

STEM CELL AND TISSUE ENGINEERING – THE CHALLENGE OF IMITATING NATURE

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Tissue Engineering

As we sail through this early part of the new millennium, it is important to look back and see where we have been in the arena of cell and tissue banking with regards to its applications in tissue and organogenesis. Only with this perspective is it realistic to look toward the future and imagine what is possible.

Tissue engineering will ultimately have a more profound impact than we can now imagine. It not only will modify the practice of medicine and help elucidate mechanisms of developmental biology, but also has the potential to influence economic development in the industry of biotechnology more than any single advance in science or medicine during the last several decades (1)

Efforts to regenerate lost tissues morphological structure and regain complex specialized function were made possible only after advances in associated fields of cell and molecular biology and biomaterial sciences. Consequently, modern tissue engineering was not possible, or even feasible, until advances in cell biology enabled the large-scale production of commercially available enzymes and nutrients to isolate a large number of cells and nourish them in an incubator. As we know, biologic tissues consist of the living cells, the extracellular matrix and the signaling systems which are brought into play through differential activation of genes or cascades of genes whose secreted or transcriptional products are responsible for tissue building and differentiation. This phenomena brought us to the well described tissue engineering triad that consist of firstly, living cells, secondly, the biomaterial matrix or scaffold and thirdly, the signaling mechanisms coming from growth factors

and hormones. It is now proven that the use of living cells will result in a higher degree of tissue function than the use of chemotactic agents, growth factors or hormones to stimulate development of tissues and organs. Indeed, the ability to isolate, culture, investigate and experiment, and safely store cells from many different specialized tissues has existed for only a few decades. Even today, in-vitro multiplication of certain cell types such as nervous tissues and dental organs has been achieved with minimal success.

Early approaches to reintroducing cells into a recipient were quite simplistic and our personal experiences as well as that of others showed that those efforts usually failed. Cells were initially injected as free suspensions in the hope that they would randomly engraft.

A further challenge to the large-scale development and applications of tissue engineering is the immunologic barrier. Improvements in the understanding of immunology and the ability to trick the host into thinking foreign cells are “self” may ultimately allow for implantation of allograft or even xenograft cells to generate functional tissue. Unfortunately, at this time in history, the development of a universal donor cell type that can be used to construct the framework of a commercially available cell / polymer construct that will meet the needs of any recipient is still a dream.

Over the last 10 years of serious efforts undertaken at the Tissue Bank in developing processed biological tissue grafts and followed thereafter by seeding living cells into them, we have now learned and shared with others several basic concepts, the most important being “never fool Mother Nature”. In this respect, many efforts have given the highest degree of success when they have mimicked nature. What we found scientifically is

Figure 1 : Human stem cells that have been isolated

Type	Source	daughter tissue
Embryonic	Embryo or fetal tissue	all types
Hematopoietic	Adult bone marrow	blood cells, brain
Neuronal	Fetal brain	neurons, glia
Mesenchymal	Adult bone marrow	muscle, bone, cartilage

only a minute amount of all the processes related to the organization, development and function of living systems. The other basic concept of health is that the human body heals itself. In this respect, the physician do nothing more than support a patient’s vital functions by optimizing the environment most conducive to healing. They remove necrotic debris, protect the wound environment, improve oxygen supply and bring in more nutrients necessary for tissue building and healing. In tissue engineering, we strive to achieve exactly the same goal. Tissue engineering efforts are focused on the microenvironment as opposed to the macroenvironment being manipulated in traditional health care.

The critical factor of utmost importance in achieving such goal is the source of cells to be utilized. Several studies have suggested that more immature cells are able to multiply to a higher degree in vitro than fully differentiated cells of specialized tissues (2). In contrast to the in vitro multiplication of fully differentiated cells, these immature or progenitor cells can be induced to differentiate and function after several generations in vitro. They also appear to have the ability to differentiate into many of the specialized cells found within specific tissues as a function of the environment in which they are placed. In this respect, the stem cell will be the cell of choice in the journey of tissue engineering.

Stem Cell Technology

Research on stem cells is unfolding the truth about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. This promising area of science is also leading scientists to investigate the possibility of cell-based therapies to treat disease, which is often referred to as regenerative or reparative medicine. Stem cells have two important characteristics that distinguish them from other types of cells. First, they are unspecialized cells that renew themselves for long periods through cell division. The second is that under certain physiologic or experimental

condition, they can be induced to become cells with special functions such as the beating cells of the heart muscle or the insulin-producing cells of the pancreas.

