Tissue Engineering: Challenges and Selected Application

Abstract

Tissue engineering has become a promising strategy for repairing damaged organs and tissues. Favorable government regulatory framework, continuous technology advancements and increasing research funding drive the market for alternative regenerative medicine therapies. Current mini-review coverskey components needed for tissue engineering -cells, scaffold and growth factors as well as method for tissue engineering graft manufacturing. Selected applications – for bone, skin and peripheral nerve regeneration are highlight in the paper.

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Introduction

Regenerative medicine, and tissue engineering now expands to practically all areas of healthcare including cardiac, corneal, nerve vascular and liver tissue engineering and regeneration [1]. Favorable government regulatory framework, continuous technology advancements and increasing research funding drive the market for alternative regenerative medicine therapies. Global tissue engineering market is expected to reach USD 11.53 billion by 2022, according to a new report by Grand View Research, Inc (2016).

Tissue engineering combines cells, biomaterials and growth factors to support and regenerate biological tissues. The key objective of tissue engineering is to improve quality of life in a secure way by avoiding various adverse effects of several standard medical therapies [2] and replace or repair damaged tissues by creating new healthy niches enabling cells to grow, proliferate and differentiate [3]. There are also multiple attempts to generate new tissues and even entire organs *in vitro*, ready to be implanted into the diseased and mechanically damaged sites. This involves e.g. the simulation or mimicry of the extracellular matrix (ECM) [4]. Thus, patient-derived cells can be expanded in culture and prompted to differentiate into a specific tissue or organ, followed by transplantation in a patient with no need of another patient-matching cell/tissue/organ donor.

The earliest clinical applications of human cells include the attempts to regenerate skin tissue using fibroblasts, keratinocytes, or a scaffold (template) in 1980th. Soon after, periodontal and alveolar bone tissues were tested for regeneration potential with use of membranes preventing undesirable fibroblasts from invasion there (guided tissue regeneration and guided bone regeneration) [5]. FDA approved marketing authorization for Maci- autologous cultured chondrocytes on porcine collagen membrane for the repair of cartilage defects of the knee in adult patients.

Components for Tissue Engineering

Three key components are needed for tissue engineering – cells, scaffold and growth factors. Whereas cells produce new tissue matrix, scaffold provides the appropriate environment for cells to be able to effectively accomplish their missions. The function of growth factors is to facilitate and promote cells to regenerate new tissue [6].

Although numerous investigations have been undertaken to regenerate various tissues, there are still many critical factors to solve in regenerative medicine [7] including cell source, scaffold construction, cell seeding, culture environment, matrix production quality, mechanical properties of cell-scaffold construct and suitable animal models.

The cell source has an enormous influence on the success of tissue engineering. Cells applicable to tissue engineering may be classified into autologous (patient's own), allogenic (human other than patient) and xenogenic (animal origin) [8]. Autologous cells are the most appropriate for tissue engineering, whereas allogenic and xenogenic cells are immunogenic and will need an immunosuppressive therapy when a new tissue is engineered. A certain limitation associated with autologous cells is harvesting a sufficient amount of healthy cells with high regenerative potential, especially when a patient is aged or diseased [9]. However, the progress in regenerative medicine area now allows for fast and efficient expansion of several different progenitor cells that are then used for the preparation or tissue engineered pro-medical constructs [10].

Mesenchimal Stem Cells (MSCs) have been isolated from a range of tissues, including bone marrow, adipose tissue, foetal tissue, placenta, umbilical cord and etc. Despite the remarkably high percentage of MSCs, BM and adipose tissue harvesting process is invasive, traumatic, and the amount of material extracted is limited and requires anaesthesia [11]. Foetal tissues, placenta and umbilical cord are potentially attractive sources of MSCs, since they contain abundant MSCs and can be collected without the requirement for invasive methods, but are not always available when needed [12]. Therefore, exploring new sources and isolation techniques for obtaining such cells is of great interest. Due to the fact that bone marrow derived stem cells circulate in peripheral blood at a very low level under steady-state conditions, it is necessary to mobilize hematopoietic stem/progenitor cells from bone marrow to peripheral blood.

