Mini Review

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# Global adaptation of engineered tissue technology; current status and future prospects

## Abstract

The tissue engineering technology/engineered tissue technology has met remarkable success in the recently concluding decade and is replacing the standard, common place medical therapies as they are rendered ineffective and less preferable because of the extraordinary advances achieved in the field of tissue regeneration owing to the global adaptation of tissue engineering technology as a regular and effective mean of therapeutic intervention against various medical conditions. The increasing trend is particularly prompted by the global regulatory framework, setup and effectively implemented by the governments and health care organizations across the globe which has allowed the consistent development of advance technologies and an exponential increase in the research funding for alternative regenerative medicine therapies. These efforts has allowed the development of tissue engineering technology /engineered tissue technology into a global market of valuable interest not only in terms of financial turnaround but also as an intellectual paradigm for other sciences and research areas. It is roughly estimated that the global tissue engineering technology is expected to reach 11.53 billion by 2022 according to a new report by Grand view research, Inc. 2016.The use of stem cells co-culturing provides more resolute approach towards the development and growth of tissue engineering technology into a more convenient and effective therapeutic tools against variety of complications including those inherited by birth.

**Keywords:** tissue engineering technology, regenerative medicine/therapy, stem cells, co-culture, scaffold, signaling molecules/growth factors, extra cellular matrix

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## Introduction

The intrinsic ability of body to heal itself more rapidly or of developing some form of bio artificial device capable of either replacing the damaged organ in vivo or working ex vivo to supplement its impaired function has led to the development of the field of tissue engineering. Tissue engineering employs the principles of engineering and cell biology to develop biological substitutes able to maintain, restore, or improve tissue function. Much of this work has been stimulated by the observation that the body naturally has at least some capacity for regeneration (for example wound healing), and if the biological mechanisms of these processes can be better understood, they may be corrected when they go wrong, enhanced, or manipulated to allow the ex vivo production of fully functioning tissues or bio artificial devices.

Several strategies suggested by Langer in 1993 to achieve this goal include

a) Replacement of malfunctioning/dead cells with isolated cells or cell substitutes.

b) Administration of growth factors or cytokines to encourage the malfunctioning organ to regenerate itself.

c) Culture of the appropriate cell type on a support matrix to produce either an extracorporeal device capable of replacing organ function or for implantation

The key objective of tissue engineering is to improve quality of life in a secure way by avoiding various adverse effects of several standard medical therapies and replace or repair damaged tissues by creating new healthy niches enabling cells to grow, proliferate and differentiate.[1] Tissue engineering combines cells, biomaterials and growth factors to support and regenerate biological tissues. There are also multiple attempts to generate new tissues and even entire organs in vitro, ready to be implanted into the diseased and mechanically damaged sites. This involves, for instance, the simulation or mimicry of the extracellular matrix (ECM).[2] Thus, patient-derived cells can be expanded in culture and prompted to differentiate into a specific tissue or organ, followed by transplantation in a patient with no need of another patient matching cell/tissue/organ donor.

The earliest clinical applications of human cells include the attempts to regenerate skin tissue using fibroblasts, keratinocytes, or a scaffold (template) in 1980th. Soon after, periodontal and alveolar bone tissues were tested for regeneration potential with use of membranes preventing undesirable fibroblasts from invasion there (guided tissue regeneration and guided bone regeneration).[3] FDA approved marketing authorization for Maci-autologous cultured chondrocytes on porcine collagen membrane for the repair of cartilage defects of the knee in adult patients.

### Components for tissue engineering

Three key components are needed for tissue engineering – cells, scaffold and growth factors. Whereas cells produce new tissue matrix, scaffold provides the appropriate environment for cells to be able to effectively accomplish their missions. The function of growth factors is to facilitate and promote cells to regenerate new tissue.[4]

The cell source has a massive impact on the practical application of tissue engineering for future medical therapies. Cells may be

classified into autologous (patient's own), allogenic (human other than patient) and xenogenic (animal origin).[5] Autologous cells are the most appropriate for tissue engineering, whereas allogenic and xenogenic cells are immunogenic and will need an immunosuppressive therapy when a new tissue is engineered. A certain limitation associated with autologous cells is harvesting a sufficient amount of healthy cells with high regenerative potential, especially when a patient is aged or diseased.[6] However, the progress in regenerative medicine area now allows for fast and efficient expansion of several different progenitor cells that are then used for the preparation or tissue engineered pro-medical constructs.[7]

The major function of scaffold is to mimic the natural extracellular matrix (ECM). The scaffold should support proliferation, differentiation, and normal cell function. In addition, a scaffold placed at the regeneration site should prevent disturbing cells from external factors.[8] To fulfill the functions of a scaffold in tissue engineering, the scaffold should meet a number of requirements– it should be biocompatible, should have appropriate porosity and porous microstructure and proper surface chemistry to allow cell attachment, proliferation and differentiation. Scaffolds should possess adequate mechanical properties and controlled biodegradability.[9] The most common reasons for using absorbable polymer scaffolds are to accomplish time-varying mechanical properties and ensure complete dissolution of the implant, eliminating long-term biocompatibility concerns or avoiding secondary surgical operations.

