TISSUE ENGINEERING- BRIDGING SCIENCE AND MEDICINE

Abstract

Over the past two decades the TERM system have aimed for the regeneration and reconstruction of tissues such as, skin, bone, cartilage, nerves, heart valves and tendons, etc., the scaffolds pooled with other bioactive materials like genes and cells are able to guide the occurrence of functionally engineered tissues. The scaffolding material used depends upon the type of tissue to be regenerated and can be made of many types of biomaterials for example natural, synthetic as well as inorganic or organic. Various types of biomaterials to be used as 3d scaffolds for tissue engineering and other emergent technologies for tissue specific considerations are discussed in depth in this chapter. The latest technologies akin to 3D behaviour and multicellular interactions are also outlined.

Keywords: TERM system, ECM, Polymers, Technologies

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I. INTRODUCTION

Tissue engineering and regenerative medicine also known as TERM for short is an approach that brings to the table advanced approaches for damaged tissue regeneration and healing. Over the past few decades this emerging field has seen many advances and there has been a multitude of research including biomaterial design and processing, surface characterization or scaffolding and functionalization for improved cell material interactions and imaging. The various approaches include:

- Direct implantation of new cells into the defects of the cells isolated from the patients.
- Bioactive materials and growth factors delivery targeting tissue specificity.
- Cell free scaffolding biomaterials
- Cell laden scaffolding structures that mimic the natural extracellular matrix

The cell laden scaffolds are the most commonly used for tissue engineering which involve 3D porous and hydrogel scaffolds on which cells grow and organize to form an extracellular matrix (ECM) used for regeneration purposes. The scaffolds provide the chemical maintenance for in vitro ECM formation along with mechanical support by being slowly degraded resorbed and metabolized on in vivo plantation. The porosity or the pore size as well as the interconnectivity between the structures of the scaffold have a direct influence over the functionality of the cells. High porosity in the scaffold means greater infiltration of the cells and extracellular matrix colonization which again is directly influenced by pore size. Open and interconnected pores contribute to the growth, migration, and proliferation of cells to an extent during extracellular matrix production. Thus, maintaining an optimal pore size becomes crucial during the process of TERM. As a result, the vascularization as well as formation of the new tissue maybe faster. On the contrary microporosity is also required for cell adhesion, spreading, and creating an initial mechanical strength between the scaffold and the tissue. Other parameters that are to be kept in mind include biocompatibility, safety, cost-efficient materials and devices as well as methodologies.

A broad variety of natural as well as synthetic scaffold materials have been applied for scaffold processing. Natural based polymers show biological properties better fit to microenvironment of the tissue meaning that they promote cellular response, biocompatibility as well as degradability. Most recent advancements show that materials made from decellularized matrix are being explored in TERM. This approach has been observed to preserve native tissue composition not only in terms of structural proteins such as collagen but also preserves the growth factors and cytokines of the native tissue which can promote cell viability as well as tissue repair and remodelling.

On the other hand, the lack of mechanical strength in natural polymers can be compensated by using synthetic polymers or combining the natural polymers with inorganic and ceramic materials to produce a scaffold with superior strength and bioresorbable. Thus, depending on the TERM strategy, optimal biomaterials and processing technologies are considered for the scaffold. Some of the strategies for scaffold processing include-

- Solvent casting with particulate leaching
- Freeze-drying
- Gas foaming

- Fiber bonding
- Phase separation
- Electrospinning
- 3D printing technologies

Some of the scaffold biomaterials are discussed in the next section.

II. SCAFFOLD MATERIALS- BIOMATERIALS

Current strategies in TERM involve usage of a wide variety of biomaterials. They are classified as-

- Natural polymers
- Synthetic polymers (poly-glycolic acid, poly-lactic acid, etc.)
- Inorganic biomaterials (include metals like titanium and its alloys)
- Ceramics (alumina, zirconia, calcium phosphate cements)

Natural polymers have an advantage that they are readily recognized by the body, their similarity with the extracellular matrix and heir susceptibility to specific enzymes. On the contrary the inorganic biomaterials are best used for their biocompatibility, bioresorbable and osteoconductive properties. Few of the biomaterials are described.

