Functionalized Scaffolds to Control Dental Pulp Stem Cell Fate

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Abstract
Emerging understanding about interactions between stem cells, scaffolds, and morphogenic factors has accelerated translational research in the field of dental pulp tissue engineering. Dental pulp stem cells constitute a subpopulation of cells endowed with self-renewal and multipotency. Dental pulp stem cells seeded in biodegradable scaffolds and exposed to dentin-derived morphogenic factors give rise to a pulplike tissue capable of generating new dentin. Notably, dentin-derived proteins are sufficient to induce dental pulp stem cell differentiation into odontoblasts. Ongoing work is focused on developing ways of mobilizing dentin-derived proteins and disinfecting the root canal of necrotic teeth without compromising the morphogenic potential of these signaling molecules. On the other hand, dentin by itself does not appear to be capable of inducing endothelial differentiation of dental pulp stem cells despite the well-known presence of angiogenic factors in dentin. This is particularly relevant in the context of dental pulp tissue engineering in full root canals in which access to blood supply is limited to the apical foramina. To address this challenge, scientists are looking at ways to use the scaffold as a controlled-release device for angiogenic factors. The aim of this article was to present and discuss current strategies to functionalize injectable scaffolds and customize them for dental pulp tissue engineering. The long-term goal of this work is to develop stem cell–based therapies that enable the engineering of functional dental pulps capable of generating new tubular dentin in humans. (J Endod 2014;40:533–540)

Key Words
Angiogenesis, dental pulp stem cells, dentin, morphogenic signals, pulp biology, regenerative endodontics, tissue engineering

A major goal of the health sciences in the 21st century is to develop clinically relevant strategies for tissue regeneration. The reasoning for this goal comes from the realization that the best substitute of an organ/tissue lost because of disease or trauma is the actual organ/tissue. Broadly speaking, this can be achieved either by transplantation or regeneration. Transplantation-based strategies have been successfully used for decades. However, organ/tissue rejection is a major threat that has been addressed with the prolonged use of immunosuppressive drugs, which carry intrinsic risks for the patient. On the other hand, tissue regeneration mediated by targeted activation of host stem cells or the delivery of autologous stem cells may allow for similar results as transplantation-based strategies without the need for chronic immunosuppressive therapies. However, tissue regeneration is certainly not devoid of significant challenges. These challenges include the development of strategies for the recruitment or isolation of appropriate stem cells and the generation of a suitable microenvironment that enables the stem cells to differentiate, proliferate, and give rise to a fully functional organ/tissue in the correct shape and size. Although these are rather substantial challenges, it is becoming increasingly evident that the successful development of tissue regeneration strategies using autologous cells might have long-lasting benefits that surpass potential risks. This review focuses on 1 aspect of tissue regeneration (ie, the development of functionalized scaffolds that provide a conducive microenvironment for controlled differentiation of stem cells and the generation of a new dental pulp for the treatment of necrotic immature permanent teeth).

Tissue Engineering
Tissue engineering is a multidisciplinary science that aims at the development of clinically relevant strategies for the regeneration of a tissue or organ (1). It involves the identification of progenitor cells capable of tissue regeneration when seeded in biodegradable scaffolds and exposed to morphogenic signals (1–3). Scaffolds must be uniquely developed for the regeneration of each specific tissue or organ. Furthermore, they share common features such as allowing cell attachment, diffusion of nutrients and oxygen, being biodegradable, and having physical properties aligned with those of the tissue/organ to be regenerated (3). In addition, the scaffolds can be functionalized by enhancing conditions for cell attachment and survival and providing morphogenic signals that supplement those coming from the host and enable guidance of stem cell differentiation (5).

