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Review Article

Growth factor release from tissue engineering scaffolds

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Abstract

Synthetic scaffold materials are used in tissue engineering for a variety of applications, including physical supports for the creation of functional tissues, protective gels to aid in wound healing and to encapsulate cells for localized hormone-delivery therapies. In order to encourage successful tissue growth, these scaffold materials must incorporate vital growth factors that are released to control their development. A major challenge lies in the requirement for these growth factor delivery mechanisms to mimic the in-vivo release profiles of factors produced during natural tissue morphogenesis or repair. This review highlights some of the major strategies for creating scaffold constructs reported thus far, along with the approaches taken to incorporate growth factors within the materials and the benefits of combining tissue engineering and drug delivery expertise.

Introduction

The recent intensive interest in the field of tissue engineering has generated a large number of strategies for the growth of functional tissues in-vitro or the enhanced repair of damaged tissues in-vivo. Examples of current goals in tissue engineering include the regeneration of skeletal tissues (bone and cartilage), neural tissue (peripheral and central), muscle tissue (cardiac, skeletal and smooth), liver tissue and skin.

There are strong scientific links between tissue engineering and drug delivery because successful tissue growth is often dependent on the delivery of growth factors to cells within regenerating tissues. Increasingly, there is an awareness of the need to develop more sophisticated growth factor delivery mechanisms to mimic the endogenous profiles of growth factor production during natural tissue morphogenesis or regeneration. This review highlights recent advances at the interface between tissue engineering and drug delivery.

Mimicking endogenous growth factor production

During natural regeneration of tissues, for example skin regeneration after wound formation or liver regeneration after a toxic injury, a complex and orchestrated delivery of numerous growth factors to cells occurs. Taking skin regeneration as an example, growth factors and cytokines, such as fibroblast growth factor (FGF), keratinocyte growth factor, interleukin 1α and vascular endothelial growth factor (VEGF) are released within the wound bed to trigger cell proliferation, macrophage activation and angiogenesis. The timing of growth factor release is precisely controlled and is triggered by the progress of repair. Similar complex patterns of

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soluble molecule release can be traced during the formation or repair of every tissue within the body.

The spatial and temporal complexity of endogenous growth factor release provides a significant new drug delivery challenge. Mimicking the endogenous release profiles within in-vitro tissue engineering scaffolds requires the following:

- maintenance of function of proteins, glycoproteins and other biological molecules during the fabrication of scaffolds,
- precise control of the kinetics of growth factor release,
- potentially independent control of two or more molecule types,
- potentially targeted delivery to specific cell populations.

The role of the scaffold

The biomaterials that regularly feature in tissue engineering applications are either solid synthetics or hydrogel-type substances. Hydrogels that are able to form in-situ have increased in popularity owing to the emergence of minimally invasive surgical procedures. Polymers tailored for these applications typically display a poorly adherent interface (thus reducing unwanted cell–protein adhesions), and may be used to deliver proteins and growth factors locally to aid wound healing (Hubbell 1996). Additionally, therapeutic strategies involving the transplantation of hormone-secreting encapsulated cells often employ natural gel substances (e.g. alginate; Rowley et al 1999). Solid synthetics are commonly used as supportive structures in the quest for systems that aid the development of cell populations into tissue structures suitable for transplantation. In this way, the scaffold is used to mimic the native extracellular matrix (ECM), an endogenous substance that surrounds cells, binds them into tissues and provides signals that aid cellular development and morphogenesis. To optimize the scaffold performance, additional considerations such as surface–peptide derivitization (to provide integrin receptor-mediated cell responses) (Hern and Hubbell 1998; Quirk et al 2001), soluble protein delivery (for growth-factor induced developmental events), sufficient surface area (for seeding adequate cell densities), porosity (for efficient gas–nutrient exchange) and acceptable biocompatibility (Ferber 1999) need to be addressed. Several points need to be considered when incorporating growth factors for release from such scaffolds (Maquet and Jerome 1997):

- loading capacity – defined as the amount of growth factor that can be mixed into the scaffold,
- load distribution – the growth factor needs to be dispersed evenly throughout the scaffold,
- binding affinity – defined as how tightly the growth factor binds the scaffold; this binding affinity must be sufficiently low to allow release,
- release kinetics – need to be controlled to allow the appropriate dose of growth factor to reach the cells over a given period of time,
- long-term stability – the stability of the growth factor when incorporated within the scaffold at physiological temperature; growth factors need to maintain their structure and activity over a prolonged period of time.

