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The Role of Biodegradable Engineered Scaffold in Tissue Engineering

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1. Introduction

Tissue engineering is fundamentally described as the generation of three-dimensional (3D) artificial tissues. Its consequential task is to regenerate human tissue or to develop cell-based substitutes in order to restore, reconstruct or improve tissue functions (Pörtner et al., 2005; Ellis, 2005). Proper processing of biological and mechanical functionality is monumental for tissue engineered structures, the ones which are not mainly sufficient enough yet. Acquiring the solution for this problem demands intensive researches and studies in every aspects and steps of TE (Sengers et al., 2007). As a matter of fact, creating a functional tissue requires efficient growth of various types of cells on a 3D scaffolds and the bulk production of one cell seems not to be adequate (Ellis et al., 2005).

The principal function of a scaffold is to direct cell behavior such as migration, proliferation, differentiation, maintenance of phenotype, and apoptosis by facilitating sensing and responding to the environment via cell–matrix and cell–cell communications (Tabesh et al., 2009). Therefore, having such abilities provides scaffolds seeded with a special type of cell as an important part of tissue engineering and regenerative medicine. The scaffold design and fabrication are major areas of biomaterial research, since biomaterial scaffold can create substrate within which cells are instructed to form a tissue or an organ in a highly controlled way. In this chapter, it is tried to provide an inclusive survey of biopolymers to be used as scaffolds for tissue engineering, fabrication methods and engineering challenges such as mass transfer and mechanical strength. In the proceeding, these factors are reviewed in vascular and nerve systems.

2. Scaffold considerations

2.1 Requirements of appropriate scaffold materials for tissue engineering

Scaffold design and fabrication are major areas of biomaterial research and they are also important areas for tissue engineering and regenerative medicine research. Scaffold provides the necessary support for cells to proliferate and maintain their differentiated functions, and its architecture defines the ultimate shape of a new organ.

An ideal scaffold should possess the following characteristics to bring about the desired biological response (1) the scaffold should possess inter-connecting pores of appropriate

scale to favor tissue integration and vascularization, (2) be made from material with controlled biodegradability or bio-resorbability, (3) appropriate surface chemistry to favor cellular attachment, differentiation and proliferation, (4) possess adequate mechanical properties to match the intended site of implantation and handling, (5) should not induce any adverse response and, (6) be easily fabricated into a variety of shapes and sizes (Liu et al., 2007; Sachlos et al., 2003).

Due to control scaffold degradation and mechanical integrity, cell-scaffold interaction as well as cell functon, one must have access to a range of materials. Therefore, an appropriate fabrication method is required with which it is possible to have a structure with different independent parameters and materials (Yarlagadda et al., 2005).

It is worth to mention that degradation of synthetic polymers, both *in vitro* and *in vivo* conditions, releases by-products. For example, for PLLA releasing Lactic acid during degradation, causes reducing the pH, which further accelerates the degradation rate due to autocatalysis which later affects cellular function. (Sachlos & Czernuszka, 2003, as cited Reed and Gilding, 1981)

In addition to degradation rate and by-products, certain physical characteristics of the scaffolds must be considered when designing a substrate to be used in tissue engineering applications. For instance, in order to allow proper cell attachment, the scaffold must have a large surface area which can be achieved by creating a highly porous polymeric foam. In these foams, the pore size should be large enough to allow cells to penetrate through the pores, to maximize nutrient and oxygen diffusion, interstitial fluid and blood flow into the interior of the scaffold, to manipulate tissue differentiation (Yarlagadda et al., 2005, as cited Le Huec et al. 1995; Tsuruga et al., 1997). These characteristics (porosity and pore size) often depend on the material and method of scaffold fabrication (Mikos&Temenoff, 2000, as cited Mooney et al., 1999; Nam et al. 2000)

2.2 Decent materials for scaffolds fabrication

In order to have an effective function, an ideal scaffold must possess the optimum structural parameters, conductivity to the cellular activities leading to neo-tissue formation; these include cell penetration and migration into the scaffold, cell attachment onto the scaffold substrate, cell spreading and proliferation and cell orientation. Such scaffold design parameters are now described with reference to these cellular activities. One of the first considerations when designing a scaffold for tissue engineering is the choice of material.

The three main material types which have been successfully investigated to be applied in developing scaffolds include (i) natural polymers, (ii) synthetic polymers, and (iii) ceramics (Willerth & Sakayama-Elbert, 2007; Radulescu et al., 2007).

2.2.1 Natural materials

Natural polymers commonly derived from protein or carbohydrate polymers have been used as scaffolds for the growth of several tissue types. In the area of tissue engineering, for example, scientists and engineers look for scaffolds on which it may successfully grow cells to replace damaged tissue. Typically, it is desirable for these scaffolds to be: biodegradable, non-toxic/non-inflammatory, mechanically similar to the tissue to be replaced, highly porous, encouragement of cell attachment and growth, easy and cheap to manufacture, and capable of attaching with other molecules (Elmstedt, 2006; Cuy, 2004). Here some examples of natural polymers that have been previously studied for biomaterials application are reviewed.

- Collagen

Collagen is considered by many scientists as an ideal scaffold or matrix for tissue engineering as it is the major protein component of the extracellular matrix. It provides support to connective tissues such as skin, tendons, bones, cartilage, blood vessels, and ligaments in its native environment, and also interacts with cells in connective tissues and transduces essential signals for the regulation of cell anchorage, migration, proliferation, differentiation, and survival. Collagen is defined by high mechanical strength, good biocompatibility, low antigenicity and ability of being cross-linked, and tailored for its mechanical degradation and water uptake properties; Twenty-seven types of collagens have been identified so far, but collagen type I is the most abundant and the most investigated for biomedical applications (Chunlin et al., 2004).

