Prospects for Organ and Tissue Replacement

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A large fraction of the nation’s health care costs are attributable to tissue loss or organ failure, and approximately 8 million surgical procedures are performed annually in the United States to treat these disorders. Current treatment of organ failure or tissue loss involves transplantation or surgical reconstruction or mechanical devices such as kidney dialyzers. These therapies have revolutionized medical practice but have limitations. Transplantation is restricted by the donor shortage—more than 70,000 patients are currently awaiting organ transplantation, but fewer than 11,000 donors (cadaveric and living) are available annually. Donor shortages increase every year, and many patients die while waiting for needed organs. Mechanical devices cannot perform all of the functions of a single organ and therefore provide only temporary benefit. With the progressive aging of the population, age-related degeneration of organs will increase in the future. Thus, the scientific and medical communities are working in multiple areas to develop new strategies for treatment of organ and tissue failure.

Historical Advances

The modern age of organ replacement began when Kolff and Berk, a physician and an engineer, and colleagues published “The Artificial Kidney: A Dialyzer With a Great Area” in 1944. These investigators reported the successful dialysis of a uremic patient for 26 days using a device that consisted of 30 m of cellophane tubing wound around a rotating drum. Murray and colleagues subsequently began the era of solid organ transplantation by performing the first successful kidney transplant between identical twins in 1954 and by implanting the first renal allograft in 1959. Heart and liver transplantation followed soon thereafter—the first human heart transplant was reported in 1967. Artificial heart devices were developed in the 1970s, and the first successful implantation in humans occurred in 1982 in a patient who survived for 112 days with an artificial heart. Since the 1950s, the sophistication of life-sustaining devices has increased with the evolution of extracorporeal membrane oxygenators, ventricular-assist devices, and automatic implantable cardiac defibrillators. For organ transplantation, organ preservation strategies (eg, University of Wisconsin and Euro-Collins solutions) and immunosuppressive regimens (eg, cyclosporine and tacrolimus) have enhanced graft preservation and allograft survival.

Damage or loss of a tissue or organ is common, costly, and tragic. Advances in mechanical artificial organs and organ transplantation have improved the treatment of organ failure, and advances in molecular immunology, tissue engineering, and stem cell biology offer the promise of even better therapeutic modalities for treating organ failure in the future. Enhancement of immune tolerance of transplanted tissues, improved understanding of cellular differentiation and tissue development, and advances in biomaterials may enable the de novo creation of implantable tissue and organs for transplantation. Innovative techniques for prevention and treatment of tissue loss and organ failure should improve the quality and length of life.

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While these efforts will not increase the organ pool per se, they should improve transplantation outcome and thereby reduce the substantial number of recipients who are awaiting retransplant. The use of xenograft organs that are derived from porcine sources may increase the organ pool eventually, but substantial scientific and immunologic hurdles currently limit their use.8,9 Development of synthetic devices to replace organ function appears to have reached a zenith. Compact devices that serve highly specialized functions, such as pacemakers, internal defibrillators, and insulin pumps, have excellent long-term reliability. More complex and lifesustaining devices, such as ventricular-assist devices,10 intra-aortic balloon pumps, and intravenous oxygenators,11 primarily serve bridging functions for patients awaiting definitive surgical intervention and may never be suitable for permanent implantation.

Limitations in the cadaver organ pool and the probable finite potential of mechanical organ replacements have spurred research into alternative strategies to develop new organs. Advances during the last 3 decades, especially in genetic engineering, stem cell biology, and tissue engineering should, in the long term, increase the pool of available tissues and organs for transplantation.

Current Research Activities

Efforts to prevent ischemia-reperfusion injury in donor organs range from antibody-mediated blockade of neutrophil adhesion to donor cell surfaces to gene transfection of the organ during preservation and transport.12 Transfection strategies involve the use of genes such as superoxide dismutase and bcl-2 to decrease cellular injury in allograft tissues. Immunotherapy for transplant recipients may be improved by induction of costimulatory blockade, in which recipient T cells are rendered dormant and unable to mount an immune response to donor antigens.13,14

Engineering of replacement tissues from autologous cells cultured on biocompatible synthetic or natural substrates is now feasible (FIGURE).15 Engineered tissues such as blood vessels and bladder are functional in preclinical studies.16,17 Engineered skin and cartilage are currently in clinical use,18 urologic tissue is being tested in advanced clinical trials, and an engineered liver is being studied as a "bridge to transplant."19 Autologous corneas engineered from limbal epithelial cells are being evaluated in patients with corneal opacification or scarring.19

The potential of tissue engineering using undifferentiated stem cells to replace organ function is even more profound. For example, it may be feasible to use pancreatic stem cells to replace...
islet function in vivo. Neural stem cells from adult animals have been stimulated to form tissues from all 3 germ layers when cultured with collections of embryonic stem cells. Thus, pluripotent stem cells may one day provide a means of culturing many required tissues for a given individual.

Critical Efforts for the Next Phase

Techniques for promoting immune tolerance of solid organ allotransplants have markedly advanced in the last 25 years but remain an important area for research. Selective suppression of immunity to alloantigens, with retention of normal immune function against infectious pathogens, is the ultimate goal of transplantation immunology. Improved understanding of the specific processes that mediate allograft immune tolerance, perhaps combined with clonal T-cell deletion or costimulatory blockade, should increase graft survival and decrease patient morbidity.

Further advances in the engineering of tissue replacements from autologous cells are necessary before widespread applicability to multiple organ systems can become a reality. In vitro culture systems for tissue growth are at best crude approximations of the complex biochemical and physical environments that are experienced by cells during organ development and repair in vivo. Likewise, the synthetic substrates that serve as scaffolds for cell growth are imperfect approximations of extracellular matrices. Development of synthetic or natural “templates” for cell culture that mimic the architecture and surface biochemistry of the target tissue (eg, collagen and fibronectin) will enhance development of functional replacement organs. In addition, techniques that promote complex tissue microarchitectures such as capillary networks will be critical for growth of solid organs having adequate mass transfer characteristics.

Stem cell biology holds enormous potential for artificial organ development and transplantation. However, current techniques to isolate multipotent and pluripotent stem cells from adult tissues are complex and can result in mixed populations of cells. Factors that determine the lineage commitment of stem cells in vitro are only beginning to be understood. Advances in the understanding of stem cell isolation, culture, and lineage commitment will enhance clinical applications of these cells for use in organ replacement.

Research Opportunities and Forecast: Organ Transplantation and Tissue Engineering

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duce totipotent cells from somatic nuclei that are transferred into enucleated oocytes^{20,21} may produce cellular clones that enable the growth of new tissues both in vitro and in vivo.

Elucidation of the control mechanisms that determine stem cell differentiation, in parallel with the development of tissue engineering strategies to culture ever more complex organs such as the kidney,^{22} may lead to the creation of autologous “spare parts” that can be transplanted into patients. There has been much progress since 1944 when Kolff and Berk described their “di- alyser with a great area”^{5}; the future should prove to be even more revolutionary.

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**REFERENCES**