Neovascularization is important in providing nutrients to the regenerating wound bed and removing waste products. MSCs have been shown to secrete and release many factors, such as epidermal growth factor, bFGF, platelet-derived growth factor, TGF-b, VEGF, hepatocyte growth factor, and insulin like growth factor-1, as well as enzymes, such as tissue-type plasminogen activator, uPA, and MMPs, that contribute to angiogenesis [13]. Human MSCs express VEGF as well as nitric oxide, which promote endothelial cell proliferation and vascular permeability [14]. Despite similar multipotency and phenotypes, MSCs from different tissue promote angiogenesis through distinct mechanisms. ASCs mediate vessel morphogenesis through the plasmin system and minimally with MMPs, whereas BMSC stimulate capillary formation solely using membrane-type MMPs [15]. Incorporating cells that secrete angiocrine factors within the scaffold, such as endothelial cells cocultured with mural cell precursors or fibroblasts, can induce de novo blood vessel development to create capillary networks and generate a prevascularized construct [16].

The major function of scaffold is to mimic the natural extracellular matrix (ECM). The scaffold should support proliferation, differentiation, and normal cell function. In addition, a scaffold placed at the regeneration site should prevent disturbing cells from external factors [17]. To fulfill the functions of a scaffold in tissue engineering, the scaffold should meet a number of requirements – it should be biocompatible, should have appropriate porosity and porous microstructure and proper surface chemistry to allow cell attachment, proliferation and differentiation. Scaffolds should possess adequate mechanical properties and controlled biodegradability [18]. The most common reasons for using absorbable polymer scaffolds are to accomplish time-varying mechanical properties and ensure complete dissolution of the implant, eliminating long-term biocompatibility concerns or avoiding secondary surgical operations.

Polymeric scaffolds for tissue engineering can be prepared with a multitude of different techniques, such as freeze drying or emulsion freezing, solvent casting or particulate leaching, phase separation, gas foaming or high pressure processing, melt moulding, 3D-printing, electrospinning, rapid prototyping of solid free-form technologies and combination of these techniques [19]. However, it is difficult to control the internal pore structure, porosity, and pore connectivity of the scaffolds in these processes, making it challenging to form scaffolds with the desired parameters to simulate suitable micro environment for cells. Scaffold manufacturing should focus on both adequate biological properties and cost effective scaffold production for fast implementation in clinical application. Furthermore, the scaffolds often contain residual organic solvent, which can damage cells [20].

Some researchers try to combine different method to prepare ideal 3D scaffold for tissue engineering. Chen H et al. [20] combine the biological 3-D printing, electrospinning, and vacuum freeze drying techniques to fabricate a hierarchical 3-D scaffold. The microporous structure of multi-scale scaffold is beneficial to the infiltration of the nutrient solution, which helps the migration of the cells into the scaffolds. It is confirmed from the HE and MT tests that there are a large number of cells inside the scaffolds, and new blood vessels and collagen fibers grows out.

Kim M et al. [21] used various processing conditions (such as applied electric field, flow rate, nozzle size, and weight fraction of the bioceramic) to obtained (α-TCP)-based scaffold using an electrohydrodynamic printing (EHDP) process. Cellular activities using preosteoblasts (MC3T3-E1) helped confirm that the newly designed bioceramic scaffold demonstrated significantly high metabolic activity and mineralization compare the traditional 3D printed material. Other researchers propose a new strategy to fabricate an alpha-tricalcium-phosphate (α-TCP)/collagen cell-laden scaffold, using preosteoblasts (MC3T3-E1), in which the volume fraction of the ceramic exceeded 70% and was fabricated using a two-step printing process. To fabricate a multi-layered cell-laden scaffold, we manipulated processing parameters, such as the diameter of the printing nozzle, pneumatic pressure, and volume fraction of α-TCP, to attain a stable processing region. A cell-laden pure collagen scaffold and an α-TCP/collagen scaffold loaded with cells via a simple dipping method were used as controls. Their pore geometry was similar to that of the experimental scaffold. Physical properties and bioactivities showed that the designed scaffold demonstrated significantly higher cellular activities, including metabolic activity and mineralization, compared with those of the controls [22]. Novel cryogenic 3D printing technique was investigated and developed by Wang C et al. [23] and all. for producing hierarchical porous and recombinant human bone morphogenetic protein-2 (rhBMP-2)-loaded calcium phosphate (Ca-P) nanoparticle/poly(L-lactic acid) nanocomposite scaffolds, in which the Ca-P nanoparticle-incorporated scaffold layer and rhBMP-2-encapsulated scaffold layer were deposited alternatingly using different types of emulsions as printing inks. The mechanical properties of the as-printed scaffolds were comparable to those of human cancellous bone. Sustained releases of Ca^{2+} ions and rhBMP-2 were achieved and the biological activity of rhBMP-2 was well-preserved. Scaffolds with a desirable hierarchical porous structure and dual delivery of Ca^{2+} ions and rhBMP-2 exhibited superior performance in directing the behaviors of human bone marrow-derived mesenchymal stem cells and caused improved cell viability, attachment, proliferation, and osteogenic differentiation, which has suggested their great potential for bone tissue engineering.

