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An Overview of Various Biomimetic Scaffolds: Challenges and Applications in Tissue Engineering

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Abstract

In current year tissue damage, repair and regeneration has become a very serious clinical problem which accounts for billions of health issues all over the world every year. Many tissue repair substitute and techniques are now available although it is having many drawback; these disadvantages give a good reason for the continued research for more acceptable tissue engineered substitutes. Research that are presently going on to improve the design strategies to overcome the surgical outcomeinvolves the development of biopolymers and synthetic polymers as primary scaffold or luminal fillers as secondary scaffold with the tailored mechanical, physical and chemical properties. Biodegradable scaffolds for regenerated tissue is preferred since no foreign body will be left in the host hence there is no need of second surgery so it involves less complications. The purpose of the review article is to discuss about the various tissue engineering researches taking place around the globe, recent developments, and different biomaterials used for it and applications of tissue engineering. The improvement and validation ofmodalities which are capable of spontaneous regeneration would be valuable to properly grade injuries and rapidly identify cases which require surgical intervention with less ambiguity. This review article focuses on different biomaterials used for tissue regeneration or tissue restoration and their methods of fabricationas well as their application in bone, nerve, cartilage, skin tissue engineering.

Keywords: Biomaterial; Tissue engineering; Scaffold; Biodegradable; Biomimetic; Regeneration

Introduction

Tissue engineering is an intriguing,broad interdisciplinary scientific field of research anda new hope for the hard to treat disorders,indeed a technique that will allow the growth of tissues and develop functional replacement tissues or entire organs for clinical uses to repair, maintain and/or augment the tissue function [1]. Succinctly, tissue engineering applies the principles of engineering and life science toward the development of biological substitutes that restore, maintain, or improve tissue function [2]. The field of tissue engineering has emerged spectacularly in the last 10 years, thereby proving its potential for regenerating almost every tissue and organ of the human body. Tissue engineering aims to restore and improve tissue functions that are defective due to pathological conditions, either by developing biological substitutes or by reconstructing the tissues. The general strategies adopted by tissue engineering can be classified into the following groups (a) *Implantation of constructs reinforced with the target cells into the organism*, (b) *Delivery of growth factors to the constructs*, and (iii) *Adhesion of cells with the surrounding tissues*. The major perspective behind this review article was to discuss the various research work done on tissue engineering focusing mainly on the biomimetic scaffolds and their contribution towards improvement of human health. In vivo, cells are entrenched in extracellular matrix (ECM), guiding their development, arrangement, and regenerative abilities by specific signals, thus providing an appropriate environment for the cells. In tissue engineering, the role of the ECM needs to be accomplished by adequate scaffolds [3]. Researchers across the globe are working on this particular area with a foremost goal to generate living cellular constructs with 3-D, tissue-like organization that mimics thefeatures of the extracellular matrix (ECM) architecture and influences the cellular behavior through different means, such as scaffold design, cell-based therapies, and factor-based tissue engineering. The biomimetic scaffolds has so far proved to be the most promisingand successful approach that shows high cellular responsethus resulting in the restoration ofthe damaged tissues. Biomimetic scaffold made of biomaterials have been improving the quality of lives for many people over the past few years. They have vast number of applications such as artificial skin and arteries, limb and joint replacements etc. Various etiological factors like extensive trauma, infections, burns, automobile accidents and extensive loss of tissue pose a challenging situation. Conditions which were refractory to routine suturing and treatment needs biomaterials, /biological dressings/skin substitutes for management of different types of wounds like surgical wounds, bleeding wounds, septic wounds, chronic wounds, ulcerated wounds, maggotted wounds. These materials are mainly used for replacing unhealthy tissues to increase life expectancy of individuals [4]. Scientists are trying to produce improved and new implant materials to meet the increasing demand. Amid all the biomaterials, bio-resorb able and biodegradable materials are being explored extensively both clinically and experimentally to design scaffolds with particular desired characteristics [5]. In general, biomaterials used in tissue engineering can be classified into two categories according to their origin, namely natural and synthetic biomaterials. Natural polymers can be classified as proteins (silk, collagen, gelatin, fibrinogen, elastin, keratin, actin, and myosin), polysaccharides (cellulose, amylose, dextran, chitin, and glycosaminoglycans), or polynucleotides (DNA, RNA). Natural biomaterials have excellent biocompatibility and shows potential viability. However, natural materials possess limited physical and mechanical stability and therefore are notpreferred for the load-bearing applications. Synthetic biomaterials are categorized into inorganic and organic synthetic polymers. Synthetic polymers represent the largest

