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Role of nanostructured biopolymers and bioceramics in enamel, dentin and periodontal tissue regeneration

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ABSTRACT

Tissue engineering approach focuses on the regeneration of deficient or damaged tissues of the body. Regeneration of dental tissues is considered as a promising therapeutic approach in dental tissue engineering. Engineering the environment for developing tissues comprises of biomaterials, growth factors, stem cells and regulation of physiological conditions in a spatial and temporal manner. To enhance the structural stability and bioactivity of polymers, a wide variety of nanomaterials are being utilized in dental regenerative medicine. Nanostructured biopolymers in the form of scaffolds, hydrogels, nanofibers, dendrimers, films, *etc.* and nanostructured bioceramics such as hydroxyapatite, bioactive glass ceramic/bioglass, *etc.* in the form of nanoparticles, nanocrystals, nanorods, paste, *etc.* are being exploited in the simultaneous regeneration of hard and soft tissues of the human body. In the dental area, these different forms closely mimic the natural constituents and framework of the dental tissues, namely enamel, dentin and periodontium. Overall this review essentially focuses on the role of polymeric and ceramic nanomaterials in the area of dental tissue engineering, highlighting their specific applications in enamel, dentin and periodontal regeneration.

Abbreviations: ECM, extra cellular matrix; HAp, hydroxyapatite; RGD, arginine-glycine-aspartic acid sequence; PA, peptide amphiphile; BRGD-PA, branched RGD-peptide amphiphile; EOE, enamel organ epithelial; PCR, polymerase chain reaction; LS8, ameloblast like cells; PAMAM, polyamidoamine; PPI, polypropylenimine; PLL, poly-L-lysine; Na_2HPO_4, disodium hydrogen orthophosphate; EMA, ethyl methacrylate; HEA, hydroxyethyl methacrylate; SEM, scanning electron microscope; BMP-7, bone morphogenetic protein-7; Dex, dexamethasone; P(EMA-co-HEA), poly(ethyl methacrylate-co-hydroxyethyl acrylate); SBF, simulated Body fluid; PVA, poly(vinyl alcohol); XRD, X-ray diffraction; HRTEM, high resolution transmission electron microscope; FFT, fourier transform; LCST, lower critical solution temperature; SHED, stem cells from human exfoliated deciduous teeth; DPSC, dental pulp stem cells; RT-PCR, reverse transcription polymerase chain reaction; PLLA, poly(L-lactic acid); ALP, alkaline phosphatase; PDL, periodontal ligament; GTR, guided tissue regeneration; GBR, guided bone regeneration; NB, new bone; NPDL, new periodontal ligament; NC, new cementum; nHAC, nano hydroxyapatite and collagen; rhBMP2, recombinant human bone morphogenetic protein2; PDLC, periodontal ligament cell; PLCL, poly(lactide-co-caproloactone); EMD, enamel matrix derivative; BrdU, bromodeoxyuridine; TCP, tricalcium phosphate; BSP, bone sialoprotein; CAP, cementum attachment protein; EGFR, epidermal growth factor derived MSCs; ERk, extracellular signal regulated kinases; Akt, serine/threonine protein kinase; FAK, focal adhesion kinase; hBMSCs, human bone marrow stromal cells; hUCMSCs, human umbilical cord MSCs; CPC, calcium phosphate cement; BCP, biphasic calcium phosphate; BGC, bioactive glass ceramic/bioglass; MG-63, human osteosarcoma cells; hPOB, human primary osteoblasts; OPN, osteopontin; nAg, nanosilver; OFD, open flap debridement; hPDLF, human periodontal ligament fibroblast cells; FTIR, fourier transform infrared spectroscopy; EDS, energy dispersive spectroscopy; CEMP1, cementum protein 1; HA, hyaluronic acid; MET, metronidazole benzoate; $CaCO_3$, calcium carbonate; SDF-1α, stromal cell derived factor-1α; OCN, osteocalcin; Runx2, runt-related transcription factor 2; SCAP, stem cells from apical papilla; DFCs, dental follicle progenitor cells; SD rat, sprague dawley rat; PLGA, poly(lactic-co-glycolic acid); PLA, polylactic acid; PCL, polycaprolactone.