A wide range of exogenous growth factors are currently being used in bone tissue engineering: transforming growth factor beta (TGF-b1), fibroblast growth factor (FGF), insulin growth factor (IGF), vascular endothelial growth factor (VEGF), PDGF, and bone morphogenic proteins (BMPs) etc.[10,11]

## Current status

### The skin

The largest organ in the human body, skin, has been one of the first true success stories in tissue engineering. The field has progressed rapidly, and there are more than six skin substitute products commonly used in clinical practice.

| Product | Description |
|---|---|
| Derma graft® | Human fibroblasts seeded on a bio absorbable scaffold |
| Epical ® | Autologous epidermal sheets |
| Integra® | Acellular dermal matrix based on bovine tendon collagen |
| Apligraft® | Human fibroblast dermal layer and keratinocytes epidermis |
| Alloderm® | Freeze-dried a cellular human dermal matrix |

Prior to the development of these products, the main treatment for patients requiring skin because of severe extensive burn wounds or the excision of large areas of skin were autologous or allogenic skin grafts. This involves the removal of some of the patient's own skin or that of a donor, usually from the legs or buttocks, which is transplanted onto the area required. Both of these transplant methods are often limited by the amount of donor tissue available, the risk of infection, and graft rejection. The process is a painful one and often results in permanent scarring. It is these problems that prompted the search for alternative therapies. In the mid-1970s Rheinwald and Green pioneered the tissue engineering of skin in the serial culture of keratinocytes, allowing the expansion of the population and the first laboratory-produced skin tissue. The theory behind this method allowed the grafting of these cells onto burn injuries or chronic wounds. A small biopsy of the patients' own skin can be partially broken down by digestive enzymes, allowing the separation of the dermis and epidermis. Keratinocytes from the epidermis are then cultured in vitro with growth factors and their population expanded until a sheet of skin is produced that will adequately cover the wound. Unfortunately, the time needed for the propagation of the host's cells can be 3 weeks or 4 weeks to cover an extensive burn wound and so to have a ready supply of skin, allogenic keratinocytes are now used. Cells isolated from neonatal foreskin samples can be cultured and the resulting sheets of cells seeded on to a gauze support scaffold prior to transplantation. During the serial culture of keratinocytes, Langerhans' cells, which are responsible for the activation of the immune system, are lost. The resulting tissue could therefore be transplanted without the risk of rejection.

### The liver

Despite advances in liver transplantation, such as the division of donor livers into several segments (which may then be transplanted into a number of recipients), there is still considerable demand for donor livers. Part of the problem is the short life span of donor organs. The hope is that if a liver could be engineered, it could be available for transplant more or less on demand. In addition, because of the tremendous regenerative capacity of the liver, the development of a liver support device may be able to either bridge the gap between liver failure and regeneration of the host organ or the finding of a suitable donor tissue. However, hepatocytes in culture have a particularly short life span, typically lasting no longer than a couple of weeks, and rapidly losing their differentiated function. For this reason much research has been focused on extending the life span of hepatocyte cultures, and maintaining their differentiation. Culturing hepatocytes on extracellular matrix constituents has been shown by several investigators to improve hepatocyte adhesion, spreading, and maintenance of the hepatocyte phenotype for prolonged periods. Matrices that have been tried include individual matrix components such as fibronectin, laminin, and collagens type I and IV, along with complex mixtures of extracellular matrix such as liver biomatrix (from regenerating and normal livers) and that derived from the Engelbreth-Holm Swarm sarcoma. Each component has been shown to have differential effects upon the hepatocyte biochemistry. Efforts to mimic the polarity of hepatocytes in vivo by culturing them between two layers of matrix, e.g., collagen, have shown striking effects on the morphology and function of the liver cells including enhanced albumin secretion, improved cytochrome P450 induction responses, bile acid transport, and formation of gap junctions and bile canalicular networks. Long-term maintenance of the normal polygonal morphology and cellular distribution of actin filaments seen in vivo has also been observed. However many of these culture systems such as the EHS matrix, in addition to enhancing hepatocyte differentiation, suppress proliferation.