Collagen may also be processed into a variety of formats including porous sponges, gels, and sheets. It can be cross-linked with chemicals to make it stronger or to alter its degradation rate (Cuy, 2004). However, for medical applications, the implantation of foreign cells causes immunological problems. Collagen has potential uses as follows (Matin, 2004):

- Collagen gel matrix maintains its shape following cell seeding and culture,
- Highly permeable bio-scaffold design,
- Production of tissue implants for reconstructive/cosmetic surgery applications, and
- Generation of spinal cord repair implants.

- Chitosan

Chitosan is a cationic polymer obtained from chitin comprising copolymers of β (1→4)-glucosamine and N-acetyl-D-glucosamine. Chitin is a natural polysaccharide found particularly in the shell of crustacean, cuticles of insects and cell walls of fungi and is the second most abundant polymerized carbon found in nature (Khor & Lim, 2003).

This polymer has many suitable properties. It can be used for wound dressing, drug delivery, and tissue engineering (cartilage, nerve and liver tissue) applications. These properties include: (Willerth et al., 2007):

- Minimal foreign body reaction,
- Mild processing conditions (synthetic polymers often need to be dissolved in harsh chemicals; chitosan will dissolve in water based on pH),
- Controllable mechanical/biodegradation properties (such as scaffold porosity or polymer length), and
- Availability of chemical side groups for attachment to other molecules.

Chitosan has already been investigated for adoption in the engineering of cartilage, nerve, and liver tissue. Current difficulties applying chitosan as a polymer scaffold in tissue engineering include low strength and inconsistent behavior with seeded cells (Madihally and Matthew, 1999). Fortunately, chitosan may be easily combined with other materials in order to increase its strength and cell-attachment potential. Mixtures with synthetic polymers such as poly (vinyl alcohol) and poly (ethylene glycol), or natural polymers such as collagen, have already been produced. These combinations promise improving the performance of the combined construct over the behavior of either component alone (Cuy, 2004).

- Agarose/alginate

Agarose and alginate are linear polysaccharides obtained from seaweed and algae, respectively. Both polygosaccharides must undergo extensive purification to prevent immune responses after implantation (Willerth et al., 2007). Moreover, encapsulation of certain cell types into alginate beads may actually enhance cell survival and growth. In

addition, alginate has been explored to function in liver, nerve, heart, and cartilage tissue engineering.

Unfortunately some drawbacks to alginate include mechanical weakness and poor cell adhesion. In order to overcome these limitations, the strength and cell behavior of alginate have been enhanced by mixtures with other materials, including the natural polymers agarose and Chitosan (Cuy, 2004). Mohan et al. described the preparation and characterization of alginate sponges to be used as scaffolds in tissue engineering. They fabricated highly porous 3D scaffolds from cheaply available sodium alginate, which exhibits good biocompatibility. The scaffold fabricated by a combination of freeze drying and particulate leaching, showed increased porosity and pore size. Better pore characteristics and swelling properties may permit more cell invasion and nutrient supply. Moreover alginate is thermally stable, non-cytotoxic and biodegradable (Mohan and Nair, 2005).

- Fibronectin

Fibronectin (FN) is a glycoprotein which exists outside cells and on the cell surface. It also exists in blood, other body fluids and on the cell surfaces of connective tissue. This protein associates with the other proteins of the extra cellular matrix (ECM) like fibrinogen, collagen, glycosaminoglycans and with suitable receptors which are in the cell membrane (Ebner et al., 2006). Fibronectin is composed of tandem repeats of three distinct types (I, II and III) of individually folded modules.

2.2.2 Synthetic materials

Synthetic polymers have been widely used for over 20 years as surgical sutures, with long established clinical success and many are approved for human use by the Food and Drug Administration (FDA). The polymers which approved by FDA are as follows: PCL, PLLA, PLGA, PEG and PGA.

However current synthetic polymers do not possess a surface chemistry which is familiar to cells, that *in vivo* thrive on an extracellular matrix made mostly of collagen, elastin, glycoproteins, proteoglycans, laminin and fibronectin; these materials have many advantages to be used as scaffolds (Sachlos & Czernuszka, 2003, as cited Alberts et al., 1994).

These polymers can be tailored to produce a wide range of mechanical properties and degradation rates. Synthetic polymers also represent a more reliable source of raw materials with the ability to provoke an immune response in body. Finally synthetic polymers can be react together to combine their unique properties (Willerth et al., 2007; Manzanedo, 2005). Here some of these synthetic polymers used in tissue engineering are described briefly.

- Poly (D, L-lactic acid)

Poly lactic acid (PLA) is a biodegradable polyester attainable by poly-condensation of lactic acid, and amonomeric precursor that can be obtained from renewable resources. Lactic acid is a chiral molecule available in the L and D stereoisomer forms. L-lactic acid occurs in the metabolism of all animals and microorganism, and thus is an absolutely non-toxic degradation product of polylactides. This is proved by the successful application of polylactides as a resorbable medical structure over a period of three decades (kricheldorf, 2001; Onose, 2008).

Since this polymer has biodegradability, biocompatibility, good mechanical properties, and ability to be dissolved in common solvents for processing, it has been successfully employed as matrixes for cell transplantation and tissue regenerations (Kim et al., 2003).

- Poly (lactic-co-glycolic acid)

Poly (glycolic acid) (PGA) and poly (lactic acid) (PLA) are biodegradable synthetic polymers, which can react to form the copolymer poly (lactic-co-glycolic acid) (PLGA). PGA is highly crystalline and has a high melting point and low solubility in organic solvents. An intensive investigation aimed at the improvement of PGA properties was undertaken by many researchers, focusing on the preparation of PGA copolymers with more hydrophilic PLA.