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Contents

1. Introduction

Tissue Engineering/Regenerative Medicine, a multidisciplinary field, is a major revolution in the field of medicine and dentistry that focuses on the replacement and regeneration of various tissues and organs of the human body [1]. The relentless damage to any tissue or organ results in the destruction and loss of extracellular matrix (ECM) with the absence of functional cells. Hence it is essential to restore the structure and functions of the native natural tissue. Regeneration of dental/craniofacial tissues may be successfully achieved from the inimitable blend of human cell seeded biomaterial scaffolds with/without growth factors and or environmental (*e.g.* electrical and or mechanical) stimuli [2–4]. This combination of stem-cells, biomaterials, and physio-biochemical factors is the basis and major contribution of tissue engineering to regenerative medicine. In this approach, the biomaterial is critical to the regeneration of tissue since it serves as a three dimensional artificial ECM or scaffold to provide structural organization and support for the proliferation and differentiation of cells to create a neo-tissue. It is the interaction of the cells' with the artificial ECM that is pivotal in re-creating and maintaining the functional and 3D structural integrity of the tissue [4,5]. These scaffolds should be biocompatible *i.e.* should not elicit any immune or other adverse response on interaction with the host tissues; porous in nature with enhanced surface area to volume ratio facilitating cell attachment, proliferation, and in-growth to fill the space with new tissue and biodegradable so that they do not require any surgical procedure for removal [6]. For the regeneration of active functioning tissue/organs, 3D tissue engineered constructs containing human cells may be implanted directly, or used to recruit appropriate tissue forming cells already present in tissues at the time of implantation. The 3D scaffolds may also be used with cells in devices called "Bioreactors" that mimic the *in vivo* conditions in a functional manner by providing both biological and physiochemical stimulations necessary to regenerate tissues *ex vivo* prior to implantation [7,8]. In general, these same broad strategies may be applied to the regeneration of tooth and periodontal tissues (Fig. 1).

Regeneration of tooth and the periodontium has been the focus of research in dental tissue engineering over the past few decades. This is because, the loss of

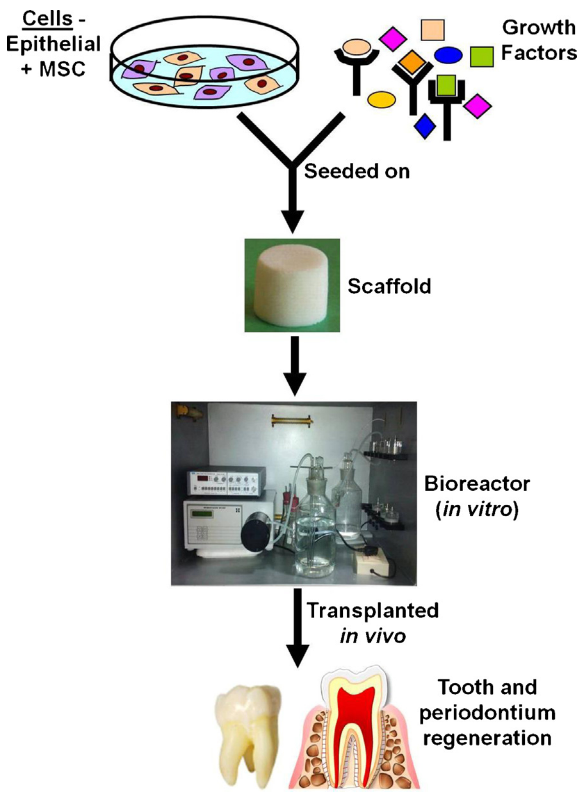

Fig. 1. Schematic illustration illustrating the fabrication of bioengineered scaffolds for tooth and periodontal regeneration. Epithelial and mesenchymal stem cells and growth factors were delivered through a composite scaffold, maintained in the bioreactor for physiological stimulation and transplanted *in vivo* leading to the functional regeneration of tooth and periodontium.

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