Broadly speaking, scaffolds can be divided into (1) casted (ie, fairly rigid and custom-made for specific purposes) and (2) injectable (ie, low viscosity gels that can be delivered and “molded” at the site that requires tissue regeneration). Both types
of scaffolds can be functionalized with morphogenic signals. Notably, these signals are typically proteins with a short half-life. Therefore, the development of a strategy for controlled release of these proteins is critical to maximize their effects for predetermined time periods. Morphogenetic proteins can be incorporated both into casted scaffolds using copolymers such as poly(lactic-co-glycolic acid) and gas-foaming approaches (4, 5). They can also be mixed with injectable scaffolds such collagen or the self-assembling hydrogel PuraMatrix (BD Bioscience, Franklin Lakes, NJ), but in this case it is very difficult to slow down the degradation rate of the proteins. To address this issue, it has been suggested that natural polymers derived from brown algae (eg, alginites), which are biocompatible and present low immunogenicity, can be used in combination with injectable scaffolds to serve as a "slow-release" device for morphogenic signals (6, 7). Notably, the gelation process in the presence of divalent ions at physiological levels is a very simple way to incorporate, protect, and release morphogenic factors from alginate microspheres in a controllable rate (8, 9).

The biological standard for the controlled release of morphogenic factors in dentin tissue engineering is the microenvironment observed during tooth development (10, 11). Investigators have attempted to understand this environment as a means to create ideal conditions for guided determination of stem cell fate and dental tissue regeneration (11, 12). The work of many investigators throughout the world identified morphogenetic signals that play major roles during tooth development and that can potentially be used therapeutically in tooth regeneration (13–15). Indeed, gene knockouts such as dentin sialophosphoprotein (DSPP) (16), dentin matrix protein 1 (DMP1) (17), Msx homeobox family (18, 19), and amelogenin (20, 21) revealed major tooth developmental defects, indicating that these morphogenetic signals are critically involved in these processes. Such findings suggest candidate morphogenetic signals that can be either recruited from the surrounding environment or delivered locally with the use of the scaffold to direct stem cell fate and optimize guided pulp tissue regeneration.

In addition to the need for guided differentiation of stem cells into odontoblasts, there is also an important need for their differentiation into supporting cells (eg, vascular endothelial cells and neural cells). Tissue innervation is critical for the functional regulation of the cells involved in pulp regeneration. In addition to the protective effect of the pulp innervation, it also plays important roles in inflammation and tissue repair (22). The rapid induction of a proangiogenic response is crucial not only as a means to provide necessary influx of the oxygen and nutrients required by the high metabolic demands of cells engaged in tissue regeneration but also to enable immunologic responses necessary to protect the emerging tissues from bacterial contamination typically associated with the clinical handling of necrotic teeth. Immune cells such as tissue-infiltrating macrophages require the presence of a functional vascular network to access the regenerated pulp tissue and protect it against bacteria that could possibly remain viable after the treatment of necrotic teeth. Indeed, it is plausible to speculate that access of immune cells to the pulp might play a major role in the successful outcome of necrotic teeth treated with regenerative endodontics–based approaches.

In addition, it is through the blood vessels that substrates required for dentin mineralization (eg, calcium and phosphate) are made available to odontoblasts, which perhaps explains the frequent presence of blood vessels in close proximity to the odontoblastic layer, particularly in pulp actively engaged in regenerative processes. Furthermore, vascularization is a key determinant of mesenchymal cell heterogeneity in dental tissue engineering, presumably by enabling the recruitment of circulating cells to the developing tooth (11). Later in this review, we discuss potential strategies proposed for the rapid vascularization of engineered dental pulps.

**Tooth-related Stem Cells**

The cells that define the pulp tissue are the odontoblasts, terminally differentiated cells that do not proliferate and that are endowed with the capacity of generating new tubular dentin. Lost odontoblasts can be replaced in normal pulps by resident multipotent stem cells (23, 24) found in permanent teeth (25) or primary teeth (26). They can differentiate into odontoblasts and also into other cell lineages such as osteoblasts, chondrocytes, and neuronal progenitor cells (25–29). Stem cells have also been identified in other oral tissues, such as the apical papilla (30), mesenchymal follicle (31), periodontal ligament (32), and gingiva (33). It is speculated that stem cells from each tissue are somewhat "primed" to regenerate that same tissue, and, therefore, it is likely that the best stem cells for dental pulp tissue engineering are pulp stem cells. However, it is rather unclear at this time what the relative potential of each of these oral stem cells for dental pulp tissue engineering is.