In the issue of cell selection for tissue engineering, there is considerable interest in the use of stem cells, the “mother” cells within the body, as a primary source for therapies based on cell and tissue replacement (3). The excitement about stem cells reached a new height with the isolation of the first lines of human embryonic stem cells in 1998.

There are a variety of different stem cells as shown in figure 1. The embryonic stem cells are of special interest since they are pluripotent, ie. capable of differentiating into many cell types, and perhaps are even totipotent, ie. capable of developing into all cell types.

The two kinds of stem cells from human are embryonic stem cells and adult stem cells. Human embryonic stem cells lines are developed from embryos created for infertility purposes through in vitro fertilization procedures and when they were no longer needed for that purpose, they were donated for research with informed consent of the donor. Adult stem cells on the other hand have been identified in many organs and tissues. Rather unfortunately, there are a very small number of adult stem cells in each tissue. These stem cells are thought to reside in a specific area of each tissue where they remain quiescent (non dividing) for many years until they are activated by disease or tissue injury. The adult tissues reported to contain stem cells include brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin and liver.

Although we are quite a long way from being able to work on embryonic stem cells due to ethical cause, there are already companies working with stem cells in the context of tissue engineering. In this case they are using mesenchymal (adult) stem cells and the applications on which they are focusing are primarily in the orthopaedic area.

To take full advantage of stem cell technology, it will be necessary to understand how a stem cell differentiates into a tissue-specific cell. This requires knowledge not just about the molecular pathways

of differentiation, but even more importantly the identification of the combination of signals leading to a stem cell becoming a specific type of differentiated tissue cell. Only with this will it be possible to channel a stem cell, for example, into an endothelial cell for use in a blood vessel substitute as compared to a hepatocyte for a tissue-engineered liver (4).

The next challenge in imitating nature is to develop a model in which these cells are organized in a three dimensional-architecture and with functional characteristics such that a specific tissue is mimicked. This design and engineering of a tissue like substitute is a challenge in its own right (5). It must include the development of cost-effective manufacturing processes. These must allow for a scale-up from making one at a time to a large production quantity that is economical and available for routine use. Much of the work on manufacturing technology has focused on bioreactor technology. A bioreactor simply represents a controlled environment - both chemically and mechanically - in which a tissuelike construct can be grown. The Massachusetts Institute of Technology MIT and Georgia Tech have large research efforts focused on bioreactor technology (6). Although it is generally recognized that a construct, once implanted in the living system, will undergo remodeling, it is equally true that the environment of a bioreactor can be tailored to induce the in vitro remodeling of a construct so as to enhance characteristics critical to the success achieved following implantation. Thus, the manufacturing process can be used to influence directly the final product and is part of the overall process leading to the imitation of nature.

The final challenge is presented by moving a tissue engineering product concept into the living system. In this phase, our experience start with transferring in-vitro laboratory results to animal experiments and we found that there is a lack of good animal models for use in the evaluation of a tissue-engineered implant. The engineered implant should also be immune acceptable and biocompatible.

Therefore the primary issues in tissue engineering today revolve around cell technology, construct technology and integration into the living system. Among these three puzzles, cell technology play the key role in meeting the challenge of imitating nature. Adult stem cell research may give promising answers to solve these problems and the closest opportunity for us at the Tissue Bank is the cord blood collection. Cord blood is defined as blood

contained within the umbilical cord in the contiguous placental circulation. Collection of cord blood for the express purpose of harvesting stem cells shall be performed in a manner which would not alter the delivery of the infant, would not increase the likelihood of any adverse reaction in the infant or mother, and / or would not preclude appropriate medical management of the infant or mother, including collection of cord blood diagnostic specimens. Over the last 10 years, the Tissue Bank has been collecting amniotic membranes from placenta donated by mothers for the development of biological wound dressings. All the placenta donors have to go through routine screening for organ and tissue donation prior to retrieval of the amniotic membranes. Thus the process of collection, processing and storage of cord blood stem cells will be an extension of the current amniotic membrane procedure albeit extra training will be needed for the attending medical technologist and scientist. This will undoubtedly revolutionize and place tissue engineering research at the competitive edge.

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