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group of biodegradable polymers such as PLA, PGA, PLGA, PVA, PVC, PLLA, Nylon, Gelatin, Polyurethrine and many more. Synthetic biomaterials can be tailored to have better controlled physical as well as mechanical properties andit can be used to replace both soft and hard tissue. Biocompatibility is the major drawback for synthetic biomaterials as cells have difficulties in attachment and growth on these materials. Henceforth, many processes modifying the surface and bulk properties have been developed to improve their biocompatibility. Composite scaffolds are the best solution to overcome the disadvantages of both natural and synthetic scaffolds, it helps in the mutual enhancement of the scaffold properties and thereby allowing controlled degradation and improving the biocompatibility in tissue engineering applications (Figure 1).

Fabrication Methods

A goal of any tissue engineering approach is to develop scaffold that can engraft tissue cells capable of functional restoration. To replace all the crucial intercellular reactions and promote native intracellular functions, the tissue engineers' goal is to mimic the native extracellular matrix (ECM). ECM analogues, or scaffolds, should conform to a specific set of requirements [7]. Fabrication technologies of scaffolds have been ameticulous area of research. During the past two decades, many works have been done to fabricate potentially applicable scaffold materials for tissue engineering. In general, these technologies can be classified into:

(1) Porogens in biomaterials

(2) Rapid prototyping technologies

(3) Woven or non-woven fibers

In the first category solid materials either dissolved in solvents or incorporated with porogens,the mixtures are processed and extruded. Porogens are removed after fabrication using methods evaporation and melting to obtain porous structure in the scaffold. Example includes solvent casting, particulate leaching, gas foaming, freeze-drying and phase separation. In the second category, sequential delivery of material or energy is needed to bond the materials.Selective laser sintering, stereolithography and 3D printing are the examples of this type of fabrication. Solid free-form fabrication technologies such as wax printing rely on simultaneous delivery of solid materials as well as removable supporting materials. In the third category, woven and non-woven fibers are bonded using techniques such as fiber bonding or generated by the electrospinningis a polymer processing technique that uses electrostatic forces to uniaxially stretch a viscoelastic jet derived from a polymer solution to generate continuous nanometric and micrometric fibres, characteristically accumulated into non-woven mats and later the fibers are casted, molded, coated or cross-linked as per the requirement [8]. Porous, biodegradable and bioresorbable polymeric scaffolds areutilized in various tissue engineering applications and are shaped typically using advanced techniques like 3-D printing, particulate leaching, phase separation, solvent casting, gas foaming, freeze drying, electrospinning and solidform fabrication. Conversely, significant issues and restrictionscontinueto exist in the polymers and additives that can be used, cost, reproducibility of the microstructure and properties of the fabricated scaffolds, and scalability of the fabrication processes to realistic manufacturing rates. These remaining major challenges require the development of alternative materials processing methods. Recently, a number of novel fabrication procedures based on the twin screw extrusion process have been established and were used in the construction of different types of scaffolds for tissue engineering, chiefly focusing on bone and cartilage applications. These new processes integrate twin screw extrusion with spiral winding, co-extrusion and electrospinning and provide significant advantages over conventional methods of scaffold fabrication. These advantages compriseflexibility, reproducibility and industrial scalability [9]. Figure 2 describes a pictorial representation of different fabrication methods.