The material selected for use as a support device for developing cells varies widely depending on the application. Some examples of reported scaffold materials are shown in Table 1. By far the most common are based on poly(α-hydroxyacid)s such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their poly(lactide-co-glycolide) copolymers (PLGA). These materials are described as degradable because they resorb by hydrolysis and are distinguished from biodegradable materials such as fibrin and collagen, which are degraded actively by cells. Poly(α-hydroxyacid)s already have applications in controlled drug delivery (Uhrich et al 1999) and have found relevance for use as tissue engineering scaffolds as their resorption results in a natural replacement tissue without the long-term complications associated with foreign implants (Babensee et al 1998; Anderson and Langone 1999). Unfortunately, the manner in which these materials degrade results in the generation of acidic species, which potentially create local inflammation in tissues (Bostman et al 1989) and initiate enzyme hydrolysis (Fu et al 2000). Despite these drawbacks, FDA approval and an established history of use ensure these synthetic polymers remain a recurring feature in tissue engineering strategies.

The rate of degradation of these polyesters can be controlled in a variety of ways, over a period of months to years, and this can be used to synchronize resorption with appropriate developmental stages in tissue growth. Factors affecting this rate are the degree of crystallinity (as amorphous regions allow easier access for water and therefore degrade faster) (Li et al 1990b), molecular weight (Li et al 1990a), copolymer ratios (Schmitt et al 1994), stress factors (Suuronen et al 1992), and the site of implantation (Matsusue et al 1992). Being thermoplastics, these polymers can be easily formed into desired shapes by moulding, extrusion or solvent processing. However, it is the creation of porous sponges or fibrous constructs that is required for tissue engineering applications in order to generate scaffolds with high surface area to volume ratios (Lu & Mikos 1996; Ferber 1999) (Table 1). This is essential for both effective cell seeding onto the support and efficient nutrient acquisition so that rapid proliferation and sufficient physiological ac-

Table 1 Methods of scaffold manufacture.

Material	Scaffold fabrication method	Reference
Poly(α-hydroxy acid)s (e.g. PLA, PGA, PLGA, PLA-ε-caprolactone)	Fibre mesh	Vacanti et al (1991, 1994); Cao et al (1994); Freed et al (1994); Fujisato et al (1996); Zund et al (1998); Kim et al (1999)
	Particulate leaching	den Dunnen et al (1996); Mooney et al (1996a); Kaufmann et al (1997); Ishaug-Riley et al (1998); Murphy et al (2000a)
	Extrusion and particulate leaching	Evans et al (1999)
	Microsphere leaching	Thomson et al (1995)
	Emulsion freeze-drying	Whang et al (1998)
	Particulate leaching and gas foaming	Mooney et al (1996a); Falk et al (1997); Kim et al (1999)
	Supercritical carbon dioxide	Hile et al (2000); Howdle et al (2001)
	3D printing	Kim et al (1998); Park et al (1998)
PEG hydrogels	Photopolymerization	Drumheller et al (1994); Cruise et al (1998); Hern and Hubbell (1998); An & Hubbell (2000)
Lactic acid-PEG hydrogels	Photopolymerization	Han & Hubbell (1996, 1997); Metters et al (2000)
Poly-L-lactic acid-co-L-aspartic acid hydrogels	Photopolymerization	Elisseeff et al (1997)
Fibrin	Enzymatic polymerization	Sakiyama-Elbert & Hubbell (2000b); Ye et al (2000)
Polypropylene fumarate	Photopolymerization	Yaszemski et al (1996); Peter et al (1997); Suggs et al (1997, 1998a, b, 1999)
PVA	Sponges	Davis & Vacanti (1996); Tokiwa & Kodama (1997); Li et al (1998); Kneser et al (1999a, b)
Polyethylene terepthalate	Fibre mesh	Ma et al (2000); Mayer et al (2000)
Natural substances (e.g. alginates, collagen, chitosan, gelatin)	Sponges, gels	Boyne et al (1997); Rowley et al (1999); Uludag et al (1999); Chenite et al (2000); Glicklis et al (2000); Kuijpers et al (2000); Kuo & Ma (2001)

tivity are achieved. Polyester scaffolds can be fabricated using various techniques (Agrawal et al 1997), but all result in different characteristics and, therefore, the most suitable method may vary depending on the application.