Dental pulp stem cells are relatively easily obtained from exfoliated primary teeth or permanent teeth extracted for orthodontic reasons. Considered a relatively rich source of mesenchymal stem cells, the interest in dental pulp stem cell isolation and banking has increased substantially in recent years. More importantly, exfoliating primary teeth and permanent teeth extracted for orthodontic reasons overlap temporally with immature permanent teeth of adolescents that are relatively prone to trauma-induced pulp necrosis. Therefore, it is suggested that these teeth are an ideal source of stem cells for dental pulp tissue engineering of necrotic immature permanent teeth. In these cases, the goal is to regenerate a functional dental pulp capable of completing vertical and horizontal root formation (Fig. 1).

In proof-of-principle experiments using the permanent tooth slice/scaffold model (34), we observed that stem cells from exfoliated deciduous teeth differentiate into functional odontoblasts and vascular endothelial cells (35–38). Notably, fluorescent lines created by tetracycline staining of newly formed tubular dentin confirmed that the stem cells from exfoliated deciduous teeth differentiated into mature odontoblasts (38). These experiments suggested the possibility of isolating stem cells from exfoliating primary teeth and transplanting them back in the same patient (autologous transplantation) in clinical scenarios involving pulp necrosis of an immature permanent tooth during the mixed dentition phase.

A critical challenge of the clinical scenario described previously is the need for quick vascularization of the engineered tissue to enable the maintenance of the viability of transplanted cells (39). Indeed, the anatomy of the dental root is a major limiting factor regarding access to vascularization, considering that all blood vessels have to come through a system of the dental root is a major limiting factor regarding access to vascularization, considering that all blood vessels have to come through a system of vascular meshwork. Even in these cases, we believe that the success rate of such therapy would benefit from the delivery of a proangiogenic stimulus.

The recent discovery that dental pulp stem cells differentiate into vascular endothelial cells in addition to differentiating into functional odontoblasts (36–38) suggests that these cells can serve as a single cellular source for dental pulp tissue engineering. However, a key observation of these studies is that although dentin-derived morphogenetic signals are sufficient to induce odontoblastic differentiation,
they are not sufficient to induce endothelial differentiation in vivo. This is despite the well-known presence of proangiogenic factors in the dentin (41, 42). Therefore, it appears imperative that strategies aiming at dental pulp tissue engineering incorporate proangiogenic signals, likely delivered locally with sustained-release carriers.

**Morphogenic Factors in Pulp Regeneration**

The observation that dentin is a reservoir of bioactive morphogenic signals that can be recruited on demand (43) constitutes a major enabling discovery in the field of dental pulp tissue regeneration. Indeed, this discovery represents a true paradigm shift in the field because it elevated the dentin to the status of a morphogenic source that enables and guides regenerative processes and tissue repair, rather than being simply an inert and passive tissue. Multiple lines of investigation have shown that dentin-derived proteins are sufficient for odontoblastic differentiation (36, 44, 45). Notably, intentional degradation of dentin-derived proteins with sodium hypochlorite eliminated its inductive potential (36). This finding corroborated previous observations of the critical role of dentin-derived morphogenic signals in odontoblastic differentiation and raised the possibility that sodium hypochlorite might not be the ideal solution for root canal irrigation in regenerative endodontics. In search for a mechanistic explanation for these findings, we and others observed that bone morphogenetic protein 2 is a key mediator of dentin-induced odontoblastic differentiation of dental pulp stem cells (36, 44).

Another important dentin-derived morphogenic signal is transforming growth factor beta 1 (TGF-β1) (44). TGF-β1 is present in sound dentin (46) and can be released by the acidic activity of cariogenic bacteria (47) or when EDTA is applied over sound dentin (48). The release of TGF-β1 has also been identified after the application of calcium hydroxide-containing materials (49), mineral trioxide aggregate (50), tricalcium silicate–based cement (51), and self-etching dental adhesives as well (52). TGF-β1 is a very complex molecule with multiple effects. Its full implications in pulp biology and pulp regeneration are yet to be determined.

In addition to the dentin, there are several other sources of morphogenic signals that include, but are not limited to, resident pulp cells (eg, fibroblasts, neural cells, and endothelial cells), circulating cells (eg, circulating progenitor cells and inflammatory cells), and the pulp extracellular matrix itself. The understanding of the role of these morphogenic signals in the maintenance of dental pulp homeostasis and in the processes that lead to pulp regeneration is emerging. An in-depth discussion of the function of each 1 of these morphogenic factors is beyond the scope of this review. However, Table 1 summarizes some of the functions of the key morphogenic signals that may play a role in pulp regeneration.