After implantation, the ester bonds that make up the backbone of the polymer can be hydrolyzed, causing the scaffold to degrade into metabolite by-products. These by-products can be absorbed by the body and may cause pH changes around the implantation site. The degradation rate of the scaffolds can be altered by varying the ratio of PGA to PLA in the scaffold.

The presence of an extra methyl group renders lactic acid more hydrophobic. The hydrophobicity of PLA limits the water uptake of films to 2%, and decreases the backbone hydrolysis rate in respect to the one of the PGA homopolymer. Moreover, PLA is more soluble in organic solvents than in PGA. It is important to note that no linear relationship exists between the ratio of glycolic acid to lactic acid and the physico-mechanical properties of their regarding copolymers. The high crystallinity of PGA is rapidly lost in PGA/PLA copolymers. These morphological changes lead to an increase in the hydration and hydrolysis rate and copolymers tend to degrade more rapidly than the homopolymers of PGA or PLA do (Reed et al., 1981).

- Poly-β-hydroxybutyrate

Poly-β-hydroxybutyrate (PHB) is a linear head-to-tail homopolymer of (R)-β hydroxybutiric acid, which forms crystalline cytoplasmic granules in the wide variety of bacteria. This material is biodegradable and biocompatible microbially produced polyester, which after implantation degrades slowly at body temperature and forms a non-toxic metabolite that is secreted in urine (Mosahebi et al., 2001). PHB has been previously used as a wound scaffolding device, designed to support and protect a wound against further damage while promoting healing by encouraging cellular growth on and within the device from the wound surface (Ljungberg et al., 1999).

- Poly-e-caprolactone

Poly-e-caprolactone(PCL), an aliphatic polyester which is bioresorbable and biocompatible, is generally used in pharmaceutical products and wound dressings (Venugopal et al., 2005). This polymer has low melting point of around 60°C and a glass transition temperature of about −60°C. PCL is degraded by hydrolysis of its ester linkages in physiological conditions (e.g. in the human body) and therefore, has received a great deal of attention for use as an implantable biomaterial (Schnell et al., 2007).

- Poly (ethylene glycol)

Poly ethylene glycol (PEG), also known as poly ethylene oxide (PEO) or polyoxyethylene (POE) is the most commercially important polyethers, which refers to an oligomer or polymer of ethylene oxide resisting protein adsorption and cell adhesion. These characteristics help minimize the immune response after implantation. Additionally, this polymer can also help to seal cell membranes after injury, making it useful for limiting cell death. Hydrophilic PEG hydrogels can be made through a variety of cross-linking schemes to create scaffolds with varying degradation as well as release rates. Further chemistry can be used to modify these gels to add sites for cell adhesion or extracellular matrix (ECM) molecules to allow cells to infiltrate into these scaffolds, extending their potential applications (Willerth et al., 2007).

PEG can be photo-polymerized under mild conditions in the presence of cells to create a hydrogel that is biocompatible and non-toxic. Bioactive molecules such as cell adhesion ligands, growth factors and proteolytic degradation sites have been previously incorporated into PEG hydrogels and shown to influence adhesion, proliferation, migration, and extracellular matrix production of vascular smooth muscle cells.

- Poly (glycerol sebacic acid)

Poly glycerol sebacic acid (PGS), also called bio-rubber, is a tough, biodegradable elastomer made from biocompatible monomers. Its main features are good mechanical properties, rubber like elasticity and surface erosion biodegradation. PGS was proved to have similar *in vitro* and *in vivo* biocompatibility to PLGA, a widely used biodegradable polymer. (Manzanedo, 2005; Sundback et al., 2005).

- Poly (2-hydroxyethyl methacrylate)

Hydroxyethyl methacrylate (HEMA) is a hydro-soluble monomer, which can be polymerized (under various circumstances) at low temperatures (from -20°C to +10°C). It can be used to prepare various hydrogels and to immobilize proteins or cells. It is widely used in medicine as an appropriate biomaterial. Poly (2-hydroxyethyl methacrylate) (pHEMA) is particularly attractive for biomedical engineering applications. Because of its physical properties and high biocompatibility, this polymer can be easily manipulated through formulated chemistry has been extensively used in medical applications, e.g. contact lenses, kerato prostheses and orbital implants. Furthermore, a pHEMA scaffold could be easily incorporated into the nerve guidance tubes (Flynn et al., 2003).

2.3 Methods used for scaffolds design

Several techniques have been developed to process synthetic and natural scaffold materials into porous structures. These conventional scaffold fabrication techniques are considered as processes that create scaffolds having a continuous, uninterrupted pore structure. An overview of such different techniques is as follows: Electrospinning, Solvent-casting, particulate-leaching, Gas foaming, Fiber meshes/fiber bonding, Phase separation, Melt molding, Emulsion freeze drying, Solution casting and Freeze drying (Mikos& Temenoff, 2003; Sachlos & Czernuszka, 2003).

2.3.1 Electrospinning

Electrospinning is a technique for nano-fibrous scaffold fabrication. Various synthetic or natural polymers can be spun to nano fibers with diameters in nano - to micrometer range. They are characterized by a high surface to volume ratio and thus offer sample substrate for cell attachment.

In this technique, polymers are dissolved into a proper solvent or melted before being subjected to a very high voltage to overcome the surface tension and viscoelastic forces as well as forming different fibers (50 nm - 30 μm) diameters, which feature a morphologic similarity to the extracellular matrix of natural tissue and effective mechanical properties. These nanofibrous scaffolds can be utilized to provide a better environment for cell attachment, migration, proliferation and differentiation when compared with traditional scaffolds (Martins et al., 2007).