1. **Natural and Synthetic Polymers:** Natural polymers are isolated from biological organisms like algae, plant, animal, microorganisms, which are similar to the biological macromolecules like proteins and carbohydrates that are easily recognized by the environment. These materials are similar to the extracellular matrix and hence are called as biopolymers and they prevent inflammation, toxicity as well as immunological reactions that are mostly seen during use of synthetic polymers. Therefore, these polymers having biological properties are effective in conducting design changes for various systems involving therapeutic's for the usage of some biologically active molecules/compounds for higher bio engineered functions such as the delivery of drugs in biological systems. Structural proteins such as elastin and fibrin are used as sutures for scaffolds and as drug delivery systems.

   Synthetic polymers have excellent processing characteristics. Hydrolytically degradable polymers are chosen over enzymatically degrading ones as to cater to the patient needs. This is also because hydrolytically degradable polymers have minimal site as well as patient to patient variation. The downside of using synthetic polymers is that they become toxic when combined with certain polymers. The solution is to create hybrids using natural polymers to increase the hydrophilicity of the cells, biodegradability, and cell attachment. Few examples of synthetic polymers are poly-ethylene-glycol (PEG), poly-lactic-acid (PLA).

2. **Inorganic Biomaterials:** These types of biomaterials have been established for orthopaedic load-bearing coatings, bone grafting, cements and dental restoration. Ceramic biomaterials are called as bio ceramic, and they are considered for their osteoconductive as well as biocompatible properties.

Inorganic biomaterials are classified as- bioinert, bioactive, and bioresorbable. Bioinert biomaterials are those which have no interaction with adjacent tissue after implantation and are typically used as support implants. Bioactive biomaterials have a direct interaction with the living tissue and are used for filling small bone defects and similar injuries. Bioresorbable materials are slowly accumulated and settled within the organism of study, overtime this is replaced by the bone itself.

A number of studies are being carried out in order to enhance the bioactive inorganic materials by the process of doping that is addition of ionic elements, that are slowly released during bone resorption and hence boost the biocompatibility and mechanical strength of implants.

3. **Hybrids of Organic-Inorganic Biomaterials:** These biomaterials are made as a result of combining organic as well as inorganic biomaterials as the name goes. The main prospect of this study was to acquire a better understanding of the compatibility/working between the different phases in order to maintain the mechanical power of this porous structure of the scaffold. Further these “nanostructured hybrids” have been preferred as the nanoparticles provide a larger surface area thus contributing to upgraded mechanical properties. Examples include PLG, PLA, PEG, bio-ceramics, bioactive glasses, carbon nanotubes, etc.

III. SCAFFOLDING STRATEGIES FOR REGENERATION AND TISSUE ENGINEERING

1. **3D Porous Scaffolds:** The requirements needed to be fulfilled by a scaffold are that they should be able to help the cell to divide rapidly and also be able to adhere and detach easily. The scaffold material is having to enable itself to withstand any mechanical distress, hence allowing it to perform the optimum functionality of adherence and detachment. [1].

2. **Natural 3D Porous Scaffolds**

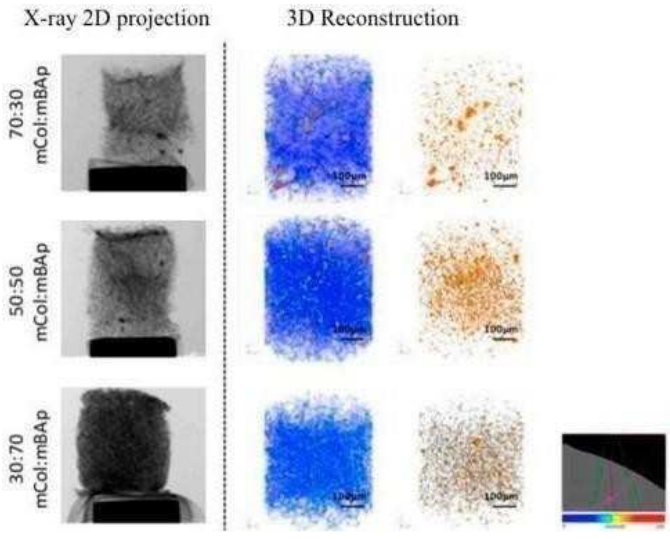

Figure 1: Scaffolds of Marine Collagen [3]