### Kidney

The active units of the kidney are nephrons, which are located within the cortex and medulla. They are able to process the blood via ultrafiltration under pressure allowing the excretion of toxic metabolic waste products and the reabsorbtion of water, glucose, and electrolytes back into the blood. Patients suffering from acute and chronic renal failure have only haemodialysis or haemofiltration as renal substitutes. These methods rely on the use of synthetic membranes that selectively filter out molecules of a specific size. This method of

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dialysis replaces the function of the glomerulus only, which means that this therapy is unable to offer the important transport, metabolic, and endocrinologic function of the kidney normally provided by the tubule. Tissue engineering a complete kidney is not hindered by the retention of their function in culture, as isolated renal cells are able to retain their phenotype. It is the limited diffusion of nutrients and oxygen to large tissue volumes that presents the greatest challenge. In engineering a complete kidney organ, tissue engineers are using biodegradable scaffolds as a cell-support matrix. This porous matrix should encourage cell attachment and proliferation while allowing the free diffusion of nutrients. In 1996 both Yoo and Fung published papers demonstrating the seeding of polymer scaffolds with distal tubule, golmeruli, and proximal tubule cells and the ability of the cells to organize into nephron segments including reconstitution of proximal tubules, distal tubules, loop of Henle, collecting tubules, and collecting ducts. These constructs were found to excrete uric acid and creatinine in a yellow urine-like fluid. Further modifications of scaffolds to those from a naturally derived acellular collagen matrix have shown kidney cell proliferation and reconstitution of both renal tubular and glomerular-like structures. This natural matrix is identical to that found in vivo and therefore contains all necessary protein components specific for the kidney cell types.

### Osteoarthritis

Osteoarthritis is a global degenerative joint disease involving the cartilage and many of its surrounding tissues. Current guidelines for OA therapy in the following defined order: first, behavioural interventions; second, simple analgesic such as acetaminophen (paracetamol); third, nonsteroidal anti-inflammatory drugs, including COX-2 inhibitors; fourth, intra-articular injection of hyaluronic acid or corticosteroid; and finally fifth, total joint replacement.[12,13] The goals of these treatment are to reduce pain, improve joint mobility, reduce disease progression and seek joint replacement surgery after failure of a series of nonsurgical therapy that are not ideal treatment options. After years of research and development, tissue engineering and regeneration medicine makes possible preventing the degeneration and promoting the regeneration of cartilage.

### Scaffold-based treatment for articular cartilage focal lesions

Articular cartilage focal lesions repair is far beyond the regenerative capacity of cartilage. Self-repair mechanism for articular cartilage defects, fibrous tissue repair, can't realize the function of cartilage at all. In contrast to the poor therapeutic effects of traditional treatment modalities, tissue engineering and regeneration medicine provided a preferable treatment strategy and developed rapidly in the last few decades. Injectable treatments, such as stem cells and cartilage regenerative factors, can hardly remain and then perform their functions of promoting cartilage regeneration in the 3D-shaped lesions. The application of scaffolds is imperative in tissue engineering and regeneration medicine strategy for OA treatment.[14]

### Cell-free scaffolds for cartilage defects

In a goat model that osteochondral defects possess a certain reparative capacity, and micro fracture is an effective treatment for full-thickness osteochondral defects reported by Jackson et al.[15] These are based on spontaneous reparative effect of BMSCs from the bone marrow beneath the defects. The scaffolds in the defects may provide a 3D environment for BMSCs and thus have the therapeutic potential in the treatment of articular cartilage defects.[16,17] The scaffolds provide a 3D environment for cell attachment, migration, proliferation, differentiation and extracellular matrix formation, and their properties determine reparative effect of BMSCs. Therefore, there are many basic requirements for the scaffolds in the treatment for cartilage defects as follows:

a) Favourable biocompatibility, non-immunogenic, and non-toxic;

b) Adequate mechanical strength: the scaffolds can fulfil the defects and maintain its shape

c) Optimal porous structure for the attachment, migration, and biological activity of BMSCs;

d) Appropriate degradation rate range: the scaffolds can neither degrade too rapidly which caused porous structural damages, nor degrade too slow which interfere with extracellular

Matrix formation.[18]