In general, the process of electrospinning is mainly affected by (i) system parameters, such as polymer molecular weight, molecular weight distribution and solution properties (e.g. viscosity, surface tension, conductivity); and (ii) process parameters, such as flow rate, electric potential, distance between capillary and collector, motion of collector, etc (Yang et al., 2005).

A study on the fabrication of a scaffold by electrospinning biomaterials such as poly lactic acid (PLA), poly glycolic acid (PGA), poly (ethylene-co-vinyl acetate) (PEVA), and type-I collagen was reported (Bowlin et al., 2001). Moreover, nanostructured electrospun PLGA membranes for anti-adhesion applications were presented (Fang et al., 2001). Electrospinning can even be used to create biocompatible thin films with useful coating designs and surface structures that can be deposited on implantable devices in order to facilitate the integration of these devices with the body (Buchko et al., 1999).
The collagen nanofibers were characterized by a wide range of pore size distribution, high porosity, excellent mechanical strength and high surface area to volume ratios, which are favorable parameters for cell attachment, growth and proliferation. In cell activity assessment, electrospun collagen nanofibers coated with type I collagen or laminin were found to promote cell adhesion and spread of normal human keratinocytes. This may be a consequence of the high surface area available for cell attachment due to their three-dimensional features and restoration of biological and structural properties of natural ECM proteins (Rho et al., 2006).

2.3.2 Freeze-drying

Many of the fabrication technologies for polymers are based on particulate-leaching techniques, heat compression, and extrusion. However, the harsh operating conditions of these processes may limit the incorporation of bioactive proteins, cells and residual amounts of the chemical solvents required may cause toxicity *in vivo*. Freeze-drying is an alternative method to produce porous scaffolds, which do not require additional chemicals relying on the water.
This method, used in hydrogels, forms ice crystals that can be sublimated from the polymer, creating a particular micro-architecture. Because the direction of growth and size of the ice crystals are a function of the temperature gradient, linear, radial, and/or random pore directions and diverse sizes can be produced with this methodology (Stokols et al., 2004).
On the other hand, the pore size can be controlled by the freezing rate and pH; a fast freezing rate produces smaller pores (Sachlos et al., 2003).

2.3.3 Molding

Graft implants manufacture is an extraordinary example of micro-architecture. One possible way of making the grafts is the particulate leaching technique (i.e. molding). A mold is made of a medium that may not contaminate the graft and that may melt off at a lower temperature melt point than that of the graft. Already widely used, this method limits design intricacy because heat stress during formation compromises the composition of the graft (Friedman et al., 2002). Another problem with this method is that it would be difficult to make a mold small enough for small animal research. As an example, Moore *et al.* used Poly (lactic-co-glycolic acid) (PLGA) with copolymer ratio 85:15 for their initial experiments.
Injection molding with rapid solvent evaporation resulted in scaffolds with a plurality of distinct channels running parallel along the length of the scaffolds (Moore et al., 2006).

2.3.4 Solid free form fabrication

The most promising production method is called solid free-form fabrication (SFF). This approach uses a machine like an inkjet printer to make the graft one layer at time by "printing" one layer on top of the other (Friedman et al., 2002). However, the main problem

with this technology is the extremely high cost. The machines have to be permanently modified from their original function. Through these methods one can manage pore size, porosity and pore distribution to produce structures to increase the mass transport of oxygen and nutrients throughout the scaffold.

Although there are several commercial variants of SFF technology, the general process involves producing a computer-generated model using computer-aided design (CAD) software. After expression of cross-sectional layers, data is implemented to the SFF machine to produce the physical model. Through building the layers from bottom to up, each newly formed layer adheres to the previous. Post-processing may be required to remove temporary support structures (Sachlos & Czernuszka, 2003). The methods that use the SSF technologies to fabricate tissue engineering scaffold are: (1) stereolithography (SLA), (2) selective laser sintering (SLS), (3) fused deposition modelling (FDM) and (4) three-dimensional printing (3-DP).

3. Challenges in engineering scaffolds

The major hindrance through tissue engineering constructs is mass transfer. Since scaffolds provide large surface area to volume ratios, it is proved that mass transfer limitation is reduced. Pore interconnectivity directly influences the mass transfer (e.g. oxygen and nutrient supply and removal of toxic metabolites).

During tissue regeneration, permeability of the matrix decreases due to the declined pore size. In addition, the size of most engineered tissues is limited as they do not have their own blood system, and the cells are only supplied by diffusion (Griffith & Naughton, 2002; Kannan et al., 2005). Meanwhile, as only cell layers of 100–200 μm thickness can absorb O_2 by diffusion, oxygen supply is particularly a critical issue. However, since tissue constructions should have larger dimensions, mass transfer limitation can be considered as one of the greatest engineering challenges (Pörtner et al., 2005).

The next challenge is mechanical effect on cells in dynamic systems. Under flow conditions, flow rate needs to be optimized based on (i) nutrient distribution, (ii) effect on assembly of matrix elements and (iii) cellular response to local shear stress (Lawrence et al., 2009). The scaffold architecture affects the local fluid flow velocities of the cell suspension which influences the number of cell-scaffold contacts per time unit and the local cell deposition rates. By changing the scaffolds design, different flow profiles and cell distributions in the scaffolds may be obtained (Melchels et al., 2011).

Although flow of growth medium improves nutrient and waste transport, shear stresses induced by fluid flow could affect the scaffold architecture as well as cellular alignment within the structures (Lawrence et al., 2009 as cited Gray et al., 1988; Huang et al., 2005).The wall shear rate determines the hydrodynamic force, that adhering cells are exposed to, which can be expressed per unit of area as the wall shear stress (in Pa), and is the product of the wall shear rate and the kinematic viscosity of the fluid medium. The critical shear stress for cell detachment has been found to range almost between 1 to 3 Pa that depends on the material on which the cells are cultured. Also the highest cell densities in the scaffolds could be observed in the regions with larger pores, higher fluid flow velocities and higher wall shear rates (Melchels et al., 2011 cited as Isenberg et al., 2006; Macario et al., 2008; Smith et al., 1995).