Perhaps one of the more straightforward strategies is to use polymer fibres in a mesh form to provide a scaffold with a large surface area (Cima et al 1991). However, their lack of structural stability means that they are not ideal for many in-vivo applications. A fibre-bonding technique has been reported to overcome this drawback (Mooney et al 1996c), whereby PGA fibres are sprayed with poly(L-lactic acid) (P-L-LA) in chloroform. The P-L-LA solidifies following evaporation of the solvent, producing a physically cross-linked PGA mesh.

The problems associated with fibre constructs have also been challenged using a solvent-casting particulate leaching approach (Freed et al 1993). This procedure involves pouring a polymer solution (e.g. PLA in chloroform) onto a bed of salt particles of defined size. The solvent is evaporated under vacuum, resulting in the polymer solidifying around the salt particles. The entrapped salt can then be leached out of the scaffold by numerous rinses in distilled water, thus creating a defined pore structure. Introducing growth factors within the polymer–solvent solution before casting results in their physical entrapment throughout the subsequent scaffold material. Unlike the aforementioned fibre method, particulate leaching can be used to control material porosity, surface area and pore size. Unfortunately, the solvent-casting process means that scaffold thickness is generally limited to a few millimetres (Lu and Mikos 1996), but the leaching strategy has found application in the creation of porous tubular conduits for peripheral nerve regeneration (Evans et al 1999).

Other common approaches in the creation of biocompatible scaffold constructs are those of phase separation, where the polymer is precipitated from a liquid–liquid system (Schugens et al 1996; Nam & Park 1999), and gel-casting, which uses solvent exchange techniques to precipitate the polymer from solution (Coombes et al 1997). A recently reported strategy is that of solid free-form fabrication, which is essentially a two-dimensional printing process that is used to create complex three-dimensional structures by building up printed layers of polymer (Park et al 1998). The technique works by using

a CAD/CAM program to control an inkjet of chloroform that binds the polymer in desired areas across a surface. This strategy can generate micro-architectured scaffolds with complex internal features and regionally selective cell-interactive properties for spatial cell development.

Examples of growth factors

Growth factors can be used to promote or prevent cell proliferation, differentiation, migration, motility and adhesion. A growth factor may be produced by a variety of different cell types and the same growth factor can act on different cell types with a diverse range of effects. The effects exerted by growth factors are concentration-dependent and this determines whether there will be a resultant up- or down-regulation in the synthesis of receptors, proteins or even other growth factors. The turnover of growth factors in-vivo is often rapid and hence their half-lives are short, often only a few minutes.

Growth factors are critical to successful tissue development and repair and, hence, they play a central role in tissue engineering strategies (Nimni 1997; Baldwin and Saltzman 1998; Babensee et al 2000). Some growth factors, such as platelet-derived growth factor (PDGF), hepatocyte growth factor and epidermal growth factor (EGF), act as potent mitogens of cell proliferation, whereas others, such as nerve growth factor (NGF), stimulate cell migration and neurite extension. All of these cellular events are essential features in developing tissues. Examples of growth factors previously reported in tissue engineering systems are detailed in Table 2. Recent advances in the understanding of growth factor mechanisms have allowed researchers

Table 2 Growth factors used in tissue engineering applications.