### Tissue-engineered cartilage

In this strategy, chondrocytes or other cell sources were seeded in a bio mimic scaffold, cultured or/and inducted in vitro for longer periods till the formation of the nonissue similar to native articular cartilage. The four important parameters of tissue engineering are scaffolds, cells, soluble growth factors, and the physical environment. Compared to the microenvironment in the cartilage defects, an ideally controllable culture system may provide a better environment for neocartilage formation and cartilage repair. Stem cell populations all have multi lineage potential, however the chondrogenic potential needed to be highly dependent on the combination of growth factors which induce chondrogenesis, such as Transforming Growth Factor-b (TGF-b), Bone Morphogenetic Proteins (BMPs), Fibroblast Growth Factors (FGFs), and Insulin Growth Factors (IGFs) and so on. BMSCs have been extensively used for cartilage tissue engineering. The chondrogenesis of BMSCs is generally stimulated by TGF-b, and Indrawattana et al. also investigated that BMP-6 and IGF-1 may promote the chondrogenesis.[19] ADSCs are also capable of chondrogenesis in the presence of growth factors. While BMSCs responds more favourably to TGF-b for chondrogenesis, ADSCs shows enhanced response to Bone Morphogenetic Protein-6 (BMP-6). However in the current induction system, ADSCs demonstrated lower chondrogenic potential than BMSCs. There are also other sources for engineered cartilage in vitro. Sakaguchi et al.[20] compared MSCs isolated from five different tissue sources, and found that SDSCs possess greatest chondrogenic potential in the same environment.[21]

## Future prospects

### Advances in tissue engineering through stem cell-based co-culture

Stem cells are the future in tissue engineering and regeneration. In a co-culture, stem cells not only provide a target cell source with multipotent differentiation capacity, but can also act as assisting cells that promote tissue homeostasis, metabolism, growth and repair. Their incorporation into co culture systems seems to be important in the creation of complex tissues or organs. Cells can be used for a variety of functions; these include synthesizing the bulk of the tissue matrices, integrating with existing native tissues, maintaining tissue homeostasis in general and providing various metabolic services to other tissues and organs. Although terminally differentiated cells are commonly used for synthesizing the matrices that compose the

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bulk of tissues, stem cells, specifically adult stem cells, are quickly gaining popularity for their favourable properties. With a plethora of competencies, either terminally differentiated or stem cells can be harnessed to drive the tissue-engineering process.

Co-culture is the culture of multiple, distinct cell types, directly or indirectly, within the same culture environment. Co-culture methods are used in tissue engineering for two purposes. The first and most common application of co-culture in tissue engineering is to drive tissue formation with the direct or indirect interaction of multiple cell types. The second is to maintain the potency of stem cells during their expansion. Co-culture systems control the behaviour and actions of cells through the interaction of the multiple cell types. The types of cells within a co-culture are termed target cells and assisting cells. In general, target cells are those that will eventually compose the engineered tissue and are responsible for the tissue's function (e.g. metabolic, mechanical). When multiple target cell types are cultured together, each can also serve as assisting cells to the other. Assisting cells guide the target cells to display a range of desired behaviours. The intimate interactions between assisting and target cells are often too complex to implement through exogenous control. Assisting cells constantly monitor and respond to the target cells' needs, effectively serving as a feedback control system that is constantly on and immediately responsive, thus creating an ideally controlled culture environment.

The use of stem cells in co-culture systems provides key missing elements that are required to overcome the critical limitations faced by tissue engineering and regenerative medicine. Stem cells are advantageous for their self-renewing and potential to differentiate toward multiple cell types. When applied in co-cultures, stem cells can, in addition, promote tissue growth and repair, both directly and indirectly, as target cells that form specialized tissues or as assisting cells that support terminally differentiated cells by enhancing, for example, cell survival, proliferation, phenotype maintenance and organization. Due to their properties and ability to regulate cell functions, stem cells serve a role in a continuous feedback loop over the cells they assist in co-culture. In turn, their intricate needs can be promptly fulfilled by the terminally differentiated cells with which they cohabit. Stem cell co-culture systems are unique and powerful tools, due to their range of design specifications and feedback control properties, and have already shown success in engineering tissues.

The design of a co-culture system often aims to recapitulate cellular interactions that take place in vivo. These interactions can be via direct cell–cell contact, cell–ECM adhesion and transfer of signaling molecules. Increasing evidence suggests that these interactions are more complicated than initially believed. Both stem cells and terminally differentiated cells simultaneously interact with each other in a way that has proved difficult to recapitulate via exogenous control schemes, such as growth factor dose and dosing regimens. It is of note that tissue engineering is also beginning to harness novel interactions that do not naturally occur. Often, it is desirable to create interactions and environments that do not naturally occur to overcome the limitations that exist in native tissue systems to drive the tissue engineering and regenerative processes. Novel co-culture strategies that manipulate this environment towards a creative collaboration between stem cells and terminally differentiated cells are a promising area for in vitro tissue engineering.

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## Conflicts of interest

The authors declare no conflict of interest.

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