3D and 4D Printing for Tissue Engineering and Regenerative Medicine

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Tissue engineering is an emerging field which merges different areas in order to construct biomaterials scaffolds that sustains, recover or improve the biological activities of injured or diseased tissues [1]. Cell based tissue engineering techniques are currently being successfully developed to repair and restore the damaged and diseased tissue functions. The fundamental principle is the use of an appropriate cell source and a biocompatible scaffold system to construct a mimic of the targeted tissue. An additional challenge is that most organs and tissues are multiphasic in nature. Thus an ideal scaffold should be capable of supporting multi-lineage cell types.

The extracellular matrix (ECM) is an essential component of the cellular micro-environment and makes a complex three-dimensional (3D) network that has important role in tissue repair or regeneration. ECM is a dynamic system that transmits mechanical and biochemical signals from the extracellular environment into the cells, which in turn modifies the behaviour of the cells [2]. Moreover, ECM provide sites for the cell attachment and supports the spatial organization of tissues. Repair of defective tissue after injury or disease depends on the synthesis of extracellular fibrous matrix to replace damaged or lost tissue. However, the development of smart scaffolds that exhibit the complex organization of natural tissues for tissue engineering application is still remains a major challenge. Therefore, 3D and 4D printing technologies are a promising approach and having great potential in the field of tissue engineering and regenerative medicine. Tissue-engineered constructs using 3D or 4D printing provide an advanced platform for the development of a synthetic ECM that mimics natural ECM microenvironment and also provide a support for the production of new cellular ECM. Conventional methods for the scaffolds production in a mesh or sponge form are achieved by electrospinning, salt leaching, lyophilization, and wet spinning [3-6]. However, it is challenging to develop well-defined and pre-determined nanoarchitectures in a precise manner using these techniques. Cells cultured onto these structures may not enter to the depths of the scaffolds. Moreover, cells may not be equally distributed everywhere in the scaffold. Therefore, the limitations of conventional scaffold fabrication techniques can be overcome by using 3D or 4D printing technologies.

3D printing, also known as rapid prototyping is one of the most popular recent technology which has shown strong potential for the development of biostructures in the field of tissue engineering. Various functionalization strategies have been used to enable smart biomaterials scaffolds system for a wide range of translational applications [7]. Previously, we have synthesized 3D printed dentures from custom-fabricated filaments which is promising prosthetic for the prevention of fungal infection. The major advantage of 3D printing is the fabrication of patient-specific scaffolds. 3D printing approaches are broadly divided into subtractive and additive techniques [8]. Several different 3D printing techniques are being used in tissue engineering. The most common one are Fused Deposition Modeling (FDM), Selective Laser Sintering (SLS), Stereolithography (SLA), Near-Field Electrospinning (NFES), and Bioprinting. 3D bioprinting system is used to synthesize structures using additive manufacturing techniques, in which the fabricated 3D structures consist of heterogenous biomaterials, active biomolecules, or even living cells [9]. Polymeric materials are largely being preferred because of their biocompatibility, biodegradability, low cost, and easy processability. These materials are utilized in the form of powders or filaments in SLS and FDM, and as a bioinks for SLA and bioprinting. Recently, 3D bioprinting technologies have transformed the fields of tissue engineering and regenerative medicine by enabling construction of highly complex biological constructs.

4D printing is an another emerging and advanced technology that has important applications in the field of tissue engineering. Smart (intelligent) materials are used in the fabrication of the scaffolds in 4D printing technology, allowing the scaffolds to closely resemble the dynamic nature of tissues. The smart materials used to synthesize the 4D scaffolds respond to various stimuli such as pH, magnetic field, moisture, heat, or light, and adapt to the extracellular micro-environment by altering their shape or other properties. 4D printing uses the same additive manufacturing system as utilized in the 3D printing technology. However, the major difference between 4D and 3D systems is the nature of the materials used in these technologies. To consider a 4D printed product, a 3D printed structure should exhibit at least one type of intelligent behavior, such as “self-actuation” or “shape memory” [10]. 4D printing technology has several advantages over 3D printing system as it gives spatial and temporal control over the developed product and produced the structures that are animate and dynamic.

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The rapid progress in 3D and 4D printing technologies for tissue engineering and regenerative medicine have enabled ease of operation, shorter manufacturing times, and economical and affordable products.

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