Growth factor	Action	Use in tissue engineering	Delivery method	Reference
Platelet-derived growth factor PDGF)	Endothelial cell proliferation	Angiogenesis Wound healing	Implanted EVA rods Alginate hydrogels PLLA, PLGA, PLA microspheres	Walsh et al (1995); Kim & Valentini (1997); Lohmann et al (2000); Park et al (2000a, b)
Fibroblast growth factor (FGF)	Cell proliferation	Bone and cartilage regeneration Nerve growth Endothelial cell proliferation Angiogenesis	Hydrogels PLGA Cross-linked fibrin and collagen Heparinized fibrin	Kang et al (1995); Fujisato et al (1996); Martin et al (1999); Shireman et al (1999); Chandler et al (2000); Hile et al (2000); Sakiyama-Elbert & Hubbell (2000b); Tabata et al (2000); Wissink et al (2000)
Nerve growth factor (NGF)	Axonal growth and cholinergic cell survival	Neurite extension in central and peripheral nervous systems	PLGA/poly(caprolactone) encapsulation	Krewson & Saltzman (1996); Cao & Shoichet (1999); Sakiyama et al (1999); Saltzman et al (1999); Benoit et al (2000)
Epidermal growth factor (EGF)	Cell proliferation	Migration and differentiation of neural stem cells Wound healing	Surface immobilization on polymers PLGA microspheres Photoimmobilization	Mooney et al (1996b); Chen et al (1997); Haller & Saltzman (1998); Watanabe et al (1998); von Recum et al (1999)
Vascular endothelial growth factor (VEGF)	Endothelial cell proliferation	Angiogenesis	Alginate hydrogels PLGA-PEG microspheres Heparinized fibrin	Weatherford et al (1996); King & Patrick (2000); Lee et al (2000); Murphy et al (2000b); Sheridan et al (2000)
Bone morphogenetic protein-2 (BMP-2)	Cell proliferation	Bone regeneration	Hydrogels PLGA	Hollinger & Leong (1996); Boden (1999); Whang et al (2000)
Transforming growth factor-β (TGF-β)	Extracellular matrix (ECM) production	Bone and cartilage regeneration Stimulates ECM synthesis	Surface immobilazation EVA rods PLA Chitosan	Nicoll et al (1995); Kim & Valentini (1997); Chenite et al (2000); Lind et al (2001); Mann et al (2001)

to make recombinant growth factors (e.g. recombinant bone morphogenetic protein-2; rhBMP-2), purify growth factors from cell extracts and use gene therapy to induce local growth factor production.

Emerging strategies in the fabrication and use of controlled-release scaffolds

Hydrogel systems

Hydrogel matrices are swollen materials fabricated by physically or chemically cross-linking networks of water-soluble polymers. These systems offer a viable approach for the delivery of biologically active molecules to regenerating tissues as, in addition to the reduced biofouling of hydrophilic polymers, hydrogels are more porous than solid polymers and therefore display rapid release profiles. An example of this approach is the delivery of a bone-inducing growth factor preparation from thermally sensitive chitosan–polyol salt combinations (Chenite et al 2000). Proteins are introduced to the material in a liquid state and, after a temperature increase to 37°C, subsequently become entrapped within the created gel network. The resultant system demonstrated de-novo bone and cartilage formation following ectopic implantation.

Hubbell and co-workers have reported a highly versatile polyethylene glycol (PEG)-containing hydrogel system with localized drug-delivery applications. This approach uses acrylate end-groups to photopolymerize water-soluble monomers in-situ, thus minimizing the need for invasive surgical procedures (Drumheller et al 1994; Cruise et al 1998). Using this system, interfacial polymerization of the monomer has been demonstrated by adsorbing the photo-initiator (e.g. eosin Y) directly to a tissue surface. After UV exposure, the created gel adheres to the cellular interface as a result of interpenetration of the liquid monomer into the textured tissue (Hill-West et al 1994; Hern and Hubbell 1998). The external hydrogel surface is then able to prevent cell and protein adhesions (that may lead to thrombus formation) to the coated area. This system has found application in wound healing for the prevention of postoperative adhesions, a process termed ''gel paving'' (Slepian and Hubbell 1997).

Acrylated PEG hydrogels have been modified for tissue engineering applications by covalently attaching adhesion peptides (e.g. RGD; Hern and Hubbell 1998) and growth factors (transforming growth factor-β; TGF-β; Mann et al 2001). Despite enhancing cell adhesion and spreading, ECM production has been observed to diminish when cells are attached to materials displaying grafted adhesion peptide motifs (Mann et al 1999). TGF-β has been shown to increase ECM secretion under such circumstances, thus ensuring the developing tissue structure has suitable mechanical properties. This growth factor retains its ability to stimulate matrix production following attachment to the hydrogel, and significantly increases production compared with an equivalent concentration of unbound TGF-β.

One important variation on the PEG hydrogel system is the development of degradable materials that incorporate lactic acid units into the monomer structure (Han & Hubbell 1996, 1997). Enzymes and growth factors can be entrapped within these materials by polymerizing the hydrogel in the presence of the active molecule. Depending on the molecular weight of the incorporated protein, release from these hydrogel networks may be controlled by either diffusive or degradative processes. Further improvements to the wound-healing methodology described above have been achieved by incorporating fibrinolytic agents, such as ancrod (Chowdhury and Hubbell 1996), tissue plasminogen activator and urokinase plasminogen activator (Hubbell 1996), into lactide-based PEG hydrogels. These local deliveries were shown to result in marked reductions of postoperative adhesions, while enabling low systemic dosing with the enzymes. Recently, Molina et al (2001) have illustrated that the release kinetics of proteins from physically crosslinked poly(lactic acid)/poly(ethylene oxide) hydrogels depends greatly on the compatibility of the gel and protein. This was highlighted by the compatible BSA–hydrogel system resulting in a concentration-dependent protein release, whereas the gel network created a reservoir-type release for the phase-separating substrate fibrinogen.