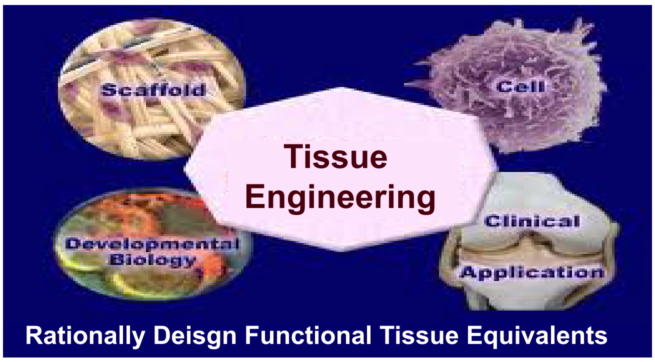

Figure 1: Different applications of Tissue Engineering [6].

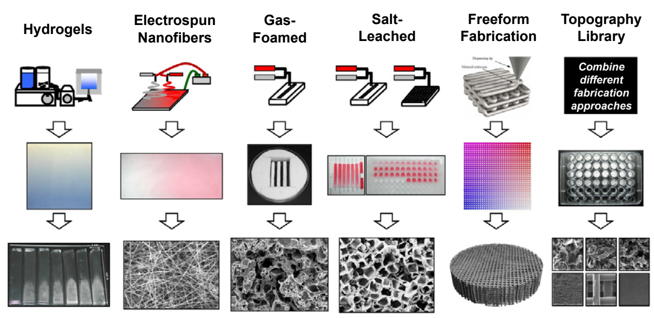

Figure 2: Different scaffold fabrication methods [10].

Application

Although mankind has always been longing for simple and easy ways to restore their youth and get rid of degenerative problems there is still a long but promising way to go, unveiling the secrets of regeneration to be available for customized problems. It seems evident to utilize all the enormous technical expertise that has been gained from the field of TE for more than tissue replacement only. Many consolidated findings that stem from TE have enhanced the comprehension of molecular and cellular processes related to various diseases and physiological processes. Not only may such knowledge be applied to different forms of medical treatment, such as creating intelligent biological drug delivery systems, but also will it be helpful to better understand mechanisms such as apoptosis and carcinogenesis. It may help us to explain mechanisms of aging, human development, and the origins of cancer, heart disease, mental illness, as well as several other conditions. Hopefully it may help to successfully treat degenerative and malignant diseases in the future. Since like in any emerging scientific field no progress can be made without substantial financing a continued support from public funding institutions as well as from industry will be necessary to succeed in this [11]. To restore the function or regenerate the tissue, a scaffold must act as a temporary matrix for cell proliferation and mimic the extracellular matrix for the cell attachment, growth and proliferation until the tissues are totally restored or regenerated as shown in Figure 3.

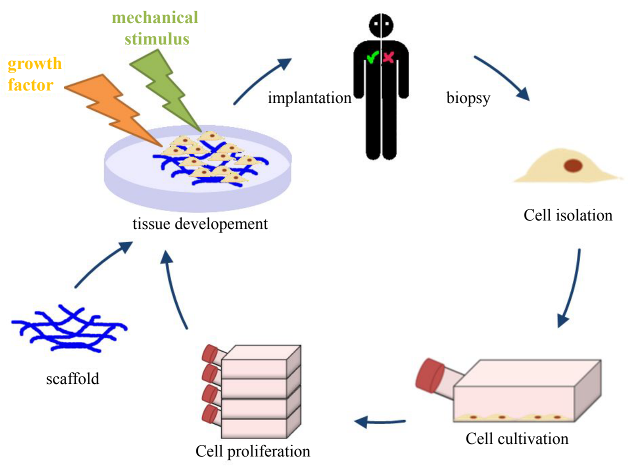

Figure 3: Schematic of Tissue Regeneration [12].

