Guest Editorial

Bioactive Molecule delivering Nanoparticle Systems for Regenerative Endodontics

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Bioactive molecules (BMs) is an umbrella term referring to a diverse group of molecules encompassing growth factors, chemokines, cytokines, extracellular matrix (ECM) molecules, and bioactive peptides. Bioactive molecules are critical to mammalian cell growth and thus are fundamental in the processes of tissue development, function, and healing. The absence of these BMs, or their presence in inappropriate concentrations in a specific tissue environment, can have diverse effects on cell activity, which results in varying biological effect on the tissue and highlights the complex multifunctional role that BMs play in tissue homeostasis. Expression of BM occurs in a temporal-controlled pattern during tooth formation and maturation. This characteristic poses a significant challenge for the use of BMs for any regenerative procedures.

Tissue healing and repair of dental pulp and reparative dentin formation are a result of distinct BM interaction, which drives cell chemotaxis, proliferation, differentiation, and extracellular matrix remodeling. Understanding BM-cell interactions is central to translational knowledge in tissue regenerative applications including regenerative endodontics. Studying how and when these interactions occur on a spatial and temporal basis facilitate this understanding and expedite the clinical application of this knowledge. Current regenerative endodontic procedures employ tissue-engineering principles that exploit BM-cell interactions. Some concerns regarding the application of BM in regenerative procedures include their short half-life, uncontrolled release, toxicity, and possible lack of effect.

Bioactive molecules can be introduced into many tissue-engineering systems by various methods, which include static administration, by genetically engineering cells to overexpress them, and by constructing polymeric systems that allow their controlled release. Challenges of BM release previously mentioned may be overcome if polymeric carrier systems are engineered to release BMs. The properties of an ideal carrier system are to provide: (1) Spatial (location controlled) release of BM, (2) temporal (time controlled) release of BM, (3) sustained biological effect over a prolonged period, and (4) optimized biodegradation following complete tissue regeneration. Examples of BM carriers include scaffold, microparticles, or nanoparticles. A porous chitosan scaffold containing chitosan microspheres loaded with transforming growth factor (TGF)-□1 has been shown to enhance chondrogenesis; the scaffolds containing the loaded chitosan microspheres significantly increased the cell proliferation and production of ECM. A similar approach using chitosan-based materials has been reported, where three-dimensional collagen/chitosan/glycosaminoglycan scaffolds were seeded with rabbit chondrocytes and combined with TGF-□1-loaded chitosan microspheres. This allowed for an evaluation of the effect of released TGF-□1 on the chondrogenic potential of rabbit chondrocytes in such a system. Nanoparticles for controlled release hold several advantages over microparticle carriers in terms of surface functionality due to scaling effects in their physicochemical properties. Functionalized chitosan nanoparticles have been shown to be effective in the temporal-controlled release of BM to an odontogenic line of stem cells and its use has enhanced cell proliferation and differentiation in dentin-pulp engineering.

In the past, and perhaps to some degree in the present, apexification has been the preferred treatment of immature teeth that have become pulpless. However, immature teeth, subsequent to successful apexification, remain at risk of fracture due to thin root dentin walls. Recognizing this, endodontists are developing biologically based treatment strategies to improve the fate of these often-fractured teeth by generating new functional tissue that they hope will improve the quality of patient's lives. An alternative to apexification is a regenerative endodontic procedure. Scaffolds, stem cells, and BMs have been used to regenerate neo-tissue at a desired site over a predictable period of time. However, at present, the outcomes of these procedures remain questionable. Thus, novel BM-releasing systems that protect BMs from denaturation and allow a controlled spatiotemporal release are required for successful translation of BM-based approaches in regenerative endodontics. Although several polymeric scaffolds have been investigated and offer only measured success, no scaffold material has gained universal acceptance. Carrier systems designed with preprogrammed release of BMs in a spatiotem-

poralcontrolled manner would aid in mimicking the natural wound-healing process and simultaneously overcome some of the challenges. The controlled release of BMs from polymeric carriers is expected to enhance and accelerate functional dentin–pulp tissue formation as the field of regenerative endodontic procedure advances in the future.

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