The electrospinning method is the most common due to its capability to produce fibrous materials with their structure and fiber diameters similar to those of natural extracellular matrix (ECM). Some advantages of electrospun scaffolds include the presence of high surface area for cell attachment and high porosity to facilitate nutrient and waste exchange [24]. Solution electrospinning is also a simple and inexpensive scaffold fabrication technique, and a wide range of polymeric solutions can be used to fabricate the scaffolds. However, the main disadvantage of electrospinning is the involvement of toxic organic solvents during fabrication, which can be harmful to cells [25]. However some methods as melt electrospinning, which does not involve the use of organic solvents and NanoMatrix3D-

electrospinning (NM3D) are now promising alternatives to solution electrospinning [26]. On the other hand side, fibers obtained from melt electrospinning process are thicker than those fabricated from solution electrospinning. NM3D has some advantage over conventional electrospinning as it uses optimized and sterilely produced products. NM3D provides cells with greater space for proliferation, and cells cultivated in NM3D are immersed in the cultivation medium bottom. NM3D products are primarily used for research of cell adhesion, expansion and differentiation *in vitro*.

Synthetic polymers (macromolecules) are the primary materials for scaffolds in various tissue engineering applications [14]. They are classified as absorbable and non absorbable polymers. The resorbable polyesters are predominant among synthetic polymers. They include polylactic acid (PLA), polyglycolic acid (PGA), polylactic-polyglycolic acid (PLGA), polyethylene glycol (PEG), PEG with PLGA (PEG-PLGA), and polycaprolactone (PCL) [27]. PLA and PGA are synthetic polymers with excellent biomaterial characteristics that are dependent on the ability to control their synthesis, which influences the final surface characteristics, they are degraded in the body by chemicals and not cell-mediated processes [28]. Their rapid degradation and low mechanical strength, difficulties associated with their production, and their uncertain interaction with cells are disadvantages as it could cause early failure of the graft. PLGA is a copolymer obtained by the union of lactic and glycolic acid through ester bonds. The different relationships between the two monomers and the different sequences that can be obtained greatly increase the variability of the final scaffold used in clinical practice, with several different formulations and resorption times [29]. PEG is a polyether with a high molecular weight and is very resistant to resorption and It has been used in combination with MSCs and peptides with good results [29]. PCL has good mechanical characteristics and very long resorption times (of up to three years) and degrades via hydrolysis of the ester bonds [30]. It has been combined with HA and chitosan to form hybrid scaffolds with better mechanical resistance and has also been used in association with MSCs and growth factors [31].

More attractive but less controlled base for scaffolds are natural polymers such as collagen, cellulose, gelatin, silk, hyaluronic acid, chitin and chitosan. Numerous research in copolymers of PLA-collagen, PCL-chitosan etc. have shown better cell response and increasing mechanical properties as well as better bio-resorption comparing isolated polymers [32].

A wide range of exogenous growth factors are currently being used in bone tissue engineering: transforming growth factor beta (TGF-b1), fibroblast growth factor (FGF), insulin growth factor (IGF), vascular endothelial growth factor (VEGF), PDGF, and bone morphogenic proteins (BMPs) etc [33,34]. Wen B et al. [35] have shown that application of BMP-2 (50 μg) to Straumann Bone Ceramic leads to significant mineralisation and new bone formation compared the non-loaded scaffolds. As shown by Chang HC et al. [36] BMP- loaded PLGA microspheres effectively promoted osteogenic potential of the gelatin/HA/β-TCP composite and facilitated supra-alveolar ridge augmentation *in vivo*. Enhancement in osteogenic differentiation and osteoinductivity of bioactive glass have also been achieved by incorporation of BMP-2 [37]. It is still not clear the safety of BMP clinical application due to possible risk of cancer induce that reported by Poynton & Lane [38]. Some researchers suggest dose depends of BMP to cancer risk [39] but optimal amount of this protein is not clear. Dynamic mechanical loading is other strong anabolic signal in the skeleton, increasing osteogenic differentiation of bone mesenchymal stem cells and increasing the bone-forming activity of osteoblasts [40]. Despite these numerous findings, the ideal stimuli for bone tissue regeneration has not been yet established.