**Functionalized Injectable Hydrogels in Dental Pulp Tissue Engineering**

The discovery that dentin-derived proteins are sufficient to induce full differentiation of dental pulp stem cells into odontoblasts has an important implication for pulp tissue engineering. It indicates that one does not need to provide additional morphogenic signals to achieve odontoblastic differentiation of stem cells transplanted or recruited into the root canal. The focus could be simply to protect these dentin-derived factors from degradation (eg, avoid exposure to sodium hypochlorite) and to enhance their mobilization by perhaps treating the dentin surface with mild organic acids (eg, EDTA), as we showed (36). However, the following complex issues need to be addressed:

1. One needs to provide adequate attachment and prevent anoikis of stem cells transplanted or recruited into the pulp chamber.
2. One needs to quickly vascularize the regenerating pulp to enable oxygen and nutrient influx as well as to allow for the arrival of circulating progenitor cells that will complement the cellular heterogeneity of the engineered pulp as shown by Keller et al (11).

Investigators have attempted to address these 2 issues by functionalizing the scaffolds used in dental pulp tissue engineering with moieties that enable better cell attachment (eg, arginine-glycine-aspartic acid [RGD]) and incorporating angiogenic factors (eg, vascular endothelial growth factor [VEGF]) (53, 54).

It is becoming increasingly evident that the ideal scaffold for dental pulp tissue engineering will be injectable, not casted. This is because of the narrow spaces within the root canal and the complexity of its anatomy, particularly in the apical region. In addition, there are concerns

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**Figure 1.** A schematic representation of a strategy for dental pulp tissue engineering that is based on the use of a functionalized injectable scaffold and transplantation of dental pulp stem cells.
related to the use of solvents (eg, chloroform, dichloromethane, and acetone) that are typically used to solubilize casted scaffold. For example, solvent-casted poly(lactic-co-glycolic acid) requires more than 2 days for significant volatilization (55), and residual levels of solvents may be toxic to cells. On the other hand, hydrogels can be injectable and therefore penetrate throughout the root canal system. Also, they typically undergo a setting reaction at a physiological pH.

Alginites are versatile natural polymers that have been used extensively as drug and growth factor carriers (56–62). The water-holding capillarity of hydrogels defines release kinetics of alginites that can be affected by pH, temperature, level of cross-linking, viscosity, and stability (57). Alginites act as mechanical barriers, decreasing the diffusivity of low–molecular-weight chemical compounds or proteins entrapped after their gelation. Substances such as phosphate-buffered

