

Review Article

Tissue Engineering and its Future Perspective in Therapeutic Medicine

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ABSTRACT:

Tissue engineering is an interdisciplinary field that applies the principles and methods of bioengineering and material science etc. The present article highlights its useful role in medicine which will be beneficial in treating many diseases.

Key words: Tissue engineering, interdisciplinary, science

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INTRODUCTION

Tissue engineering is an interdisciplinary field that applies the principles and methods of bioengineering, material science, and life sciences toward the assembly of biologic substitutes that will restore, maintain, and improve tissue functions following damage either by disease or traumatic processes. The general principles of tissue engineering involve combining living cells with a natural/synthetic support or scaffold to build a three dimensional living construct that is functionally, structurally and mechanically equal to or better than the tissue that is to be replaced. The development of such a construct requires a careful selection of four key materials: 1) scaffold, 2) growth factors, 3) extracellular matrix, and 4) cells.¹

Scaffold materials are three-dimensional tissue structures that guide the organization, growth and differentiation of cells. Scaffolds must be biocompatible and designed to

meet both nutritional and biological needs for the specific cell population.

FUNDAMENTALS OF TISSUE ENGINEERING

In 1933, the concept of tissue engineering was first introduced when mouse tumor cells demonstrated survival when encased in a biocompatible polymer membrane and implanted into the abdominal cavity of chick embryos (11). Studies demonstrated that pancreatic beta cells from neonatal rats, cultured on synthetic capillaries and perfused with medium, released insulin in response to changes in glucose concentration.^{2,3}

Current approaches to tissue engineering can be stratified into substitutive, histioconductive, and histioinductive (1). Substitutive approaches (ex vivo) are essentially whole organ replacement, whereas histioconductive approaches (ex vivo) involve the replacement of missing or damaged parts of an organ tissue with ex-vivo constructs. In contrast, histioinductive approaches facilitate self-repair and may

involve gene therapy using DNA delivery via plasmid vectors or growth factors.⁴

In orthopedics and craniomaxillofacial surgeries, tissue engineering has been applied to reconstruct bone structures and repair bone defects. In bone tissue engineering (BTE) or bone engineering, osteogenesis is initiated by osteoblasts, which are mostly differentiated forms of stem cells provided by graft material. After the initiation of osteogenesis, local and distant stem cells and also osteoblasts would be attracted to the field and participate in bone regeneration. The application of different types of cells, such as embryonic stem cells, fetal cells, placenta and amniotic fluid cells, umbilical cord cells, bone marrow haematopoietic stem cells, mesenchymal stem cells, adipose tissue- derived cells and dental-derived tissue stem cells have been investigated for bone tissue engineering. However, Bone marrow stem cells (BMSCs) have been used more frequently.⁵

For regenerative medicine strategies to be successful, the material used, mostly combinations of scaffolds, growth factors, and stem cells, must be able to replace the damaged tissue and be able to function as the original tissue or be able to stimulate regeneration of the original tissue. Cells used in regenerative medicine and tissue engineering can come from the same patient (autologous) or from another individual (allogeneic). In addition, xenogenic cells such as those from animals can also be adopted in regenerative medicine strategies. Cells that have been used so far include stem cells, fibroblasts, chondrocytes, and keratinocytes.⁶

Though allogeneic cells might illicit an immune reaction, this can be alleviated by prescribing immunosuppressants to patients. Depending on the age of the patient, some regenerative medicine strategies can utilize and accelerate the body's own natural healing process. These strategies are aimed at changing the tissue environment by the introduction of exogenous material and biological factors with the sole aim of accelerating and improving the body's healing process. Materials and biomimetics of the extracellular matrix have been in use for several years now and do more than just providing the physical structure. Materials and biomimetics can stimulate regeneration on their own but can also be used to present biomolecules such as growth factors to promote the growth of cells. Initially thought to be necessary for physical support for cells, the biomaterial or scaffold can now incorporate biological cues or signals to enhance or promote tissue regeneration and function.⁷

3D BIOPRINTING OF TISSUES

Cartilage Regeneration

Cartilage in the joints provides humans and other animals the ability to move without feeling any pain. Accidents and pathological conditions such as osteoarthritis can lead to cartilage loss and cause painful movements in humans.

This is because cartilage lines the surface of joints and provides lubrication and “cushions” the body weight during movement. Cartilage is mainly made up of ECM proteins such as type II collagen and aggrecans, and these interact with synovial fluids to provide lubrication and weight-bearing functions. For successful regeneration of cartilage, scientists need to mimic both the surface of the cartilage and its stromal tissue. The use of artificial derivatives from plastics and metals is ridden with disadvantages. For example, plastic and metal implants for cartilage have a short lifespan and can form foreign particles due to wear and tear. Lately, both chondrocytes and MSCs have been used to repair cartilage defects through regeneration.⁸

Heart

Heart failure is usually treated via organ transplantation, and with the obvious organ shortages, 3D bioprinting is likely to be a solution to this problem. Several reports show that several heart constructs and grafts are under evaluation. The heart requires proper vascularization and innervation for it to function properly. Therefore, heart constructs and grafts must have adequate vascularization, and this represents a huge challenge. The heart ECM is a major player in cellular differentiation and determination of protein expression. The heart ECM is mainly made up of collagen.⁹