Heparin-binding growth factor delivery

Fibrin-based biomaterial scaffolds have increased in popularity in recent years as fibrin already acts as a natural matrix for tissue regeneration, is non-toxic and biodegradable, and can be created using a patient's own blood supply. Systems based on this natural product have already been used in peripheral nerve (Sakiyama et al 1999; Schense et al 2000) and cardiovascular (Ye et al 2000) regeneration studies. The performance of these scaffolds in the area of peripheral nerve regeneration has been enhanced by the incorporation of basic FGF (bFGF) (Sakiyama-Elbert & Hubbell 2000a). This growth factor was used to actively promote neurite extension by employing a heparin-based delivery system. Bi-domain peptides, containing factor XIIIa and heparin-binding sequences, are covalently cross-linked to fibrin during the coagulation process. Heparin is then

introduced and electrostatically associates with the heparin-binding domain, after which heparin-binding growth factors (e.g. bFGF) can be attached. These materials are then able to act as reservoir devices, releasing factors both passively and in response to fibrin and heparin degradation, which may be augmented by enzymes (e.g. plasmin) secreted by migrating cells. Controlling the initial relative concentrations of heparin and bFGF within the matrix, thus ensuring that growth-factor delivery is predominantly cell-mediated, can minimize passive release. This concept of controlled release via the cleavage of susceptible peptide sequences has previously been demonstrated in the area of chemotherapy. Here, preselected oligopeptides were incorporated into synthetic polymer structures, their enzymatic degradation resulting in the release of the active molecule within targeted cells (Putnam et al 1996). The fabrication of biomaterial scaffolds exhibiting such cell-mediated release mechanisms holds great potential for tissue engineering applications as they enable long-term growth-factor delivery owing to localized release confined to the area in which they are required for cell growth and migration.

In addition to bFGF, growth factors unable to bind heparin effectively, such as β-NGF, brain-derived growth factor and neurotrophin-3, have also been immobilized and released from modified fibrin materials (Sakiyama-Elbert & Hubbell 2000b). This is made possible by the presence of basic domains along their native structures that, to some degree, mimic heparin-binding sites. By displaying a large excess of heparin within the matrix, diffusion of these neurotrophins is sufficiently slowed to enable a controlled release profile. Following both the bFGF and non-heparin-binding neurotrophin modifications, neurite extensions from dorsal root ganglia have been shown to increase by up to around 100% relative to unmodified fibrin. Unbound growth factors present within the matrices did not enhance neurite extension.

Encapsulation by double emulsion methods

The encapsulation of growth factors in microspheres involves first generating an initial water-in-oil (w/o) emulsion. The growth factor is dissolved in the water phase and the polymer, typically a polyester, is dissolved in the organic phase (ethyl acetate or methylene chloride), before the two solutions are mixed at an appropriate ratio. A second emulsion (w/o)/w is next formed by dispersion in an aqueous phase using homogenization or sonication. This emulsion is then stirred to evaporate the solvent, thus forming microspheres that can be subsequently isolated by centrifugation or filtration. This approach has been used by a number of groups to produce degradable microspheres that incorporate the growth factors NGF, EGF, PDGF and VEGF (see Table 2). Microsphere morphology studies of these delivery systems, typically determined by scanning electron microscopy, reveal either a hollow core surrounded by a porous surface or scattered internal pores depending on the precise method of production and the starting material used.

The harsh conditions of this technique, namely exposure to organic solvents, may have unfavourable effects on the integrity of the growth factor and may result in deactivation during the encapsulation procedure (Crotts & Park 1997; Fu et al 1999) or aggregation at the solvent–water interface (van de Weert et al 2000). For example, carbonic anhydrase forms non-covalent aggregates on exposure to the oil–water interface, leading to a significant loss in activity.