<table>
<thead>
<tr>
<th>Protein (class)</th>
<th>Symbol</th>
<th>Potential role in odontogenesis and tissue regeneration</th>
<th>Potential role in dental pulp engineering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone morphogenetic protein 2, 4, 7 (growth factor)</td>
<td>BMP-2, 4, 7</td>
<td>BMP-7 mediates epithelial-mesenchymal interactions during the initiation phase of odontogenesis and morphogenesis (80); experiments using BMP-7 (81, 82), BMP-2, and BMP-4 (83, 84) induced dentin regeneration in vivo</td>
<td>BMP-2 induces differentiation of SHED into dental pulp cells (36) and mineralized tissue formation using DPSC (85) in vivo; BMP-7 induces up-regulation mineralization on dental pulp stem cells in vitro (86)</td>
</tr>
<tr>
<td>Bone sialoprotein (sibling)</td>
<td>BSP</td>
<td>BSP stimulates the differentiation of dental pulp cells into odontoblastlike cells and induces regenerative dentin in vivo</td>
<td>Unclear</td>
</tr>
<tr>
<td>Core-binding factor subunit alpha 1 (transcription factor)</td>
<td>Cbfa1</td>
<td>Regulates epithelial-mesenchymal interactions in during morphogenesis and histodifferentiation of the epithelial enamel organ (89), but it plays a stage-specific role in the lineage determination and terminal differentiation of odontoblasts (90)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Dentin matrix protein 1 (sibling)</td>
<td>DMP-1</td>
<td>DMP-1 is expressed in mature odontoblasts (91), plays an essential role in dentin mineralization (17), and appears to have a regulatory function in the nucleus (92); besides, it activates the synthesis of IL-6 and IL-8 from pulp fibroblasts (93)</td>
<td>Induces an organized matrix formation similar to that of pulpal tissue, which might lead to hard tissue formation in vivo (94)</td>
</tr>
<tr>
<td>Dentin sialophosphoprotein: dentin sialoprotein, dentin phosphoprotein (sibling)</td>
<td>DSP, DPP</td>
<td>DSP is expressed by odontoblasts and is cleaved into 2 smaller polypeptides with unique physicochemical characteristics (DSP and DPP) (95); DPP is down-regulated by the shortage of DMP-1 during the dentinogenesis (96); DPP binds to collagen and initiates formation of apatite crystals in dentin (99)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Fibroblast growth factor-2 (growth factor)</td>
<td>FGF2</td>
<td>Induces differentiation of HDPC in mineralized tissue and up-regulates chemokines in vitro (100)</td>
<td>Induces cellularization and revascularization of human teeth implanted into the dorsal of rats (86) and upregulates the dental tissue mineralization (101)</td>
</tr>
<tr>
<td>Canonical Wnt pathway (signal transduction)</td>
<td>Wnt/β-catenin</td>
<td>Appears to mediate the downstream events of TGF-β1 during pulp regeneration (102)</td>
<td>Appears to inhibit the differentiation of DPSC into odontoblastlike cells (103)</td>
</tr>
<tr>
<td>Transforming growth factor beta 1 (growth factor)</td>
<td>TGF-β1</td>
<td>Induces up-regulation of dentin matrix by odontoblasts (56); TGF-β is a physiological regulator of osteoblast differentiation (104)</td>
<td>Induces odontoblastlike cell differentiation in vitro (56) and DPSC-mediated mineralization (105)</td>
</tr>
<tr>
<td>Twist-related protein 1 (transcription factor)</td>
<td>TWIST1</td>
<td>Appears to be involved in the development of the supernumerary teeth (106)</td>
<td>Required in terminal events that drive differentiation of DPSC into odontoblastlike cells in vitro (107)</td>
</tr>
<tr>
<td>Vascular endothelial growth factor (growth factor)</td>
<td>VEGF</td>
<td>Induces endothelial cell survival and differentiation of new blood vessels and may be used therapeutically to induce tissue neovascularization (108, 109)</td>
<td>Induces differentiation of SHED into endothelial cells (38)</td>
</tr>
</tbody>
</table>

DPSC, dental pulp stem cell; HDPC, human dental pulp cell; IL, interleukin; SHED, stem cells from exfoliated deciduous teeth.
saline that are used as carriers for growth factors can be encapsulated in high-viscosity clinical grade alginites (58). On the other hand, because of their hydrophilic nature, alginites present low absorption of serum proteins and consequently low levels of adhesion and cellular interaction (7, 59). Consequently, no cell proliferation is typically observed when alginate is used as a synthetic extracellular matrix (7). This observation led to the possibility of using alginate microspheres (as slow-release devices for morphogenic signals) combined with an injectable scaffold that is more conducive to stem cell survival and proliferation. The association between alginate hydrogels and other materials such as nanofibers (60) or modification of the alginate’s structure (eg, by peptide functionalization) (61) have been investigated to improve the attachment of cells. To address this issue, Gallen et al (53) recently showed the development of a customized self-assembling peptide hydrogel designed specifically for dental pulp tissue engineering. The advantage of this innovative system is the possibility of incorporating signaling molecules and the RGD amino acid sequence for cell adhesion to the structure of the scaffold. Additionally, the incorporation strategy involving adsorption of growth factors in porous microspheres with posterior encapsulation with alginate has been investigated (62).

A commercially available self-assembling injectable hydrogel (ie, Puramatrix) presents favorable viscosity for use as an injectable scaffold. Its mixture with a sucrose-based solution and/or cell culture medium triggers fast self-assembling, leading to its gelification and generation of a tridimensional environment that provides cell adhesion and enables cell proliferation. We have recently shown that Puramatrix allowed for odontoblastic differentiation of dental pulp stem cells in vitro (63). Ongoing work in our laboratory is attempting to combine the cell-friendly environment provided by Puramatrix with the controlled release of morphogenic factors provided by alginate microspheres in the context of dental pulp tissue engineering (Fig. 2).