It has been seen that the pore size is a variable strongly affecting the predicted shear stress level, whereas the porosity only influence the statistical distribution of the shear stress

(Sadir, 2011). Furthermore, it has been showed that porosity and pore size affect pressure drop which is important to be determined during tissue regeneration (Lawrence et al., 2009, cited as Sodian et al., 2000). For the same pore size with decreasing porosities, pressure drop increases, and for the constant porosity with reducing pore size, which could limit the fluid flow and nutrient transport, pressure drop is increased (Sadir, 2011). Here these challenges are investigated by the revision of two case studies.

3.1 Vascular system

The primary functions of blood vessels are the delivery of nutrients and oxygen to the tissues and organs of the body and removal of their respective metabolites for clearance or re-oxygenation (Boland et al., 2004). Diseases of the heart and blood vessels are the most life threatening factor in developed countries (Ikada, 2006). Surgical replacement of vessel segments or bypass surgery is the most common intervention for coronary and peripheral atherosclerotic disease with at least 550,000 bypass performed per year (Chung et al., 2010).
Autologous vessels harvested from the patient for bypass surgery include the saphenous vein (SV) from the leg and the internal mammary artery (IMA) from the chest wall. The IMA with elasticity maintains the ability to vasoregulate and is less prone to atherosclerosis (Wise et al., 2011). Apart from the fact that implantation of native vessels is limited by the mismatch of dimensional and mechanical properties (Chung et al., 2010), the acceptable vein is not available in 30 %of patients (Boland et al., 2004).
An artery is composed of three layers having different matrix-tissue compositions. The innermost lumen layer (intima) is composed of endothelial cells (ECs) on extracellular matrixes such as type IV collagen and elastin, providing the necessary antithrombogenic nature for contact with the bloodstream. The middle layer (media) is usually the thickest of the three layers and is composed of multiple layers of smooth muscle cells (SMCs) within a surrounding extracellular matrix (ECM) composed of collagen types I and III, elastin fibers and various proteoglycans. The outermost layer (adventitia) is made of fibroblastic cells on randomly arranged type I collagen. In short the collagens impart tensile strength to the vessel wall while elastin provides the elasticity (Boland et al., 2004) (Thomas et al., 2007).
With respect to this construction, the combined structure is particularly attractive for vascular tissue engineering applications. By designing a multilayered tube, it is now possible to seed or co-culture different cell lines in layers with controlled orientation (Chung et al., 2010).
Tissue engineering uses vascular cells and supporting scaffolds to build functional blood vessels (Tillman et al., 2009). In the domain of cells, both the EC and SMC are critical components of a tissue engineered vascular graft. ECs play an integral role in tissue homeostasis, fibrinolysis, and anti-coagulation while SMCs perform many functions, including vasoconstriction and dilatation, synthesis of various types of collagen, elastin and proteoglycans (Ju et al., 2010). Bare scaffolds without ECs showed abundant platelet adherence, while scaffolds lined with ECs resisted adherence of blood elements. While it is evident that cells play a major role in achieving patent vessels, designing a vascular scaffolds that provide structural support, enabling cells to proliferate and growing into a three-dimensional (3-D) tissue is important (Chung et al., 2010; Tillman et al., 2009)
Developing scaffolds that can withstand the pulsatile nature, high pressure, and high flow rate of the bloodstream (Boland et al., 2004) is especially necessary in cardiovascular applications. The ideal vascular prostheses must be a presentation of its functional characters such as flexibility with kink resistance and biocompatibility (non-thrombogenic)

(Boland et al., 2004). Ability of ECs adherence to form an anti-thrombogenic luminal surface, and SMCs migration, exhibit vasoactive properties, (Williamson et al., 2006 cited as Tiwari et al., 2001; Seifalian et al., 2002), capability of withstanding physiological hemodynamic forces while maintaining structural integrity until mature tissue forms *in vivo* (Ju et al., 2010), and also the compliance is matched with that of the native artery (Boland et al., 2004).
Additionally, providing interconnected pores, generating high porosity so as to promote cell–cell and cell–matrix communication and having sufficient mechanical stability are key factors (Chung et al., 2010) for the engineering of blood vessels. Small pore size does not bring about a problem for ECs but would limit the ability of SMCs to colonize the outer portion of neo-vessel. Several approaches have been proposed to generate large sized pores which include the use of the salt leaching technique (Ju et al., 2010, cited as Nam et al., 2007) and coelectrospinning with water-soluble polymers which serve as sacrificial fibers. Researchers indicated that a larger pore size can be achieved by increasing the fiber diameter and that this would facilitate cell infiltration. They showed that the mechanical strength of the scaffolds decreases as fiber diameter increases (Ju et al., 2010).
Of the countless synthetic materials evaluated over the years, expanded poly tetrafluoro ethylene (e-PTFE) and woven or knitted polyethylene terephthalate (PET) fibers have proven to be satisfactory in terms of medium (6-10 mm internal diameter (ID)) and large (>10 mm ID) vascular prosthetics, respectively (Boland et al., 2004). However, clinical success for small diameter (<6 mm) vessels has yet to be demonstrated due to complications such as occlusion, thrombosis and intimal hyperplasia (Chung, 2010).
In addition, biodegradable synthetic polymer scaffolds from polyglycolic acid (PGA), poly-L-lactic acid, polyhydroxyalkanoates such as poly-4-hydroxybutyrate, polycaprolactone - copolylactic acid and polyethylene glycol have been explored. On the other hand, natural polymers such as collagen and fibrin have also been utilized to construct biological vascular grafts, populated and compacted by smooth muscle cells, and exhibiting high tensile strength and flexibility (Zhang et al., 2008).
However, future attempts are addressed as: (i) maufacture of scaffolds with ECM-like nano-fibrous structure; (ii) development of the electrospun structures to manage pore size which improves the ingrowth of large sized cells; (iii) test the structural integrity of these scaffolds during degradation and under dynamic culture conditions (Vaz et al, 2005).
In some cases these materials have been coated with cell-adhesive proteins such as fibronectin, vitronectin and laminin to facilitate EC attachment, which effectively renders the surface to become antithrombogenic However, such modifications can also provide good substrates for platelet adhesion and thrombus formation. EC must be able to resist detachment by the high shear forces exerted by blood flow and turbulence, thereby providing an anti-thrombotic surface. They should also retain vasoactive function but not induce immune reactions to the implant (Williamson et al., 2006, cited as Tiwari et al., 2001).
Based on these results, Ku and Park. suggested that Poly dopamine (PDA) coating generally facilitates the cell adhesion process of culturing human umbilical vein endothelial cells (HUVECs) on electrospun PCL nanofibers. The increase of cell adhesion on this coated nanofibers are attributed to the adsorption/immobilization of serum proteins on PDA ad-layer (Ku & Park, 2010).
As it was mentioned about vascular tissue construction, designing a multilayered tube is attractive to seed or co-culture different cell lines in layers with controlled orientation. Vaz et al. fabricated a bi-layered tubular scaffold of PLA (outer layer) and PCL (inner layer) by multi-layering electrospinning (ME) using a rotating mandrel-type collector. The tensile

