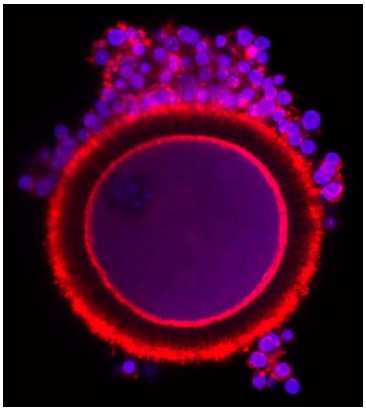
Tissue Engineering

Tissue engineering evolved from the field of biomaterials development and refers to the practice of combining scaffolds, cells, and biologically active molecules into functional tissues. The goal of tissue engineering is to assemble functional constructs that restore, maintain, or improve damaged tissues or whole organs. Artificial skin and cartilage are examples of engineered tissues that have been approved by the FDA; however, currently they have limited use in human patients.

How do tissue engineering and regenerative medicine work?



Source: Northwestern University

Cells are the building blocks of tissue, and tissues are the basic unit of function in the body. Generally, groups of cells make and secrete their own support structures, called extra-cellular matrix. This matrix, or scaffold, does more than just support the cells; it also acts as a relay station for various signaling molecules. Thus, cells receive messages from many sources that become available from the local environment. Each signal can start a chain of responses that determine what happens to the cell. By understanding how individual cells respond to signals, interact with their environment, and organize into tissues and organisms, researchers have been able to manipulate these processes to mend damaged tissues or even create new ones.

The process often begins with building a scaffold from a wide set of possible sources, from proteins to plastics. Once scaffolds are created, cells with or without a "cocktail" of growth factors can be introduced. If the environment is right, a tissue develops. In some cases, the cells, scaffolds, and growth factors are all mixed together at once, allowing the tissue to "self-assemble."

Another method to create new tissue uses an existing scaffold. The cells of a donor organ are stripped and the remaining collagen scaffold is used to grow new tissue. This process has been used to bioengineer heart, liver, lung, and kidney tissue. This approach holds great promise for using scaffolding from human tissue discarded during surgery and combining it with a patient's own cells to make customized organs that would not be rejected by the immune system.

1. Introduction

Nowadays, losing an organ or a tissue is a noticeable challenging in human health care. Tissue/organ transplantation, surgical operation, or mechanical device application (like dialysis) are common treatments. However, limitations of the current strategies have increased the interest in tissue engineering (Lee, Rim, Jung, & Shin, Citation2010). Appropriate cell type, effective cell modification, and proper supportive matrices are three main bases of tissue engineering. In this review study, a comprehensive view of tissue engineering and its different aspects are described.

2. Tissue engineering strategies

Tissue engineering strategies can be divided into two main categories: scaffold-based and scaffold-free approaches. Autologous or allogeneic cells can be used in both categories (Vapniarsky, Arzi, Hu, Nolta, &Athanasiou, Citation2015). On the other hand, some researchers have introduced exogenous cell-based and endogenous cell-homing approaches in tissue engineering (Li et al., Citation2017). Application of exogenous cellular materials in cell-based strategy has become a major concern for both economic and safety reasons with limitations such as availability of cell sources, the excessive cost of commercialization, the anticipated difficulties of clinical translation and regulatory approval. Recent insight into cell movement and homing help recruiting endogenous cells in cell-homing approach. The administration of chemokines as signals potentiates cell homing in an anti-inflammatory microenvironment (Aibibu, Hild, Wöltje, &Cherif, Citation2016; Andreas, Sittinger, &Ringe, Citation2014; Chen, Wu, Zhang, Zhang, & Sun, Citation2011). The cells can also be genetically or epigenetically modified (Sheyn et al., Citation2010), e.g. in order to enhance the efficiency of tissue regeneration (Gersbach, Phillips, & García, Citation2007).