Polymeric Scaffolds

These polymeric scaffolds utilize polymeric materials are drawing great attention due to their unique properties such as light weight, high mechanical strength thehigh surface-to-volume ratio, high porosity with very small pore size, and biodegradation [13]. They also tender distinct advantages of biocompatibility and the otherbiological properties that significant in the application of tissue engineering. Research has been done on to regenerate various tissues such as skin and cartilage, bone and cartilage, liver, heart valves and arteries, bladder, pancreas, nerves, corneas, and various other soft tissues, ligament, vascular tissues, neural tissues, and skeletal muscle and alsoas vehicle for the controlled delivery of drugs, proteins, and DNA. Scaffolds are classified into various type based on their pore structure, solubility, stability, mechanical strength and composition or the origin.

Porous scaffold

Porous scaffolds are having higher porosities and homogeneous interconnected pore network are highly useful for tissue engineering especially for the development of artificial blood vessel, peripheral nerve growth and soft tissue engineering.

Hydrogel scaffold

Hydrogels are used as scaffolds and guide the growth of new tissues. The design and application of biodegradable hydrogels has vividly increased the impact of hydrogel materials for the development of controlled drug delivery and numerous tissue engineering applications.

Fibrous scaffold

Nanofiber has enhanced the possibility for fabricating scaffolds that mimics the architecture of natural human tissue at the nanometer scale. The high surface-area-to-volume ratio along with themicroporous structure provides the best environment for cell adhesion, proliferation, migration, and differentiation, all of which are highly desired properties for tissue engineering applications such as bone, cartilage, ligament, and skeletal muscle, skin, vascular, neural tissue engineering, and as vehicle for the controlled delivery of drugs, proteins, and DNA.

Microsphere scaffold

Microsphere scaffolds provides the stiffness gradients for interfacial tissue engineering. Microsphere scaffolds are progressively more used in drug delivery systems, gene therapy and antibiotic treatment of infected bone. Microsphere scaffolds are usually preferred for drug encapsulation for the release of drugs at a relatively slow rate over a prolonged period of time.

Polymer-bioceramic composite scaffold

Development of composite scaffold for is very promising as their properties can be engineered to suit the mechanical and physiological demands of the host tissue. Composite scaffold has excellent biocompatibility, high osteoconductivity and bioactivity. Composite scaffolds support uniform cell seeding, cell ingrowth, and tissue formation.

Acellular scaffold

Acellular tissue matrices are fabricated by removing cellular components from tissues by mechanical and chemical manipulation to produce collagen-rich matrices which supports the cell growth and regeneration of genitourinary tissues, including urethra and bladder, with no evidence of immunogenic rejection. Polymer coating improves the mechanical stability and enhances the hemocompatibility of the protein matrix [14]. Figure 4 explains about various applications of the scaffolds.

Future Directions

Tissue engineering is handling the most momentous and widespread clinical issues. For scaffolds, pore distribution, surface to volume ratio and porosity play a major role in the final outcome of the regenerative process. Depending on the fabrication process, scaffolds with various architecture can be obtained. In the recent years, rapid prototyping and many computer-controlled techniques are being used forthe fabrication of scaffolds as per the necessity of the application or requirement [18]. Stem cell has already become a significant part of tissue engineering to regenerate any organ or tissue. Stem cell and progenitor cell research is avery exciting field that shows high potential in numerous areas from cancer to diabetes to neurogenerative diseases.

Stem cells are undifferentiated cells that can renew themselves and generate specialized cell types with specific functions in the body. Patient-specific pluripotent stem cells might offer a limitless source

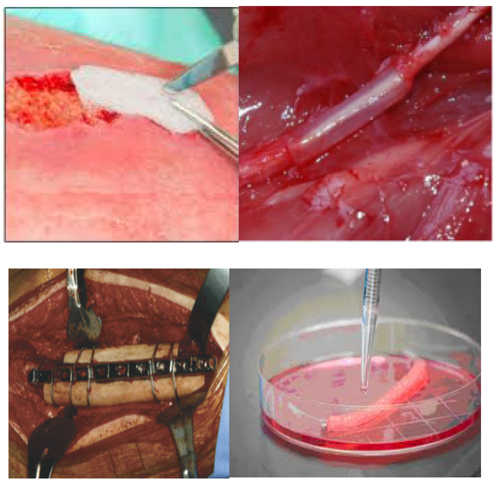

Figure 4: Different types of tissue engineered scaffold a) 2D scaffold for wound healing b) Nanofibrous nerve scaffold c) Bone scaffold d) Urethra scaffold [15-17].

