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치아 지지조직 재생을 위한 생체재료기반 조직공학적 접근

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〈Abstract〉

Biomaterial-Based Tissue Engineering for Tooth-Supportive Complex Regeneration

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조직공학은 질병이나 사고등으로 인해 손상된 조직을 대체하는 인공 보철물 개발에서 자기 조직으로의 재생과 성장을 통해, 본래의 생리학적 기능 회복을 이끄는 재생의학으로 발전해왔다. 줄기세포등을 주입하여 재생을 이끄는 기술을 비롯해, 다양한 단백질과 성장인자들을 전달하여 손상 조직이나 장기를 복원하는 기술들이 개발되면서 조직공학 및 재생의학은 새로운 패러다임을 만들어가고 있다. 특히, 치아를 지지하는 치주조직의 재생은 수백 마이크론단위의 공간내에 특정 방향성을 지닌 섬유결합조직이 골조직과 융합하여 치아를 단단히 지지하는 복합구조를 지니고 있어, 기존의 재생술식으로는 한계가 있다. 이를 극복하고 백악질-치주인대-골조직으로 구성된 치주복합조직의 재생을 유도하기위해, 천연 및 합성 생체고분자재료를 기반으로한 다양한 의공학적 접근법들이 최근 소개되고 있다. 본고에서는 생체재료가 지니는 생물학적 특성을 기반한 치주조직재생유도 구조체 개발의 최신 연구개발 현황 및 전망을 기술하였다.

Key words : Biomaterials, Dental tissue engineering, Regenerative medicine, Biopolymers

Ⅰ. INTRODUCTION

1. Tissue Engineering and Regenerative medicine

Tissue engineering and regenerative medicine are rapidly emerging in the medical, dental and engineering fields as a viable tool for regenerative medicine applications. Currently, various studies are progressing that seek to regenerate lost tissues as a consequence of disease destruction by using developed biocompatible and biofabricable materials, containing stem cells or bioactive signaling molecules (Fig. 1) (Somerman *et al.*, 1999; Wang *et al.*, 2005). However, new tissue formation for hierarchical multiple tissue structures is still unpredictable and challenging for regenerations of biologically-responsible and physiologically-restorable complex structures (Park *et al.*, 2012). In order to improve tissue restoration rate, bioactive molecules (including growth factors or proteins) have been actively considered for the stimulation of tissue formation or the optimization of tissue maturation in preclinical and clinical scenarios (Chen *et al.*, 2011; Jin *et al.*, 2004; Kaigler *et al.*, 2006; Singh and Suresh, 2012). In addition to bioactive molecules, bioengineered microenvironments or scaffolds

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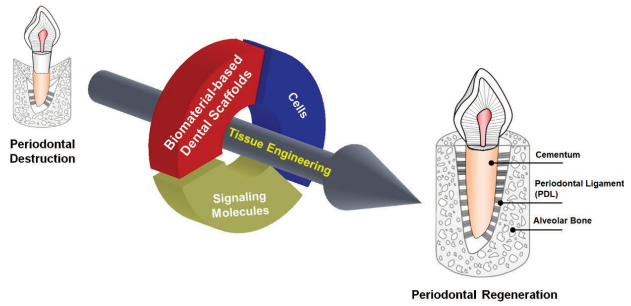

Figure 1. The schematic illustration for the tissue engineering strategy in periodontal tissue regenerations. Biomaterial-based scaffold, signaling molecules, and various cell types contribute to guide tissue formations and functioning restorations to support tooth structures.

have been focused on the key element to guide tissue regenerations (Taba *et al.*, 2005). Of various transplantable materials, biodegradable materials for scaffolding systems are widely applied to control biomolecule-releasing mechanisms with local delivery systems, guide target tissue regenerations as spatiotemporal platforms, or provide optimal space for new tissue growth and maturation in diseased defects or wound sites (Bartold *et al.*, 2016; Ivanovski *et al.*, 2014; Mao *et al.*, 2006; Moioli *et al.*, 2007).

As revolutionary paradigm shifts from tissue replacement to tissue regeneration, scaffold designing and manufacturing have rapidly developed in order to provide appropriate biological and engineered microenvironments for tissue regenerations (Chan and Leong, 2008). In particular, for complex-heterogenic dental tissue formation, multi-layered constructs by polymer/polymer or polymer/ceramic materials are utilized for periodontal complexes or multiple tissue repairs(Jin *et al.*, 2008; Schek *et al.*, 2006; Wei and Ma, 2004; Wei *et al.*, 2007).

Of many different dental tissue regeneration approaches, the periodontal tissue engineering is challenging due to micro-scaled hierarchical tissue constructs, soft-/hard-tissue interfaces, and tissue integrations for tooth-supportive functioning restorations (Ma, 2004). In the aspect of biopolymeric material applications, there are recent advancements using natural polymeric materials; artificial extracellular matrix (ECM) with nano-fibrous morphologies (Holzwarth and Ma, 2011; Ma, 2008; Song *et al.*, 2012) and fibrous tissue-guiding scaffolds with nano-/micro-longitudinal pores (Park *et al.*, 2014a).