measurements showed that PLA/PCL scaffolds presented a much lower elongation and a four-fold increase of maximum stress compared to electrospun PCL ones. The PLA/PCL bi-layered scaffold supported the attachment, spread and growth of mouse fibroblasts (Vaz et al, 2005).

Morever, Venugopal et al. proved that PCL nanofibrous matrixes coated with collagen support cell growth or make the three-dimensional structured multilayer of PCL nanofibers and collagen nanofibers suitable for blood vessel engineering. Their report defines the initial adhesion mechanism of SMCs to the sebiocompatible poly (caprolactone) nanofibrous matrixes coated with collagen. These results may be relevant to other cell types (Venugopal et al., 2005c).

Wise et al. reported the production of synthetic human elastin and poly caprolactone multilayered vascular graft which mimics the mechanical properties of the human IMA. They showed that conduits constructed from synthetic elastin (SE) alone had insufficient strength for vascular applications. This graft was systematically modified by addition of PCL, which was selected on the basis of its appropriate mechanical properties and a slow degradation time. On the other hand, they found that PCL interacts with platelets, which can contribute to thrombogenicity. For this reason, the graft lumen was made of pure SE i.e. devoid of PCL to significantly reduce platelet adhesion, in contrast to PCL/collagen hybrids which showed abundant platelet adherence. It should also be mentioned that the outer layer of the graft, a hybrid of SE/PCL modulated the graft mechanic (Wise et al., 2011).

On the other hand, the nanolayer can mimic the ECM, whereas the micro layer provides larger pores which facilitate superior cell infiltration; a micro -and nano-combined structures can be advantageous.

Chung et al. combined electrospinning and melt spinning of poly (L-lactide-co-e-caprolactone) (50:50 PLCL) to fabricate a multilayered tubular construct using a rotating mandrel for both techniques, which makes the nano layer able to adhere completely to the micro layer. They showed that copolymers of PLCL exhibit a range of mechanical properties from rigid solids to elastomers, depending on their composition. Furthermore, it has a slow rate of degradation compared to other bioresorbable polymers such as PGA and PLA (Chung et al., 2010).

Additionally, Surface patterns such as microgrooves have been successfully used to induce both alignment of cell shape and directional cell migration. Uttayarat et al, incorporated both electrospun microfibers and surface microgrooves in the fabrication of 3D synthetic polyurethane (PU) grafts. They found that grooved patterns induced the uniform alignment of endothelial cell monolayers with morphology similar to naturally aligned endothelium under hemodynamic flow. They also extended these findings by demonstrating that a groove depth or a fiber diameter of about 1 μm can guide the alignment of endothelial cells inside tubular PU grafts (Uttayarat et al., 2010).

3.2 Nerve and spinal cord system

The nervous system is classified into the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS comprises the brain, spinal cord, optic, olfactory and auditory systems. Considering these organs, the CNS comprises of a vast number of neurons, astroglia, microglia, and oligodendrocytes.

The spinal cord which is approximately 1 cm thick and 42 cm long has four anatomical divisions; the cervical, thoracic, lumbar, and sacral regions. About 27 %of human spinal cord injuries are lacerations caused by penetrating objects that tear the spinal tissue (Open

injuries) resulting in a discontinuity of the cord. The majority of the clinical cases are the result of a temporary compression of the cord that leaves the cord surface intact (closed injuries 73%). Three types of compression injuries are described: massive compression, contusion, and solid cord injury (E.Schmidt et al., 2003; Erschbamer, 2007).

CNS axons do not regenerate appreciably in their native environment. Several glycoproteins in the native extracellular environment (myelin) of the CNS are inhibitory for regeneration. Regeneration in the adult CNS requires a multi-step process. First, the injured neuron must survive, and then the damaged axon must extend its cut processes to its original neuronal targets. According to Horner and Gage investigation, once contact is made, the axon needs to be re-myelinated and functional synapses need to form on the surface of the targeted neurons (Horner and Gage., 2000).