**Challenges ahead in Dental Pulp Tissue Regeneration**

The optimization of ideal release kinetics of morphogenic factors for use in regenerative endodontics is a major challenge. The adsorption of proteins has been broadly used for the delivery of growth factors in tissue engineering, but there are issues associated with this approach. This method relies on physical retention and release via the natural affinity of the biodegradable material. Chemical binding with disulfide bonds or heparin have also been used (53, 64). Notably, heparin has natural affinity with growth factors such as VEGF (65, 66). We recently observed a sustained release of VEGF from alginate microspheres (<275 μm in diameter) for 21 days (Fig. 2). However, although appropriate levels of VEGF mediate the induction of angiogenesis, excessive VEGF can promote vascular leakage leading to edema and increased interstitial pressure (67). This is a critical challenge in dental pulp tissue engineering because the pulp is encapsulated within nonexpanding dentin walls. In this case, excessive interstitial pressure may result in cell death, as was shown in the context of the brain after a stroke (67).

The determination of how much morphogenic factor is ideal goes hand in hand with the definition of how quickly it should be released and for how long. There are many ways to control release kinetics of growth factors. They include structural modifications of alginate by the addition of dextran in semi-interpenetrated networks (68), heparin (69), chitosan (66), sulfated alginate (70, 71), and alginate photocrosslinking (72). Ultraviolet light initiator systems have been used to promote photopolymerization of alginate while maintaining its biocompatibility (73, 74). These are examples of the complexities involved with the local delivery of morphogenic factors and show that this is an area that will require much attention as regenerative endodontics moves toward clinical application.

It is possible that multiple morphogenic factors combined with other agents (eg, antibiotics) will have to be used for ideal dental pulp regeneration. Layering approaches have been proposed for the controlled release of multiple growth factors, inhibitors of inflammation, and/or antibiotics from microspheres (75, 76). The combination of growth factor and drug delivery has attracted attention because of the potential benefits of antibacterial compounds in the treatment of necrotic root canals (3). In addition, it will be important to find the ideal material to be used to seal the newly regenerated pulp tissue. This material should be biocompatible to maintain cell viability of the regenerated pulp. At the same time, it should provide a good interfacial seal that minimizes microleakage and also provides adequate adhesion to the overlying restorative material.
It is becoming apparent that revascularization alone without cell transplantation in necrotic teeth is accompanied by the resolution of periapical lesion and partial apical closure, but it does not enable the generation of a fully functional dental pulp tissue throughout the full length of the root canal (77, 78). On the other hand, transplantation of human stem cells generates a dental pulp throughout the entire length of human premolars transplanted in the subcutaneous space of immunodeficient mice (79). However, the translation of stem cell–based dental pulp tissue regeneration into routine clinical use faces significant challenges. For example, it is still unclear what the ideal source of multipotent stem cells for pulp regeneration is. We do not know if dental pulp stem cells are necessarily better than gingival stem cells or bone marrow–derived mesenchymal stem cells in regenerative endodontics. An additional challenge is that one would have to establish cell handling protocols that follow good manufacturing practice standards, defined by the Food and Drug Administration as ex vivo manipulation of clinical-grade cells that are safe for the patient while being effective therapeutically, in dental clinics and supporting laboratories.

It is becoming increasingly evident that although there are many aspects that can be learned from the broad literature on tissue regeneration, there are questions that are unique to the field of regenerative endodontics. They include, but are not limited to, the development of strategies to mobilize while protecting dentin-derived morphogenic signals, the development of functionalized injectable scaffolds that allow for cell attachment/survival and can be used within root canals as a slow release device for angiogenic factors, the development of strategies that eliminate bacterial contamination in necrotic teeth, and the definition of the sources of multipotent stem cells that can regenerate fully functional dental pulp tissue. It is unquestionable that the most effective way to address such challenges is through integrated work of multidisciplinary research teams that bring together experts in cell and molecular biology, dental clinicians, and material scientists.

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References