2. Natural Biopolymeric material Applications for Periodontal Tissue Regeneration

Gelatin material (or denatured collagen matrix) is generally utilized for periodontal tissue regeneration in preclinical and clinical situations (Chen and Ma, 2004; Ma, 2004). Although the collagen material have been widely utilized for preclinical and clinical regeneration treatments, it has the immune responses, uncontrollable physical properties, or unpredictable pathogen transmission rather than gelatin. Gelatin has good engineering properties like easy fabrication and limitedly controllable mechanical properties in the cross-linking process (Kamaly *et al.*, 2016; Liu *et al.*, 2009). Therefore, many advanced tissue engineering strategies significantly consider gelatin materials to manufacture highly porous scaffolds for tissue repair and regeneration (Ma, 2004). Nano-fibrous constructs based on natural polymeric materials have been manufactured using phase separation or peptide self-assembly methods (Beachley and Wen, 2010; Ma, 2004). For this approach, natural biopolymers like gelatin or collagen, which is FDA-approved are characterized to use as natural tissue platforms and has bioactive components like ECM compositions (Qi *et al.*, 2015; Zhu and Marchant, 2011). In structural, nano-fibrous morphologies facilitate to promote cell activities, tissue neogeneses, or maturation of regenerated tissues (Wang *et al.*, 2013).

In periodontal complex surrounding tooth structures, specific orientations of periodontal ligament (PDL) play a critical role to support tooth structures under mastication

and occlusion microenvironments. Due to micron-scaled interfaces around tooth surface, oriented PDL regeneration has been challenging with traditional manners like randomly porous architecture transplantations or membrane placements (Park *et al.*, 2014b; Park *et al.*, 2016). Recently, Park *et al.* investigated spatiotemporal geometries in gelatin architectures using the freeze-casting method (Park *et al.*, 2014a). To mimic the oblique PDL interface, which is approximately 70-80% of four different classified PDL interfaces, this study attempted to control the directions of ice crystal formations (Park *et al.*, 2014a). Therefore, the directional freeze-casting of gelatin materials facilitate to have structural similarity to natural oblique PDL architectures (Park *et al.*, 2014a).

3. Biomaterials to Develop Engineered Microenvironments for Dental Tissues: Scaffolding Systems

Of various tissue regeneration strategies, the scaffolding system plays a crucial role in defining the 3-D geometry and biomimetic microenvironment for cells and tissues (Lutolf and Hubbell, 2005; Ma, 2004; Messenger and Tomlins, 2011). A variety of materials for the developments of implantable devices have been explored for mineralized tissue regeneration like bone or teeth (Moffat *et al.*, 2008; Spalazzi *et al.*, 2008). Although certain metallic materials are excellent choice for medical implants for mechanical properties (Catledge *et al.*, 2004), the main drawback as scaffold materials is non-biodegradable properties in physiological environments for regenerative medicine (Liu and Ma, 2004). The inorganic or ceramic materials like calcium phosphate (CaP)-based materials are widely applied for bone tissue regeneration due to the high osteoconductivity such as tooth-extraction socket healing as socket filling materials (De Coster *et al.*, 2011), alveolar bone regeneration after periodontal treatments (Isidor *et al.*, 1985; Polimeni *et al.*, 2006), or bone ridge augmentation for dental implant stabilities (Handelsman, 2006; Kang *et al.*, 2015). However, they have brittle properties or unpredictable spatial shrinkage in the procedures of sintering materials for manufacturing porous architectures at high temperature (Shahrjerdi *et al.*, 2011).

For regenerative approaches instead of replacement of damaged tissues, synthetic polymer-based biomaterials with biocompatibility and biodegradability have great design potential to chemically or physically fabricate for the specific required characterizations (Liu *et al.*, 2012; Ma, 2004). In particular, poly(lactic acid) (or polylactide; PLA), poly(glycolic acid) (or polyglycolide; PGA), and their copolymers (PLGA) have been mainly fabricated to manufacture biodegradable scaffolds with the Food and Drug Administration (FDA) approvals due to the rapid biodegradability (Liu *et al.*, 2012; Ma, 2004; Wei and Ma, 2008; 2009). During degradation procedure, the products of PGA, PLA and PLGA by hydrolysis or enzymatic degradation are nontoxic, natural metabolites, and completely formed as carbon dioxide andwater. Using highly porous spatiotemporal scaffolds by biopolymeric materials, the dental tissues like enamel, dentin, and pulp tissues have been regenerated in various preclinical scenarios (Horst *et al.*, 2012; Sharma *et al.*, 2014). Moreover, drug-loaded biopolymeric scaffold strategies have the significant potential to control release rates of gene therapy vectors, proteins, or growth factors as well as provide spatiotemporal microenvironments for tissue growth and cell activities like differentiation, proliferation, or migration (Vo *et al.*, 2012).Therefore, the biopolymeric materials are actively utilized for tissue engineering and regenerative medicine. However, the major challenge in the dental tissue engineering is recently the strategic developments of micron-scaled complex geometries to guide optimal tissue complexes using biodegradable polymeric materials (Albuquerque *et al.*, 2014; Park *et al.*, 2014b).Therefore, customized or flexible approaches using biopolymers are significantly required for complex

geometries or non- standardized, unpredictable defects inthe periodontal tissue engineering.