In addition to the nerve graft and other natural tissues, such as autologous muscle and vein grafts, biopolymers can be a practical tool to provide neurotrophic and/or cellular support while simultaneously guiding axonal regeneration (Stokols et al., 2004; Rodriguez et al., 2000). Indeed, numerous natural and synthetic polymers have been used as scaffolds or within scaffolds for peripheral and central nerve regeneration.

Filling of the interior channels with appropriate cell facilitates axon regeneration. The Schwann cell (SC) and its basal lamina are crucial components in the environment through which regenerating axons grow to reach their peripheral targets. They produce myelin, which has important effects on the speed of transmission of electrical signals and are shown to enhance the regeneration of axons in both the peripheral and central nervous systems (Erschbamer, 2007; Alovskaya et al., 2007). Therefore, it seems that application of a nerve grafts (scaffolds) coated with SCs can be an appropriate method for spinal cord regeneration.

Considering the requirements of scaffolds in general and in particular, i.e. in neural tissue engineering, materials appropriate for SC seeding should posse some additional features. In order to successfully design a scaffold that can be used as treatment for SCI, many considerations must be taken into account. The scaffold should lessen glial scar formation, while containing sites for cell adhesion to allow regenerating neurons to extend axons into the injury site (Willerth et al., 2007; Radulescu et al., 2007).

Among natural materials, Matin in 2004 found that implants coated with collagen are more successful than the bare ones. Stokolos et al. chose to fabricate scaffolds with agarose for several reasons. First, when implanted into lesion cavities in the spinal cord as an unstructured solid agarose hydrogel, it did not evoke an immune or inflammatory response and was stable for at least 1 month. Second, it was observed that neither axons nor cells penetrated solid agarose hydrogels, which suggested that walls composed of agarose could effectively delineate pathways for regenerating axons. Third, freeze-drying could be used to fabricate agarose into soft and flexible scaffold. Finally, neurotrophic factors, proven to elicit robust axonal growth could be easily incorporated into these scaffolds.

In other researches, Alvskaya et al. described that by using fibronectin as a substrate in an *in vivo* model of spinal cord repair, the growth of neuritis within the material is accompanied by migration of SCs into the graft and the presence of reactive astrocytes at its surface continued. Within the first 2 weeks of implantation, a number of cells and cellular elements replaced the FN mat as it dissolved. The first cells to infiltrate FN mats were macrophages. The presence of integrin receptors on Schwann cells may be responsible for the extensive infiltration of Schwann cells. The close spatial correspondence between laminin tubules and Schwann cells suggests that they were deposited by the Schwann cells (Alovskaya et al., 2007; King et al., 2006).

Along with natural materials, synthetic polymers have been widely used for tissue engineering. Recently, Patist et al. demonstrated that the implantation of a macro porous PLA tubular scaffold in the transected rat spinal cord elicited a modest axonal regeneration response. These particular scaffolds were prepared by a thermally induced polymer-solvent phase separation process and contained longitudinally oriented macropores connected to each other by a network of micropores (Patist et al., 2004).

Moore et al. described multiple-channel, biodegradable scaffolds that serve as the basis for a model to investigate simultaneously the effects of scaffold architecture, transplanted cells, and locally delivered molecular agents on axon regeneration. PLGA with copolymer ratio 85:15 was used for their experiments. Primary neonatal Schwann cells were distributed in the channels of the scaffold and remained viable in tissue culture for at least 48 h. Scaffolds containing SCs implanted into transected adult rat spinal cords contained regenerating axons at 1 month post-operation. Axon regeneration was demonstrated by three-dimensional reconstruction of serial histological sections (Moore et al., 2006).

Also it is showed that PGS which have similar *in vitro* and *in vivo* biocompatibility to PLGA, had no harmful effect on Schwann cell metabolic activity, attachment, or proliferation, and did not induce apoptosis (Manzanedo, 2005; Sundback et al., 2005).

PHB has been previously used as a wrap-around implant to guide axonal growth after peripheral nerve injury (Ljungberg et al., 1999). Novikova et al. prepared a biodegradable conduit made of PHB fibers which compressed together and running in parallel directions in two perpendicular layers to form a sheet. Implantation of these PHB conduits coated with alginate hydrogel and fibronectin and seeded with SCs has been found to reduce spinal cord cavitation as well as retrograde degeneration of injured spinal tract neurons (Novikov et al., 2002).

PCL is interesting for the preparation of long term implantable devices, owing to its degradation, which is even slower than that of polylactide. Schnell et al. designed biodegradable, aligned poly-e-capro- lactone (PCL) and collagen/PCL (C/PCL) nanofibers as guidance structures were produced by electrospinning and tested in cell culture assays. They compared fibers of 100% PCL with fibers consisting of a 25:75% C/PCL blend. Both types of electrospun fibers supported oriented neurite outgrowth and glial migration from dorsal root ganglia (DRG) explants. SC migration, neurite orientation, and process formation of SCs, fibroblasts and olfactory ensheathing cells were improved on C/PCL fibers, when compared to pure PCL fibers (Schnell et al., 2007).

About PEG, it was showed that focal continuous application of this polymer has minimal toxicity (Cole and Shi, 2005). Duerstock et al. used three-dimensional computer reconstructions of PEG treated and spinal cords to determine whether the pathological character of a 1-month-old injury is ameliorated by application of PEG. In PEG-treated animals, the lesion was more focal and less diffuse throughout the damaged segment of the spinal cord, so that control cords showed a significantly extended lesion surface area (Duerstock and Borgens, 2002).