Majorly the marine sources are extracted for various biologically active resources. This allows to reduce the cost production and also increases the amount of biodegradable product index. The fabricated 3D scaffolds are made by using the skin of a shark species named as *Prionace glauca* along with Calcium phosphate which is collected from the teeth of two different shark species through freeze-drying technique *[2]*. Other scaffolds were prepared by using a natural polymer containing silk fibroin and β-TCP containing strontium, zinc, etc. This matrix of collagen is able to support the cell adherence and the cell division rate of the osteo blast like-cells. The main property of these scaffolds is that they have high inter-connected ultra fine porosity of 500μm. They also showed porous crystals and globular structures also, along with this when they were dipped in silk a ceramic spherical structure was found.*[3]*.

3. **3D Printed Scaffolds:** The word 'TERM' is used in order to classify any type of tissue engineering involving 3-D structures. 3D scaffolds help in providing great freedom for positioning the cell and its biomolecular components in specific designs *[4]*. Collagen usage greatly increased the hydrophilic property by 9 degrees of change and the physical strength also increased and improved. *[5]*.

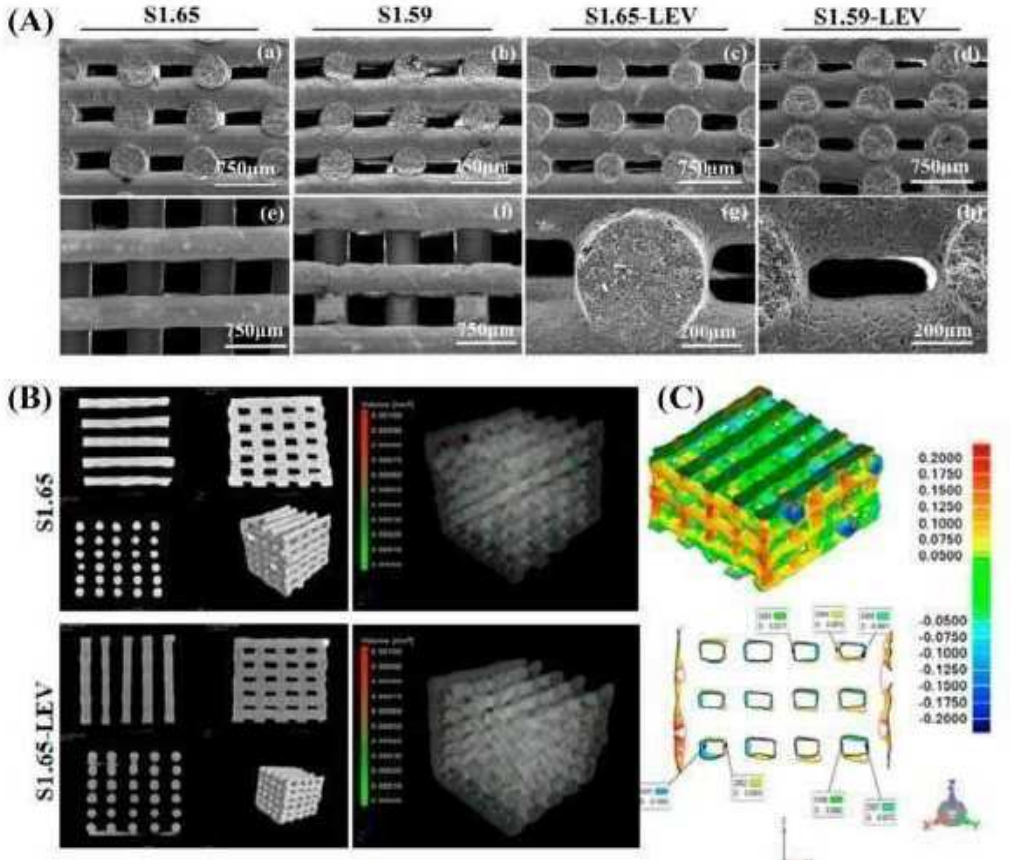

Figure 2: (A) Electron micrographs, (B) 2Dand 3D images, (C) 3D and 2D with colour coding, [6]