Liver

Adult stem cells are the best choice for 3D bioprinting of hepatic tissue since they can be obtained from the patient, allowing personalized tissue bioprinting. Stem cells also express hepatocyte-like genes. The fabrication of microlivers has allowed the study of several candidate drugs in high-throughput studies. 3D hepatic tissues have been developed using bioprinting techniques. Embryonic stem cells have been bioprinted using valve-based bioprinting to create liver constructs, and the cells differentiated to be hepatocyte-like cells. The cellular sources used in liver constructs or grafts include adipose-derived stromal cells, Wharton-jelly derived stromal cells, and hepatic progenitor cells.¹⁰

Other applications

Immune Deficiency

Defective development of leukocytes often leads to immune deficiency. This can be corrected by transplantation of bone marrow. This often leads to graft versus host rejection reactions. Rejection reactions can be prevented through the use of autologous bone marrow in conjunction with gene therapy. In the meantime, numerous gene defects have been identified which cause immune deficiency diseases. Therefore, one method of treatment is the withdrawal of some of the patient's own bone marrow cells, which then are equipped in vitro with functional copies of the defective gene. Finally, the modified bone

marrow cells are reinserted via infusion.¹¹ If successfully integrated into the bone marrow cell population, a permanent cure could be possible. Graft versus host reactions do not occur with this method, but the effective transfer of genes into bone marrow stem cells is still very difficult.

Defects in Articular Cartilage

Hyaline cartilage, which covers the surface of joints, is of particular clinical importance. Very limited damage to a joint surface will heal, but fibrocartilage is produced instead of mechanically resistant hyaline cartilage. Large-scale damage of cartilage never heals and poses a special medical problem. Thus, regenerative medicine seeks to fill the damaged areas with autologous chondrocytes or, as we will see later, a construct of artificial hyaline cartilage.¹²

Restoration of cartilage seems to be a relatively simple method, which has been used for years in many hospitals. This therapy is used in the restoration of mechanically stressable joint surfaces after large separations. The damaged cartilage cannot produce material resistant to mechanical stress. No regeneration takes place nor is relatively soft fibrocartilage produced. In therapy, a piece of the patient's cartilage is isolated from a part of a joint not under mechanical stress, such as an epicondyle. The isolated tissue is sent to a special laboratory, which specializes in the isolation and multiplication of chondrocytes.¹³

Large-scale Burns

Apart from bone marrow transplantation or leukemia, the longest clinical experience in the area of cell therapy exists mainly in the therapy of patients with the most serious burns, whose lives have been saved by cultivated keratinocytes. There are many instances of accident victims with burns on more than 90% of their body surface. Apart from basic care for these seriously wounded patients, keratinocytes from undamaged areas of the axilla, groin or the foreskin are isolated and placed in culture. The keratinocytes are then multiplied within special culture flasks with a removable cover, mostly on a layer of fibroblasts.¹⁴

Muscular Dystrophies

Muscular dystrophies are marked by a progressive loss of skeletal muscle and belong to the group of frequently deadly hereditary diseases. Despite great advances in the identification of mutated genes, the possibilities of therapy are very limited. Potential future opportunities are offered by cell therapy and tissue engineering. The origin of muscular dystrophy is traced back to the *dmd* gene, which is located on the short arm of the X-chromosome. With its 79 exons and 2.5 megabases, it is one of the largest known genes. It codes for the cytoskeletal protein, dystrophin, with a molecular weight of 427,000 Da, which is located on the inner layer of the cellular membrane. Its N-terminal end is

connected to actin filaments and its C-terminal end to a dystrophin-associated glycoprotein complex (DGC).¹⁵

Myocardial Infarction

When the heart reaches its definitive size during development, the cardiomyocytes also end their cell cycle in a terminal phase of differentiation, by a yet unknown mechanism. Afterwards they are not regenerative. A cardiac infarction leads to necrosis of the heart muscle with irreversible tissue and cell damage.¹¹ An effective form of therapy could be the implantation of artificially produced heart muscle tissue in the damaged area. Cardiomyoblasts that are able to proliferate are required during the generation of heart muscle tissue. The implantation of skeletal muscle cells, satellite cells and cells from smooth muscle shows that these cells can still be detected after some time, but that they do not form the necessary gap junctions and desmosomes, and therefore a functional tissue.¹⁶

Bone

Most importantly, graft integration with host tissue will improve with new knowledge on graft vascularization and innervation. Improved techniques with regard to the release of growth factors within 3D-bioprinted constructs and organs once transplanted will allow the controlled healing and regeneration process. Modulation of the immune system can lower the rejection of 3D-bioprinted tissues and organs or at least allow scientists to achieve a desirable immune response. Increased knowledge on stem cell behavior and controlled differentiation of the cells can be achieved, allaying fears of their safety.¹⁷

CONCLUSION

Tissue engineering will prove to be beneficial in medical field. Graft integration with host tissue will improve with new knowledge on graft vascularization and innervation. Improved techniques with regard to the release of growth factors within 3D-bioprinted constructs and organs once transplanted will allow the controlled healing and regeneration process.

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