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Short Communication

Smart Biomaterials and Systems for Bone Tissue Engineering

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Bone is a part of the skeletal system and supports body shape and its movement [1]. Bone fracture generally occurs because of traumas, specific bone diseases, high force impact or stress. This clinical problem can finally lead to instability and poor alignment of the body structures and depression [2]. Although autografts are the common method of tissue replacement, some disadvantages such as pain at the donor site have limited their application. On the other hand, several disadvantages such as disease transmission, low viability of the grafts are the most significant limitations of the allografts and xenografts [1,3]. Bone tissue engineering (BTE) as an emerging field focuses on alternative treatment options that will overcome many limitations of the current treatments (i.e. additional surgery, disease transmission, immune rejection, and limited availability) [4,5].

There are three main components namely biomaterial, cell, and growth factor/drugs in the field of BTE [6,7]. The purpose of BTE is to provide 3D scaffolds, which mimic the function of natural bone extracellular matrix (ECM) to stimulate proliferation and formation of new bone [8]. There are three strategies in bone tissue engineering: first, is cell therapy so that cells are directly injected into the tissue; second is grafting of scaffold loaded with cell, and third is application of scaffolds loaded with signaling molecules, drug delivery or both. Recently, the focus of BTE is toward the use of scaffolds capable of controlled release of drugs in order to heal and prevent recurrent infection in the bone defect [9,10]. The main goal of sustained drug delivery systems is to deliver drugs at a desired rate and duration, to prevent sudden delivery of high dose of drugs to the action site. Targeted delivery of drugs, bioavailability and drug stability against enzymatic degradation are some advantages of drug delivery systems compare to conventional systems [11]. Drug targeted delivery systems also by avoiding repeated doses reduce side effects of the drugs [12].

Smart drug delivery system is an advanced method to deliver drugs to specific part of the body. These systems have been introduced as intelligent systems because of their ability in distinction of the environment conditions. These smart systems are able to control drug release and deliver drug targetedly to stimulate osteoblast proliferation and differentiation. A new strategy is stimuli-responsive materials that have developed for drug delivery. Stimuli-responsive materials deliver drugs in response to stimuli such as electric field, temperature, pH, and ionic environment [13,14]. Wang., *et al.* (2018) used a cationic polymer, polyspermine imidazole-4,5-imine (PSI), as a pH-responsive and non-cytotoxic transfection agent, to deliver Chordin (a bone morphogenic protein inhibitor) siRNA to bone mesenchymal stem cells. PSI is a cationic polymer that condenses siRNA into a polyplex and helps to release the siRNA from the endosome into cytoplasm. PSI is degraded at endosomal pH values which is non-toxic to human bone mesenchymal stem cells. Chordin knockdown improved osteogenesis and bone regeneration. It has been reported that cationic polyimines such as PSI are appropriate and smart carriers for siRNA delivery [15].

Application of nanoparticles is another new strategy in drug delivery systems. In this system, drugs are encapsulated in nanoparticles to control drug release. Mesoporous silica nanoparticles (MSNs) are one type of nanoparticles for drug delivery. Small size, variable pore size, and high surface area are favourable biological properties of these nanoparticles. Gan., *et al.* (2015) designed a dual-delivery system of pH-responsive chitosan-functionalized mesoporous silica nanoparticle bearing BMP-2 and dexamethasone to enhance bone regeneration [16]. In this study, dexamethasone was loaded into the mesopores and the BMP-2 was incorporated into the chitosan coating. In early release, BMP-2 was released from the Chitosan-MSNs and after endocytosis of this scaffold, dexamethasone showed a controlled release with the decreased pH value in cells. This dual delivery not only can promote bone regeneration but also can stimulate osteoblast differentiation *in vitro* and *in vivo*.