4. **Injectable Hydrogel:** These hydrogels are mainly fillers soft and hard tissues that promote good physical integration into a wounded or defective point in the body. This procedure allows the recovery of patients without requiring any surgeries or the removal

of a ligament or a body part. The amount of water present in these hydrogels allow them to be easily manipulated in order to induct any stimuli and these are injected at the site of injury or abnormal formation of a muscle allowing the inter cross-linking to a greater parameter [7]. Covalent bonds are formed between the polymeric chains by agents like genipin and enzymes present in these hydrogels [8] [9]. These methods for inter linking involve gelation by thermal heating allowing easy processing without limiting injection level inside the body [10]. The inter linking mechanisms is harder to execute in the case of the natural polymers. This is due to the change in the pH of the solution affecting its gelation temperature, compatibility, and timing within the gel matrix [11].

A way this issue was addressed was as in case of chitosan to produce thermosensitive injectable which are pH dependent hydrogels and the combination with starch was performed. The addition of starch to the chitosan gel solution did not change the transition temperature and allowed heating induced hydrogelation for applications in minimal invasive injectable systems [12].

5. **3D Printed Hydrogels:** These hydrogels are produced with the help of computer assisted technologies. This allows the coating of some engineered tissues hence providing superior control over the shape and reproducibility. The control of the physical strength and properties of the different layers and gradients allows complex tissue copying architecture. The 3D printing technologies have been proposed by using different hydrogel technologies/systems coupled with conventional TERM strategies *[13]*. E.g.: Li and the team proposed 3D printed hydrogels act as an OC defect filler and by using alginate and hyaluronic acid as photo- polymerized bioinks. These 3D printing technologies that are applied to the tissue engineering processes do only involve in silica mechanisms but also product/resource and material science allowing the development of new technologies in the biotechnology sector. This partnership between various technologies allows the development of therapeutic procedures that are less complicated as compared to other native processes available commercially *[14]*.

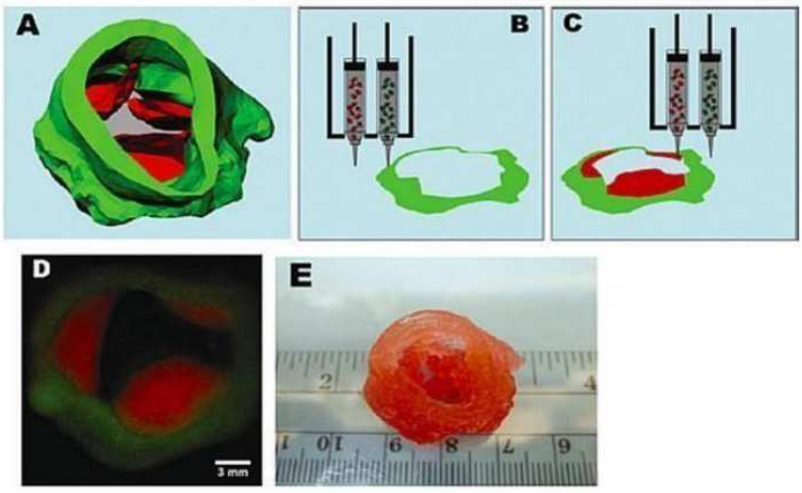

Figure 3: (A) 3D reconstruction of aortic valves, (B) 3D reconstruction of Sinus smooth muscle cells, (C) Aortic valve leaflet interstitial cells, (D) Fluorescent image of 3D bio printed layers of aortic valve conduit and Macroscopic image of a 3D printed aortic valve conduit [15].

