Pharmaceutical Research, Vol. 14, No. 7, 1997

Commentary

Tissue Engineering: A New Field and Its Challenges

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Received April 8, 1997; accepted April 21, 1997

KEY WORDS: tissue engineering; cell transplantation; polymers.

Tissue loss or organ failure is one of the most tragic as well as costly problems in human health care. It has been estimated that annual U.S. health care costs associated with tissue loss or organ failure exceed 400 billion dollars. Currently, the major approaches to tissue or organ loss are either reconstructive or transplantation surgery, or the use of mechanical devices (e.g. kidney dialysis machines). Surgical reconstruction can result in long-term problems. For example, colon cancers often develop after surgical treatment of incontinence because urine may enter the colon. Transplantation is currently limited by increasing donor shortages. 30,000 deaths result from liver disease annually but only 2,000 to 3,000 transplants are performed each year. Finally, mechanical devices cannot perform all of the functions of a single organ and therefore cannot prevent progressive patient deterioration.

To address these problems, a new field, known as tissue engineering, has emerged. Tissue engineering is an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function (1). Three general strategies have been adopted for the creation of new tissue:

1) Isolated cells or cell substitutes. This approach avoids the complications of surgery, allows replacement of only those cells that supply the needed function, and permits manipulation of cells before infusion. However, this approach is limited in that the cells may not maintain their function for long time periods *in vivo*, and immunological rejection can occur.

2) Tissue-inducing substances. The success of this approach depends on the discovery, purification, and large-scale production of appropriate signal molecules, such as growth factors. In many cases, the development of methods to deliver these molecules to their targets (e.g. using controlled release polymer systems) will be critical.

3) Cells placed on or within matrices, most commonly in polymer matrices. This is the most widely used approach. In one case, in what are considered closed systems, the cells are isolated from the body by a membrane that allows transport of nutrients and wastes but prevents large entities such as antibodies or immune cells from destroying the cell transplant. These systems can be implanted into the recipient or used as extracorporeal devices. In another case, in what can be considered an open system, cells attached to matrices are implanted and become incorporated into the body (Fig. 1). The matrices are

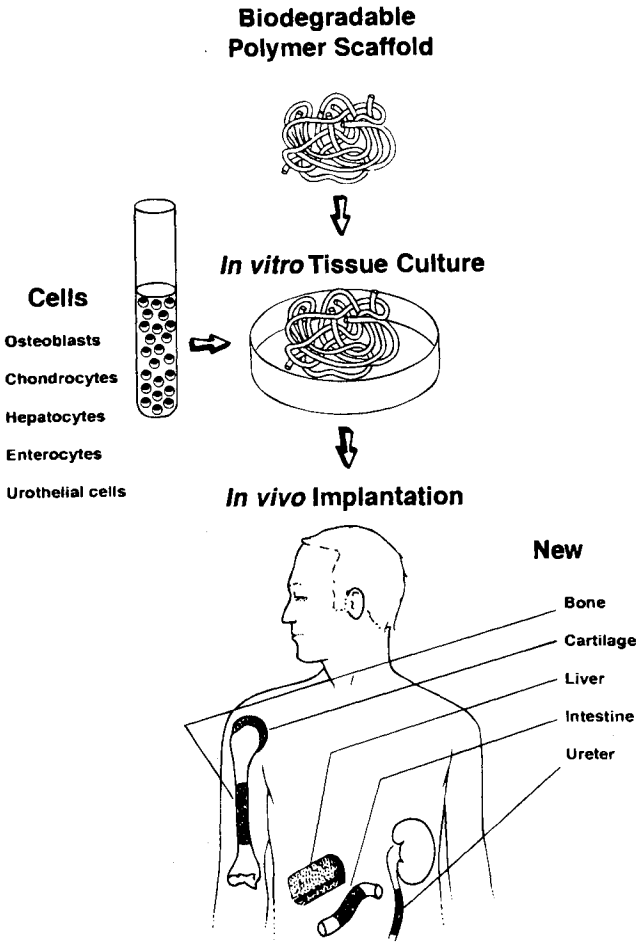

Fig. 1. In one major approach to tissue engineering, three-dimensional highly porous scaffolds composed of synthetic polymers serve as cell transplant devices. (Used with permission from Science (1).)

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0724-8741/97/0700-0840$12.50/0

fashioned from natural materials such as collagen or, most commonly, from synthetic polymers. Immunological rejection may be prevented by immunosuppressive drugs or by using the patient's own cells.

In the past few years, enormous progress has been made in tissue engineering (2). Several new types of artificial skin based on collagen-glycosaminoglycan composites, or skin (or skin-like) cells placed on synthetic or natural polymers have been approved by the U.S. Food and Drug Administration (FDA) or will be shortly. Insulin producing cells encapsulated within polymer membranes have begun to be tested in clinical trials as have extracorporeal approaches of encapsulating animal liver cells in hollow fibers for patients with liver failure to serve as a "bridge to transplant" while the patient is waiting for a new liver. Clinical trials of tissue engineered cartilage are ongoing, as are approaches for placing encapsulated cells in the brain to treat neurologic problems.

The challenges in tissue engineering are many. Biomaterials, which serve as a support for mammalian cells, represent a major area of future research. Natural materials (such as collagen) are advantageous in that they contain information (for example, particular amino acid sequences) that may facilitate cell attachment or maintenance of differentiated function. However, many natural materials suffer batch-to-batch variations or scale-up difficulties. Synthetic polymers, on the other hand, allow precise control over molecular weight, degradation time, hydrophobicity, and other attributes, yet they may not interact with cells in a desired manner. Recently, the advantages of both natural and synthetic polymers have been combined by synthesizing degradable polymers containing informational amino acid sequences from natural polymers (3). The discovery of molecules that can regulate cell behavior and the development of materials that incorporate the information containing sequences of such molecules represent major areas of future research. Polymer processing is another important area. Many implants will need to be made of composite materials or highly porous structures; methods of manufacturing such implants reproducibly may be crucial to their successes. An interesting development is the application of three-dimensional printing to create complex tissue structures (4).

The creation of controlled release systems, which deliver molecules for long time periods, will be important in administering numerous tissue-inducing factors (e.g. bone morphogenic proteins), growth factors, and angiogenesis stimulators (5). Cell preservation is another important issue. Cryopreservation has been used successfully for certain cells, but procedures need to be broadened and developed so that cell banks can be created for many different tissues. Another important area is the design of cell culture systems to produce engineered tissues. Large-scale cell bioreactor systems are critical to ensure proliferation of mammalian cells in vitro prior to transplantation and to solve nutrient transport issues (6). Sterilization of the tissue engineered system is also critical. In addition, advances in immunology and molecular genetics may someday contribute to the design of cells or cell transplant systems that are not rejected by the immune system. Finally, lessons on how tissues are able to regenerate will be valuable in developing optimal tissue engineering strategies (7,8).

Finally, progress in tissue engineering may be important to the success of ex vivo gene therapy. For example, in many potential gene therapy applications, target cells are removed from the patient's body, exposed to the viral gene delivery system and returned to the patient to achieve cells capable of producing the desired gene therapy product (9). Tissue engineering approaches involving polymer scaffolds which have large surface to volume ratios capable of supporting large cell numbers may be important in optimally implanting large numbers of genetically engineered cells to patients.

In summary, tissue engineering represents a field of enormous promise and one in which there should be many exciting future developments (10). However, interdisciplinary research and discoveries in many areas of science will be important in achieving such goals.

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