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EDITORIAL

Regenerative dentistry in periodontics

Regenerative Medicine is "the application of tissue science, tissue engineering, and related biological and engineering principles that restore the structure and function of damaged tissues and organs" (Groll et al., 2016). *Regenerative Dentistry* can be viewed as the branch of regenerative medicine focused on the regeneration of oral and dental tissues. *Tissue Engineering* was initially defined as "an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function" (Groll et al., 2016). Subsequently, a newer definition was proposed to combine *Tissue Engineering* and *Tissue Science* as, "The use of physical, chemical, biological, and engineering processes to control and direct the aggregate behavior of cells" (Groll et al., 2016).

Regenerative dentistry in periodontics follows the concept of tissue engineering, which consists of scaffolds, implanted cells, signaling molecules, and an adequate blood supply to obtain new periodontal ligament, cementum deposition, and bone formation (Bartold et al., 2016). In a case report, Nyman and colleagues was first to demonstrate clinically that periodontal Guided Tissue Regeneration (GTR) can be achieved with wound stabilization, space maintenance, and selective cell repopulation (Nyman et al., 1982). However, the clinical efficacy of GTR remains unpredictable in more complex periodontal defects because it is an open wound adjacent to an avascular tooth surface and exposed to a microbial biofilm (Vaquette et al., 2018). To solve these current clinical limitations, Vaquette et al. (2018) proposed, in a recent concise review, the use of three dimensional (3D) multiphasic scaffolds combined with bioactive molecules, drugs, gene and cell delivery to fulfill the requirements of GTR (wound stabilization, space maintenance and selective cell repopulation), in addition to enabling a spatio-temporal control of the periodontal wound healing process. *Multiphasic Scaffolds* are characterized by possessing multiple distinguishable compartments of different architectural nature (pore size, shape, porosity) and biochemical composition. These characteristics allow for the presence of bone, cementum, and periodontal attachment compartments, which favor tissue healing and regeneration (Vaquette et al., 2018). *Additive Manufacturing (AM)* has facilitated the development of multiphasic scaffolds. AM is defined as a process of joining materials to make parts from 3D model data, usually layer upon layer, for the fabrication of 3D structures directed by digital information. There are seven different categories of AM technologies according to the terminology proposed by the International Standards Organization (ISO/ASTM52900:2015). The AM techniques most commonly used for polymeric materials have been from the categories of: Vat Polymerization (such as stereolithography), Material Extrusion (such as fused deposition modeling), Powder Bed Fusion (such as selective laser sintering), and Material Jetting (such as inkjet printing) (Zadpoor and Malda, 2017). "*3D printing*" is a term commonly used, in a non-technical context, as a synonym for AM. However, because 3D printing represents only one technology, it is not recommended to use this as a general term for all AM technologies (Moroni et al., 2018). In 3D printing, a jet of binder is directed at a powder bed to define a pattern controlled by a computer-aided design and computer-aided manufacturing (CAD/CAM) software. The solvent binds the powder, thus forming a slice of solid material. Subsequently a new layer of powder is laid down and the process is repeated to build the scaffold layer-by-layer (Moroni et al., 2018).

Multiphasic scaffolds are particularly suited for tissue engineering of complex structures such as the soft and hard tissue interfaces of the periodontal complex. Studies to date can be divided into those that have utilized either a biphasic or a triphasic scaffold (Vaquette et al., 2018). Biphasic scaffolds are designed to facilitate the regeneration of the alveolar bone and periodontal ligament, while the deposition of a new cementum layer is not addressed. Triphasic scaffolds involve the incorporation of a third layer (i.e. the cementum compartment) consisting of a biological cue or bioactive biomaterial to trigger cementum formation (Vaquette et al., 2018).

There are challenges that still need to be addressed with AM techniques in the fabrication of multiphasic scaffolds. First is that all relevant mechanical, physical, and biological properties should be considered simultaneously when designing the architecture of the biomaterial and scaffold (Zadpoor and Malda, 2017). Second is the still limited availability of biomaterials that

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are compatible with current AM processes. Third is that recent developments in scaffold designs and fabrication technologies for regenerative periodontics are still in their early stages of translation to the clinic (Vaquette et al., 2018).

The use of stem cells for regenerative periodontics has recently been tested in several clinical trials. Yang et al. (2017) listed 8 clinical trials using stem cells as a therapy for periodontal regeneration (there should be more now, including the ones from our co-author Y. Sumita). The two sources of postnatal stem cells tested to date for periodontal regeneration have been the mesenchymal stem cells (MSCs) from the periodontal ligament and from the bone marrow (Yang et al., 2017). Ongoing clinical trials are also testing MSCs from the adipose tissue (i.e. adipose-derived stem cells). There is variability in results regarding whether stem cells improved bone and periodontal attachment levels. Some studies reported an improvement, while other studies that used a control group implanted with biomaterials found no added benefits with the incorporation of stem cells. These discordant findings may be due to using different patient populations between each study. Still, on a positive and concordant note, all studies reported that no clinical safety problems were identified with the use of stem cells, and thus this therapeutic approach would merit further investigations.

There are currently additional technologies with great potentials for periodontal regeneration. These include *Biofabrication, Bioprinting*, and *Bioassembly*. For applications in regenerative dentistry, Biofabrication can be sub-categorized into two distinct approaches, bioprinting and bioassembly (Groll et al., 2016). These approaches can generate biologically matured and functional products with structural organization from living cells, bioactive molecules, and biomaterials to be used in regenerative dentistry, pharmacokinetics, and basic cell biology studies (Groll et al., 2016, Moroni et al., 2018). In summary, advances in regenerative periodontics have been significant since the first clinical report of GTR. Ongoing developments in the fields of tissue engineering, cell therapy, and biofabrication are critical and applicable for the successful regeneration of periodontal tissues.

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