for transplantable cells and tissues to treat sufferer without causing immune-rejection. Current reprogramming methods to generate pluripotent stem cells involve viral transduction or plasmid transfection that rely upon transient expression of the reprogramming factors without integration of ectopic DNA into the genome [19]. New stem cell technologies such as somatic cell nuclear transfer and reprogramming are now available to convert partially or completely differentiated cells back to their embryonic routes. An advantage of these technologies is the potential of using autologous cells, thus overcoming the problem of immune rejection common with ES cells [20]. Stem cells based tissue engineering is thought to be a promising way to replace the missing tooth and regenerate damaged tooth structures. The successful use of all types of stem cells in regeneration therapy may be achieved only after understanding of the basic molecular mechanisms underlying cell fate switching of stem cells. It will be an essential contribution to ensure their safe use in regenerative medicine [21]. Recent studies also demonstrated that bioglass can be considered as a promising way of promoting tissue repair. It shows a superior in vitro apatite-forming ability, and is able to directly bond to living bone *in vivo* [22]. Nano-particles are the latest area of interest of the researchers involved with tissue engineering and biomaterial research. Marine organisms are being modified and hybridized to create biomaterials that are certainly more than mimics; they are nature in the lab exemplified [23]. 3D cell culture systems or the 3D Scaffolds, provide 3D environments in which cells shows enhanced abilityto mimictheir in vivo counterparts. Numerous technologies are now available to create 3D biomimetic scaffolds with control over their physical and mechanical properties, cell adhesion and release of the growth factors. At present researchers are working ontools whichwill enable better understanding of thecell-scaffold interactions and will also help in identification of the relationships of cell response which willfurther facilitate toimprove thedesign of future scaffold-based medical products. Synthetic 3D extracellular microenvironments that mimic the structure and functions of the ECM have already been developed, but synthetic biology holds tremendous potential for improving these matrices and making them structurally programmable [24]. These measurement tools and standards advance the ability of researchers to develop scaffolds that direct tissue or organ regeneration, replacement and restoration (Figure 5).

Conclusion

Despite the immense advancement in the field of tissue engineering, there are many challenges as well as drawbacks, which need to be addressed. Scaffolds are classified in to six categories explicitlybiotoxic, bioinert, bioresorbable, biodegradable and bioactive. Among these, a good scaffoldeither comes under the biotoxicor the bioinert groups, where as biodegradable, bioactive and bioresorbable materials are mostly used as composite. Concerns that are associated with the biodegradable scaffolds include mechanical strength and degradation. Scaffolds fabricated with the metallic/ceramic materials can overcome the limitations with respect to strength and toxicity but it involves complications during surgery, infectionand shows immunological rejections. Scaffolds mustbe designed in such a way that it should be capable of regaining their mechanical, structural, and biological veracity after implemented surgically inside the body and should be compatible with the in-vivo environment. It is essential to consider these principles of tissue engineering to fabricate a potential scaffold capable of replacing the ECM and to regenerate or restore the damaged tissue [11].

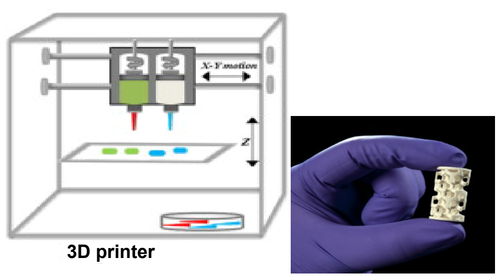

Figure 5: Latest instrument for scaffold fabrication and 3D scaffold [25,26].

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