2.1. Scaffold-free approaches

In scaffold-free approaches, the cells can be directly administrated, even systemically (Burra et al., Citation2012) or locally (Kitahara et al., Citation2008). Also the cells can be administrated through three-dimensional cell microsphere (Kodali, Lim, Leong, & Tong, Citation2014) or cell sheet techniques (Gonçalves, Rodrigues, & Gomes, Citation2017; Zhang et al., Citation2017). Due to trigger the intrinsic repair mechanisms of a tissue, co-application of the cells and some

additive biomolecules seems to be more effective (Foster, Puskas, Mandelbaum, Gerhardt, & Rodeo, Citation2009; Luyten, Lories, Verschueren, de Vlam, &Westhovens, Citation2006).

2.1.1. Biomolecules

Growth factors are soluble diffusible signaling polypeptides that regulate different kinds of cell processes inducing cell survival, migration, differentiation, and proliferation. Platelet-rich plasma is rich in a variety of growth factors with wide application in cartilage and skeletal disorders (Kon et al., Citation2010). It has been shown that applying growth factors could facilitate tissue regeneration. For instance, basic fibroblast growth factor (J. W. Yang, Zhang, Sun, Song, & Chen, Citation2015), insulin-like growth factor-1 (Mullen et al., Citation2015), and bone morphogenetic protein-2 (CitationKim et al., 2015) have been used for different tissue engineering purposes (Table 1).

2.2. Scaffold-based approaches

In scaffold-based approaches, both topological and biochemical aspects of the scaffold should be investigated for differentiation, adhesion, or viability of the cells (Kilian, Bugarija, Lahn, &Mrksich, Citation2010; Mansouri &SamiraBagheri, Citation2016). The geometrical properties and fabrication methods of the scaffolds have remarkable influences on cellular behavior (Norman & Desai, Citation2006; Parker et al., Citation2002). Many of these methods were established in other research areas, but their usage was further demonstrated in biology, like photolithography (Su, Citation2007), electrospinning (Hasan, Alam, &Nayem, Citation2014), and soft lithography (Kim et al., Citation2008).

Another approach is to utilize the natural extracellular matrix (ECM) entitled whole-organ tissue engineering. In this method, the cellular and nuclear content of a tissue is removed by chemical agents or enzymes and the remaining can be used as a scaffold. These naturally occurring scaffolds can then be seeded with certain cell populations (Dahl, Koh, Prabhakar, &Niklason, Citation2003; Petersen, Calle, Colehour, &Niklason, Citation2012).

Although some promising results have been achieved in animal models, many challenges such as *in vivo* viability and functionality remain to be solved. Interestingly, it has been shown that the repopulation of the organ by patient's own cell is possible *in vivo*.

In order to *de novo* synthesize of a natural ECM scaffold, sheets of cells can be cultured and wrapped into tubes (L'Heureux et al., Citation2006) or other 3D structures (Tsuda et al., Citation2007). After removing the cells, there would be a scaffold in the desired shape made of the secreted ECM. Some common steps of scaffold-based approach are described as follows:

2.2.1. Scaffold pretreatments

In order to improve the efficiency, some peptides and biomolecules can be simply loaded on the surface of the scaffolds (Mohamadyar-Toupkanlou, Vasheghani-Farahani, Bakhshandeh, Soleimani, &Ardeshirylajimi, Citation2015; Reis et al., Citation2012) or can be chemically

immobilized through covalent bonds (Chiu &Radisic, Citation2010; Karageorgiou et al., Citation2004). There are also other surface treatments such as plasma treatment (Martens, Bronckaers, Politis, Jacobs, &Lambrichts, Citation2013), wet chemical method (Madhumathi et al., Citation2009), co-electrospinning of surface active agents and polymers (Lelkes et al., Citation2007). The surface treatment methods are used to maximize absorption of bioactive molecules on the scaffolds (Bose &Tarafder, Citation2012; Yoo, Kim, & Park, Citation2009).

2.2.2. Scaffold fixation

In tissue engineering of large defects, the construct has to be fixed at the site of interest. The sterilization step has to be done very carefully, in a way that neither bioactivity of the scaffold nor the viability of the cells is affected (Ferraris et al., Citation2012). The scaffold can be fixed using mechanical strength, through fibrin glue, pins, or magnetic force (Bekkers et al., Citation2010; Knecht et al., Citation2007; Russo et al., Citation2012). Using a biocompatible magnetite-based Ferro fluid, the scaffold becomes a soft ferromagnetic material; application of internal magnet pins or external magnet ring can fix the scaffold at the site.