4. Advanced Strategies for Tooth–Supportive Tissue Regenerations

The periodontium is composed of four specific tissues: gingiva (fibrous tissue), cementum (mineralized layer on the root surface with 150-200 μm thickness), PDL (250-300 μm thick space with perivasculature and Sharpey's fibers), and alveolar bone (mineralized tissue to support tooth structures) (Park *et al.*, 2014a). The PDL, a fibrous connective tissue bundle is oriented perpendicular/oblique to the tooth root surface with anchorage between the bone surface and cementum layer (Park *et al.*, 2012; Park *et al.*, 2014b) and provide mechanical anchorage to support occlusion/ mastication loading (Park *et al.*, 2014a). However, periodontal disease, which is a common and highly prevalent inflammatory infectious disease affecting periodontia leads to destruction of the periodontal complex involving alveolar bone-PDL interface degeneration and subsequent tooth loss (Park *et al.*, 2012).

To regenerate periodontal complex from disease-associated destructions, fiber-guiding scaffoldswere currently developed with the architectural compartmentalization for periodontal complexes composed with PDL, alveolar bone, and cementum (Park *et al.*, 2010; Park *et al.*, 2012; Park *et al.*, 2014b). The 3-D reconstructed images after CT-scanning the periodontal fenestration defects, the wax molds for multi-layered scaffolds were designed and manufactured by the computer design tools and the 3-D wax printing system (Park *et al.*, 2012; Park *et al.*, 2014b). After casting the biopolymeric material (PCL), customized PCL scaffolds were transplanted to promote tooth-suportive structures; bone formation, PDL regeneration with perpendicular/oblique orientations to the tooth root surface, and cementum deposition on the root surface (Park *et al.*, 2012; Park *et al.*, 2014b). Interestingly, the fibrous connective tissues were integrated with the mineralized tissue and the restoration of tissue functioning was identified using the periostin staining method (Park *et al.*, 2012).

In addition to 3-D printing technology the cell sheet technology is one promising approach for clinical applications in periodontal tissue regeneration (Bartold *et al.*, 2016; Iwata *et al.*, 2010; Iwata *et al.*, 2015). After cultivation of PDL cells on chemically-modified cell culture plates for a single sheet, multiple PDL cell sheets were stacked using woven PGA membrane and transplanted to periodontal defects with β-tricalcium phosphate (β–TCP), which is an osteoconductive material for bone regeneration (Iwata *et al.*, 2009; Washio *et al.*, 2010). Particularly, PGA having high hydrophilicity facilitates to inhibit shrinkage of a mono-layered cell construct (Iwata *et al.*, 2009), easily and rapidly stack multiple cell sheets (Iwata *et al.*, 2009; Washio *et al.*, 2010), and adjust to any defect geometries with the high flexibility like a paper (Ishikawa *et al.*, 2009). Moreover, rapid biodegradability of woven PGA constructs can promote the tissue integration with mineralized tissues, which β–TCP with osteogenic characterization contributed to regenerate (Tsumanuma *et al.*, 2011; Washio *et al.*, 2010). As results demonstrated, multi-layered PDL cell with an osteoconductive material (β–TCP) promote to orient PDL fibrous tissues with tissue integration on cementum and bone surfaces in multi-compartmentalized periodontia (Iwata *et al.*, 2009; Tsumanuma *et al.*, 2011).

The biphasic scaffold with PDL cell sheets was developed using electrospun nanofibrous PCL membrane which was for immobilization and positional transplantation of PDL on the periodontal defect sites (Ivanovski *et al.*, 2014; Vaquette *et al.*, 2012). Moreover, this highly porous PCL membrane can be easily fabricated to improve osteoconductivity after calcium phosphate (CaP) deposition on surface and facilitated osteogeneic acceleration to

regenerate tooth-supportive mineralized tissues (Dan *et al.*, 2014; Obregon *et al.*, 2015; Vaquette *et al.*, 2013).

II. CONCLUSIONS

Tissue engineering and regenerative medicine is one of promising interdisciplinary strategies to introduce new tissue neogeneses around diseased or injured destructions and improve tissue functions. There are three components in tissue engineering such as signaling biomolecules, bioactive cell types, and biomaterial-based scaffolds. In particular, complicated geometries or systematic tissue integrations should be considered highly biocompatible platforms to guide and grow cells and tissues with customized architectures. Therefore, as we have demonstrated in this review, the developments of novel biomaterials-based tissue engineering techniqueshave been crucially required and clinical reconstructions should be considered for periodontal complex regeneration due to the physiologically complicated and difficult accessible topographies. As Rasperini *et al.* recently reported the first clinical approach using the 3-D printed scaffold for periodontal regeneration (Rasperini *et al.*, 2015), we still need to explore and investigate the optimal and ideal biomaterials to have better characteristics for specific target tissues in periodontal and dental applications.

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The author has no conflict of interest for this work.

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