The enhanced retention of growth factors within microspheres prepared using double emulsion techniques may be achieved by the addition of stabilizers that reduce surface aggregation during manufacture (Fu et al 1999; Sturesson & Carlfors 2000; van de Weert et al 2000). Stabilizers, such as gelatin, poly(vinyl alcohol) (PVA), sucrose, poloxamer 407 or trehalose, may be added to either or both of the emulsion steps, although studies by Bezemer et al (2000) have shown that these have the greatest effect when introduced during the formation of the first emulsion where up to a third of the biological activity may be lost.

Supercritical carbon dioxide processing

Supercritical fluid technology has traditionally been used for chemical extraction and synthesis (McHugh & Krukonis 1994). The properties of supercritical fluids, in that they possesses densities and solvating powers similar to those of liquids, but have the diffusivity and viscosity similar to those of gases, make them ideal media for such chemical reactions. In the mid-1980s the field of supercritical fluids was applied by several groups to bio-catalytic reactions, allowing control of such processes by simply altering either temperature or pressure (Hammond et al 1985; Randolph et al 1985; Nakamura et al 1986). Supercritical fluid technology was used to develop protein powders of defined size that could be utilized for drug delivery without the use of solvents (Tom et al 1993; Winters et al 1996). Furthermore, there was no loss of protein activity within these powders (Yeo et al 1993; Johnston et al 1996). Advances in the design of biodegradable polymers for drug delivery applications led to the use of supercritical carbon dioxide

($scCO_2$) to create porous polymer scaffolds that entrap growth factors (Mooney et al 1996a; Howdle et al 2001).

CO_2 becomes supercritical by raising the temperature and pressure above its critical point (72 bar and 31.1°C). Under these conditions, CO_2 has enhanced solvent properties, thus enabling the glass transition temperature (T_g) of an exposed polymer to be depressed. By choosing a polymer with a relatively low T_g (such as poly(D,L-lactide); Tg = 50–60°C, depending on molecular weight), it will become plasticized below physiological temperatures. Depression of the T_g increases the motility of the polymer chains as the gas enters the polymer phase. Therefore, physical mixing may simply incorporate growth factors throughout the polymer material. On depressurization, nucleation of gas bubbles occurs as the gas attempts to escape from the polymer phase. The foamed structure is preserved, entrapping the growth factor, as the polymer rises above its T_g. This method does not require the use of organic solvents or thermal processing.

Two methods have been described. In the first, a gas-foaming process using either supercritical or non-supercritical CO_2 is used in addition to the traditional method of salt leaching described above (Mooney et al 1996a; Hile et al 2000). In the second, Howdle et al (2001) have incorporated several proteins, at high loadings (up to 70%, w/w), into poly(D,L-lactide) scaffolds in a one-step process. The enzyme ribonuclease was shown to retain full activity after processing and its release was monitored for 80 days.

DNA delivery

A novel alternative to growth factor encapsulation is the proposed replacement of the actual protein in the polymer matrix with plasmid DNA encoding the growth factor of interest. Ideally, the plasmid encoding the growth factor is incorporated into the DNA of regenerating cells and is expressed at physiological levels without any further need for systemic delivery of growth factor. Local gene delivery has been used in wound healing (Bonadio et al 1999) and bone repair (Chandler et al 2000), where a gene-activated matrix consisting of the plasmid DNA, collagen and poly(α-hydroxyacid)s was used to deliver plasmid encoding cytokine, PDGF and human parathyroid hormone. Recently, Shea et al (1999) have introduced plasmid DNA encoding for the PDGF gene into PLGA matrices by gas-foaming, with efficiencies of up to 60%. The PDGF plasmid DNA was subsequently released and transfected cells in both in-vitro and in-vivo studies, leading to enhanced vascularization of tissue. Unfortunately, the delivery of plasmid DNA in-vivo is typically associated with low transfection rates. It remains to be seen whether this technique will be viable for large vascular tissue demands such as that required for liver regeneration.

Conclusions and future directions

The controlled release of growth factors is essential in many tissue engineering applications because co-ordinated cell responses, such as proliferation, differentiation and angiogenesis, are required to regenerate functional tissues. Many current technologies in this field have been borrowed from conventional concepts of controlled release of small drug molecules. However, there is an increasing appreciation that the molecular nature of growth factors and the demands for more complex release kinetics will necessitate the design of new delivery devices. In the future, the rate of progress in tissue engineering may be determined by the availability of controlled release systems that exceed current capabilities.

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