6. **Porous Hydrogels:** The big problems of hydrogels include maintaining control over the porosity and some physical properties, The amount of scaffold porosity required for the cells to proliferate depends on the type of tissue and every type of tissue has certain requirements for tissue formation. More the amount of porosity, more will be the absorption and diffusion of nutrients when there is no vascular system available at the site [16] [17]. When the process of salt-leaching is combined with freeze-drying technologies and increase of micropores. This process allowed the improvement of the hydrogel's structural stability by allowing efficient protein folding. The formation of inorganic hybrid hydrogels along with bioactive hydrogels caused an increase in the mechanical stability and porosity of the hydrogels. This strategy allowed the production of hard tissues such as bone and OC complexes which can include the incorporation of certain of growth factor inductions [18].

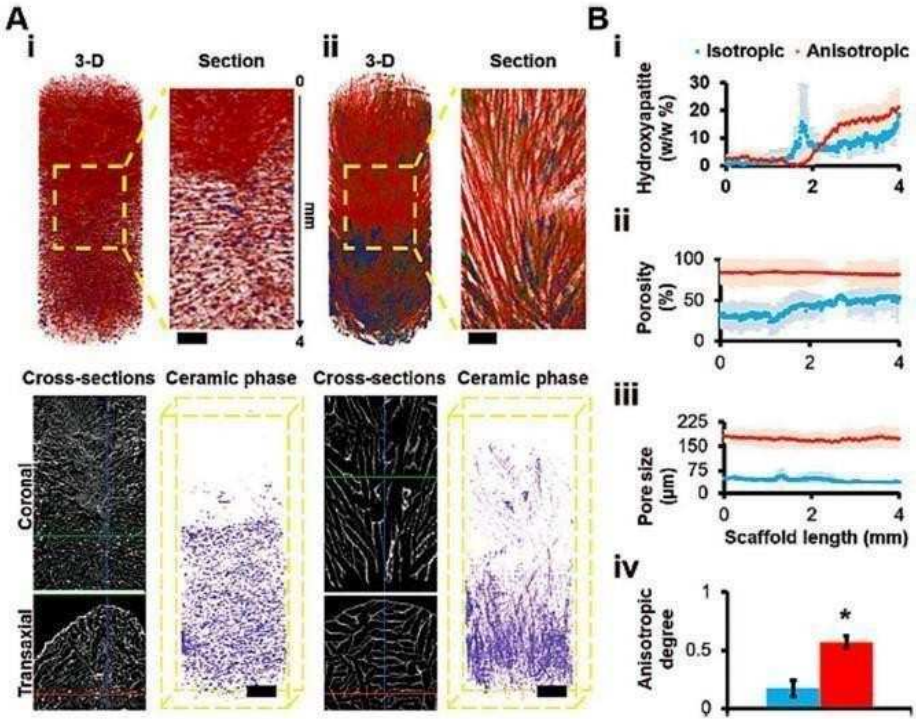

Figure 4: (A) 3D reconstruction of isotropic and anisotropic porous architectures, (B) Quantification profiles [19].

IV. FUTURE PROSPECTIVES

The TERM technology is an upcoming innovative field involving material sciences, biology and medical sciences has helped in providing and alternative for better tissue regeneration and repairing the damaged tissue. The socioeconomic need to make sure that these strategies to be an effective tool for treating a patient and allow them to have a normal life again can make this field extremely important.

All of the above-mentioned tool of scaffold technologies enables to make a new, efficient tissues, the new methods and technologies are still in progress which can help in producing different or more complex types of tissues. The future of tissue engineering and its development will ensure that even in this changing world, the ability to minimize the raw

material usage to produce new organs will be vital. This field will in future will be normalized as more and more people become acquired with its knowledge and them comprehending it as technology of giving people new health improvements. The further methods and technologies in this field will ensure that there is accessibility provided and even more options of tissue regeneration in the case of the usage of scaffolds.

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