Tissue Engineering Selected Application

Treatment of skeletal defects has remained a challenging part of many reconstructive surgeries. Currently, autologous bone is assumed to be the gold standard for bone grafting [41]. Bone substitute materials are recommended when the quantity of autogenous bone needed is greater than available amounts of autogenous bone [42] and when there is a risk of morbidity at the donor site [43]. Bone tissue engineering is emerging as a possible solution for regeneration of bone in a number of applications. For effective utilization, scaffolds still need modifications to impart biological cues that drive diverse cellular functions such as adhesion, migration, survival, proliferation, differentiation, and biomineralization [34]. A top-down approach for building bioactive and cell instructive biomaterial scaffolds is to create scaffold-ECM hybrid constructs by depositing extracellular matrix secreted by tissue-specific/stem cells on bare biomaterial scaffolds. Different synthetic materials have been used for scaffold construction. Because synthetics are chemically created, and are part of a controlled manufacturing process, their physical properties (i.e., composition, morphology, and resorbability) are exceptionally reproducible. Combination of natural and synthetic polymers shows some advantages in bone tissue engineering. Some studies indicate positive effect of PCL/chitosan [44], PCL/collagen [45], PLA/hydroxyapatite [46], TEA/tBOC-treated chitosan [47] for bone regeneration. Natural and synthetic polymers has been used to improve some existing solution for bone engineering e.g. bioactive glass scaffolds, that have weak mechanical properties. Wei Xiao et al. [48] and coauthors suggest to use of adherent polymer layer to the external surface of strong porous bioactive glass. These bioactive glass-PLA composites, combining bioactivity, high strength, high work of fracture and an internal architecture shown to be conducive to bone infiltration, could provide optimal implants for healing structural bone defects. But the ideal combination of scaffold/cell type and growth factors for tissue engineering constructions is not yet defined.

Chronic wounds affect over 4 million individuals and pose a significant burden to the US healthcare system [49]. Advances in tissue engineering have allowed for the development of cell-based wound dressings that promote wound healing by improving cell migration and differentiation. Most cell-based dressings utilize a scaffold upon which cells are seeded. Scaffolds are designed to easily integrate with host tissue and provide an optimal environment for cell growth and differentiation. The

cells themselves further encourage the progression of tissue formation [50]. Skin transplantation cannot be performed in large skin defects because of low diffusion and limited interaction with the host environment for nutrients, gas exchange, and removing the waste products. Collagen, chitosan, hyaluronic acid, fibrin, and gelatin are all natural materials used to produce biomimetic scaffolds, which have been applied for the repair and reconstruction of various tissues [51]. Synthetic polymers have some advantages compared with natural polymers. They are strong and have controllable degradation rates, are less expensive, having more reliable sources of raw material and can provide a wide range of physical properties using various fabrication techniques [52]. Despite acceptable results in epithelialization of keratinocytes with synthetic polymers, no successful epidermal graft has been achieved, due to their limited cellular recognition and tissue compatibility. Synthetic polymers in combination with natural polymers can be used for temporary dressing, epidermal/dermal cell carriers, or full-thickness skin equivalent [53]. PLGA/collagen [54], PLA/chitosan [55], PCL/chitosan [56], PCL/collagen [57] currently used for skin graft development.

Patients who have injuries or traumas in the nervous system often suffer from the loss of sensory or motor function, and neuropathic pains because nerves have a very limited capacity to regenerate [58]. In the peripheral nervous system, direct end-to-end surgical reconnection is a common method of treatment for nerve transection injuries when the injury gap is small. The use of autograft, allograft or xenografts has many limitations, including donor scarcity, multiple surgeries, donor site morbidity, scarring, and the need for an allograft patient to take immunosuppressants indefinitely after surgery to avoid rejection [59]. The application of cell-based nerve regeneration therapies has been considered as a promising strategy for the treatment of large peripheral nerve injuries. Some 3D grafts for nerve conduits were developed and successfully tested both *in-vitro* and *in-vivo*. Gelatin-based nanoporous [60], silk fibroin/silk sericin [61], water-based biodegradable polyurethane, PLGA, PLA/collagen, PCL [62] with Mesenhimal Stem Cells (MSCs), neural stem/progenitor cells (KT98/F1B-GFP) and Schwann cell have shown promising results during long term *in-vivo* studies.

Conclusion

Tissue engineering is expanded to all the areas of reconstructive surgery but still has some limitation for wide clinical application due to gaps between experimental research and clinical practice. Polymers and Biomolecules, such as collagen and chitosan are agents of choice for scaffold development but it is desirable to improve their mechanical properties and custom manufacturing. Growth factors and drug-delivery concept in tissue engineered materials can manage tissue development, decrease bacterial inflammation and enhance tissue regeneration. Combination of different methods for scaffold development (electrospinning, 3D printing, sol-gel) allow to create custom scaffolds for tissue replacement.

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Conflict of Interest

None.

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