Scaffolds play an important role in bone tissue engineering by providing a 3D environment. A good scaffold should be porous and induce osteoconduction. Some surface modifications enable scaffold to increase attachment, proliferation and differentiation of stem cells on the scaffold. These smart scaffolds are able to stimulate bone repair and regeneration [17,18]. It should, however, be noted that several criteria must fulfill to this system behave as "smart" in tissue engineering. In this regard, two categories have been proposed. First, the biomaterials and constructs possess inductive effects on cells and tissues against to internal or external stimuli. Second, these biomaterials with controlled functions and intelligent properties effectively participate in repair and regeneration [19]. Modification of the physic-chemical properties of the scaffolds and designing smart scaffolds can influence on interactions between scaffold and cell and enhance the osteogenic differentiation for bone healing [20]. Biomimetic smart scaffolds are important groups of smart scaffolds that are similar to biological materials in term of structure and function. The interaction between cells and biomaterials is an important event in tissue engineering and application of smart scaffolds can induce an appropriate and desired cell responses [21]. For instance, biomimetic scaffold incorporated with cannabidiol-loaded microspheres has been used to construct biomimetic environments for bone tissue engineering. Based on the results' Kamali., *et al.* (2019) designed a scaffold that could stimulate mesenchymal stem cell recruitment and regeneration in bone defects [22]. Thus, an smart scaffolds can mimic the functions of the natural bone tissue *in vivo* and improves bone repair and regeneration.

A major challenge in tissue engineering is poor biocompatibility of scaffolds that induce the host immune system and trigger severe reactions *in vivo*. Hence, developing smart immunomodulatory biomaterials can enhance cell survival and regeneration [23]. Physicochemical features of scaffolds is a main factor that influence immunogenicity. In the meantime, hydrophobicity plays an important role in the extent of interactions with immune cells. The materials with high hydrophobic portions are recognized as foreign bodies that can trigger pattern-recognition receptors [24]. In addition, hydrophobicity, surface charge, size and shape of a scaffold can also impact on modulation of immune system. Several studies have shown that molecular weight and size of biomaterial degradation affect on immunogenicity [24]. During degradation process, the material properties change and form fragments with different molecular weights which can induce immune system [25]. It has been shown that surface modification of scaffolds such as adding hydrophilic molecules could reduce immunomodulatory responses [26]. Zakeri Siavashani., *et al*. (2020) explored an immunomodulatory strategy for implantable biomaterials. In this study, nicotinic acid was incorporated into the 3D silk scaffold to control inflammatory reactions. This scaffold also showed a sustained drug release and great cytocompatibility. The smart design of this scaffold was that the nicotinic acid was incorporated into 3D silk scaffold and decreased gene expression of pro-inflammatory cytokines [27]. In addition, a multifaceted coating scaffold was developed to evaluate its effects on osteogenesis, angiogenesis, and osteoimmunomodulation [28]. In this study, a microporous TiO_2 loaded with hydroxyapatite (HA) nanoparticles was generated by micro-arc oxidation and followed annealing. The annealing temperature of 650°C (MAO-650) created new physicochemical properties such as superhydrophilicity. On the basis of *in vitro* findings this scaffold was able to stimulate proliferation and differentiation of both osteoblasts and endothelial cells. Beside, MAO-650 coating decreased immunomodulatory responses to facilitate osteo/angio-genesis. Therefore, osteoimmunomodulatory smart biomaterials can produce by altering the annealing temperature and creating the new physical and chemical properties in scaffold which dictates osteoimmunomodulation and osteo/angio-genesis towards ameliorative osseointegration [28]. Taken together, although reducing immune responses elicited by the

materials is one of the most important goals in designing smart scaffolds, Crupi., *et al.* (2015) showed that these reactions may positively affect stem cell recruitment and differentiation. On the basis of Crupi's findings, modulating the immune response instead of its suppressing might be more effective in designing smart scaffolds [23].

Scaffolds with shape-memory property are another class of smart scaffolds. Shape-memory materials can memorize their physical properties and recover them with variation of the light or temperature change, and magnetic field [29,30]. Predesigning is the best advantage of this smart scaffolds that can conveniently be implanted into bone defects in the minimally invasive manner. Interestingly, this deformed scaffold can expand to fill the bone environment [19,29]. Shape-memory smart scaffolds play an important role in treating osteoporotic bone defects with irregular shapes. Wang., *et al.* (2019) fabricated bioactive glass (SiO_2-CaO) nanofibers with maximum bending. Assembling SiO_2-CaO nanofibers with chitosan significantly improved mechanical properties and exhibited an elastic behavior. This elastic behavior resulted that the scaffold to be fit into bone defects with irregular shapes [31]. Totally, smart scaffolds and smart drug delivery systems are promising opportunities and provide great potential to improve bone tissue engineering and deliver drugs with controlled releases.

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