Furthermore, a pHEMA scaffold could be easily incorporated into the nerve guidance tubes. Flynn et al. developed a method to create longitude in ally oriented channels within (pHEMA) hydrogels for neural tissue engineering applications. They found that these scaffolds have the potential to enhance nerve regeneration after section injuries of the spinal cord by increasing the available surface area and providing guidance to extending axons and invading cells (Flynn et al., 2003).

Several techniques have been developed to process synthetic and natural scaffold materials into porous structures as H. Tabesh et al. reviewed. Among these techniques, creating tissue

engineering scaffolds in nano-scale may bring unpredictable new properties to the material-such as mechanical (stronger), physical (lighter), more porous (tunable),optical (color emission), chemical reactivity (more active and less corrosive), electronic properties (more electrically conductive),and magnetic properties (super paramagnetic which are very important in nerve regeneration). Such scaffolds may come up with new functionalities as well-which are unavailable at micro or macro scales (Tabesh et al., 2009).

The process of electrospinning is used for nano-fibrous scaffold fabrication. Electrospinning can even be used to create biocompatible thin films with useful coating designs and surface structures that can be deposited on implantable devices inorder to facilitate the integration of these devices with the body. Silk-like polymers with fibronectin have been electrospun to make biocompatible films used on prosthetic devices aimed to be implanted in the central nervous system (Buchko et al., 1999).

Moreover, an elegant way to produce nanofibrous scaffold using PLLA by a liquid–liquid phase separation method quite similar to natural extracellular matrix (ECM) was developed by a group of scientists. They showed its efficacy in supporting the neural stem cell (NSC) differentiation and neurite outgrowth (Yang et al., 2004).

In addition, a new and facile method for the creation of longitudinally oriented channels in pHEMA gels using a fiber templating technique was described. Biodegradable polycaprolactone (PCL) fibers were extruded and embedded in transparent pHEMA gels, leading to the creation of a pHEMA–PCL composite.

4. Conclusion

In this chapter, efficacious biomaterials (natural and synthetic) for scaffolds in tissue engineering and cell seeding were discussed and also techniques to their fabrication were reviewed. Considering results using such materials and the mentioned criteria for an appropriate scaffold, it is proved that the selection of materials and method of fabrication depend on the cells and their characteristics. The reasons are: scaffold candidates should mimic the structure and biological activity of the native ECM proteins which provide adequate mechanical support and regulate cellular activates. In addition, scaffolds must support and define the three-dimensional structure of the tissue engineered space and maintain the normal state of differentiation within the cellular compartment.

Furthermore the structure of scaffold, pore size and porosity, may affect the mass transfer, shear rate and pressure drop. Mass transfer is the major hindrance in tissue engineering. Although surface area to volume ratios of a scaffold can decrease mass transfer limitations, it is still one of the greatest challenge in tissue engineering. It has been observed that the pore size and shape influence the shear stress level and distribution, while the porosity affects only the distribution. Therefore the wall shear stress is an important parameter in cell adhesion processes.

Two case studies, blood and nerve systems, with regard to their challenges have been investigated. First, for blood system, a scaffold must have the function of native blood and must provide appropriate mechanical, endothelialization and antithrombogenic properties. Therefore choosing a proper biomaterial which provides these characters is prominent. With respect to multilayered construction of blood vessels, the combined structure is particularly attractive for vascular tissue engineering applications. For a better simulation, various types of materials and cells have been used to form different layers of this tissue.

Secondly, for nerve regeneration, it is suggested that blending a synthetic and natural polymer (e.g. poly-e-caprolactone and collagen) is the best choice for Schwann cell seeding to regenerate the spinal cord injuries, considering all results using different materials and the mentioned criteria for an appropriate scaffold. The two suggested polymers have the potential to play role of a scaffold in SCs seeding.

Collagen is a protein of ECM and exists in the basal membrane of the cell. It is easily purified, which can be proposed as a proper substance; however, collagen has less strength to withstand long time, support force adhesion, and degrades enzymatically within short periods. Therefore, using another polymer such as PCL to enhance the stability and mechanical strength of collagen would be crucial. In this sence, an excellent scaffold for Schwann cell adhesion, migration, orientation, and proliferation can be provided.

Also electrospinning is considered as the excellent method for the fabrication of such scaffolds. Additionally, electrospun nanofibers exhibit excellent supports for nerve growth because they can provide large surface area to volume ratios, pore sizes tailored to Schwann cells dimensions, functionalized surfaces, and multiple sites for interaction and attachment, and low mass transfer limitation.

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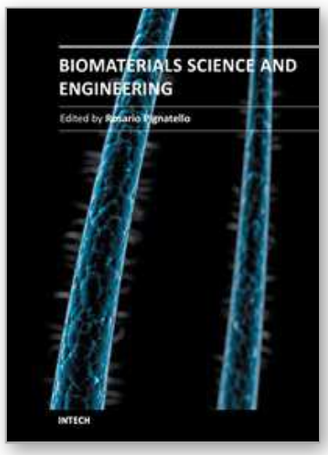

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These contribution books collect reviews and original articles from eminent experts working in the interdisciplinary arena of biomaterial development and use. From their direct and recent experience, the readers can achieve a wide vision on the new and ongoing potentials of different synthetic and engineered biomaterials. Contributions were not selected based on a direct market or clinical interest, than on results coming from very fundamental studies which have been mainly gathered for this book. This fact will also allow to gain a more general view of what and how the various biomaterials can do and work for, along with the methodologies necessary to design, develop and characterize them, without the restrictions necessarily imposed by industrial or profit concerns. The book collects 22 chapters related to recent researches on new materials, particularly dealing with their potential and different applications in biomedicine and clinics: from tissue engineering to polymeric scaffolds, from bone mimetic products to prostheses, up to strategies to manage their interaction with living cells.

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