Biological Molecules for the Regeneration of the Pulp-Dentin Complex

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KEYWORDS

• Biological molecules • Signaling molecules • Growth factors • Biological cues
• Pulp-dentin complex • Tubular dentin • Odontoblast

KEY POINTS

- The pulp-dentin complex plays a crucial role in fueling immune defense and tissue regeneration on infection or trauma.
- The regeneration of the pulp-dentin complex has been reported in several animal studies using exogenous biological cues or stem/progenitor cells.
- The animal and human studies using endogenous biological molecules released from ethylenediaminetetraacetic acid–conditioned dentin or evoked bleeding have shown the formation of tissues that are of periodontal origin.
- Endogenous biological molecules have a release profile with a high initial burst followed by rapid reduction, perhaps accounting for the lack of regeneration in clinical studies using current regenerative endodontic protocols.
- Delivery methods that allow for the controlled release of biological molecules may enhance the histologic outcome of regenerative endodontic therapy.

INTRODUCTION

The pulp-dentin complex, as a dynamic functional structure in teeth, plays a pivotal role in the immune defense against noxious stimuli and tissue repair and regeneration during trauma and infection.[1] From a tissue engineering perspective, it is considered one of the most difficult tissues to regenerate because of its unique anatomic and physiologic nature. Unlike bone, which requires constant remodeling to maintain homeostasis, dentin rarely remodels in normal physiologic conditions. Only in pathologic conditions is dentin remodeling, such as resorption or repair, observed.[2] Dental pulp is a loose fibrous connective tissue but anatomically distinct from periodontal ligaments or other connective tissues in that it has functional odontoblasts to be coupled with dentin.

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A tenet of regenerative endodontic therapy is that dentin and pulp are anatomically restored to function as a physiologic unit, that is, the pulp-dentin complex. However, clinical regenerative endodontic treatment is not effective yet in the regeneration of the pulp-dentin complex.[3,4] The histologic observations in a few case reports showed that the regenerated tissues in infected necrotic teeth comprise mineralized tissues with the characteristics of bone and cementum and periodontal ligamentlike connective tissue.[3,4] In contrast, several animal studies found the robust pulp and dentin regeneration in pulp regeneration models using stem cells or biological molecules.[5–10]

The biological molecules, whether their source is endogenous or exogenous, control the cellular activities such as migration, proliferation, and differentiation so that homeostatic and regenerative needs in a specific tissue can be met during injury or infection. In regenerative endodontic therapy, endogenous signals can be released from conditioned dentin or bleeding evoked into the root canal. A few exogenous biological molecules to be most effective in pulp regeneration can be selected and introduced into the root canal in anticipation of energizing certain cellular behaviors toward robust pulp and dentin regeneration. The knowledge of how biological cues modulate cellular events during the pulp regeneration process is instrumental in identifying the limitations of clinical regenerative treatment and devising improved regeneration protocols. This review discusses the biological and clinical significance of regenerating the pulp-dentin complex, the role of biological molecules in pulp regeneration, the delivery limitation of biological molecules in current regenerative endodontic treatment, and the delivery methods of signaling molecules to direct cellular behaviors toward regeneration.

THE SIGNIFICANCE OF REGENERATING THE PULP-DENTIN COMPLEX

The regenerated tissues in root canals after the application of clinical regeneration protocols seem to be of periodontal origin as evinced by the presence of periodontal ligamentlike, cementumlike, bonelike tissues in animal and human studies.[3,4,11–19] Notably, however, various clinical protocols used in regenerative endodontic treatment reliably have yielded the excellent clinical results such as healing of apical periodontitis, increased root lengths and thicknesses, or return of vitality.[20] The evidence inferred from histologic and clinical outcomes suggests that the radiographic findings from successful regenerative endodontic cases only reflect ectopic tissue formation in the root canal space.[3,4,11–19] From a clinical perspective, the need for regenerating the pulp-dentin complex may not be well justified if the goal of regenerative endodontic therapy is to prevent and cure apical periodontitis and to render immature necrotic teeth less susceptible to fracture by increasing the root volume. By contrast, from a biological standpoint, the pulp-dentin complex is crucial in activating the immune defense mechanisms and inducing the regeneration/repair on tissue injury or infection (**Fig. 1**). For instance, neuropeptides, such as substance P and calcitonin gene-related peptides, released from activated sensory nerves initiate neurogenic inflammation, availing the regeneration of the pulp-dentin complex by control of the immune responses and by stimulating tissue-forming cells.[21] Historically, the formation of fibrous connective tissue in the root canal space has been well documented since the earlier efforts by Ostby[22] and Nygaard-Ostby and Hjortdal,[23] but tubular dentin and odontoblastic layers to be regenerated in the context of immune defense and homeostasis have received less attention by researchers.

Tubular Dentin

The tubular structure of dentin results from odontoblastic differentiation of the outer cells of dental papilla and subsequent dentin matrix deposition and its mineralization