclast differentiation during experimental tooth movement. The results of this study suggested that local administration of rhVEGF enhances the number of osteoclasts and may increase the rate of orthodontic tooth movement. Still regarding orthodontic movement, Kohno et al. (68) investigated the expression of VEGF in the periodontal tissues using immunohistochemistry. In addition, the authors assessed the effect of recombinant human VEGF (rhVEGF) injection on the rate of tooth movement and compared the number of osteoclasts induced by rhVEGF injection and recombinant human macrophage-colony–stimulating factor injection. The findings of this study showed VEGF expression in the periodontal tissues 10 days after the beginning of tooth movement. Several osteoblasts were detected in the periodontal ligament at the tension side. Moreover, the rate of tooth movement was significantly increased in the rhVEGF injection groups compared with the controls. In the orthodontic movement group, the (rh)VEGF + recombinant human macrophage-colony–stimulating factor combination produced a significant increase in the number of osteoclasts. According to the authors, these results suggest that VEGF and macrophage-colony–stimulating factor might function independently for osteoclast recruitment and that the combination of both would be more efficient for orthodontic movement. The reported studies have correlated the presence of VEGF and its consequences regarding the different dental specialties, thus indicating that further clinical investigations should be conducted in order to extrapolate the results obtained until this moment only in laboratory experiments.

Further research will investigate the expression of VEGF in primary teeth with and without physiologic root resorption because the effects of VEGF on bone remodeling during experimental tooth movement have been shown. The studies discussed in this review of literature are concise with respect to the presence of VEGF protein in the human dental pulp. It would be of interest that further studies are conducted to assess and quantify the presence and distribution of VEGF and its receptors in the pulp. In this way, therapies may be instituted to modulate VEGF in the dental pulp by its expression and/or the expression of its receptors. Additionally, the expression of these proteins should be evaluated in sound teeth and in teeth with active and inactive carious lesions.

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