Regenerative implants for cardiovascular tissue engineering

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A fundamental problem that affects the field of cardiovascular surgery is the paucity of autologous tissue available for surgical reconstructive procedures. Although the best results are obtained when an individual's own tissues are used for surgical repair, this is often not possible as a result of pathology of autologous tissues or lack of a compatible replacement source from the body. The use of prosthetics is a popular solution to overcome shortage of autologous tissue, but implantation of these devices comes with an array of additional problems and complications related to biocompatibility. Transplantation offers another option that is widely used but complicated by problems related to rejection and donor organ scarcity. The field of tissue engineering represents a promising new option for replacement surgical procedures. Throughout the years, intensive interdisciplinary, translational research into cardiovascular regenerative implants has been undertaken in an effort to improve surgical outcome and better quality of life for patients with cardiovascular defects. Vascular, valvular, and heart tissue repair are the focus of these efforts. Implants for these neotissues can be divided into 2 groups: biologic and synthetic. These materials are used to facilitate the delivery of cells or drugs to diseased, damaged, or absent tissue. Furthermore, they can function as a tissue-forming device used to enhance the body's own repair mechanisms. Various preclinical studies and clinical trials using these advances have shown that tissue-engineered materials are a viable option for surgical repair, but require refinement if they are going to reach their clinical potential. With the growth and accomplishments this field has already achieved, meeting those goals in the future should be attainable. (Translational Research 2014;163:321–341)

Abbreviations: BM-MNC = bone marrow-derived mononuclear cell; BM-MSC = bone marrow-derived mesenchymal stem cell; ECM = extracellular matrix; EPC = endothelial progenitor cells; FDA = Food and Drug Administration; iPS = inducible pluripotent stem cell; MSC = mesenchymal stem cell; PCL = poly-E-caprolactone; PGA = polyglycolic acid; PGS = poly-glycerol sebacate; PLA = polylactic acid; SIS = small intestine submucosa; SMC = smooth muscle cell; TAH = total artificial heart; TEHV = tissue-engineered heart valve; TEVG = tissue-engineered vascular graft

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A fundamental problem that affects all fields of surgery is the paucity of autologous tissue available for surgical reconstructive procedures.[1] When a surgeon removes a tissue that is diseased or damaged, or when a surgeon replaces a tissue that is congenitally absent, the best results are obtained when an individual's own tissues are used for the surgical repair. When this is not possible the surgeon is forced to use alternative biomaterials, and usually selects from either prosthetic, man-made synthetic materials or from biologic materials derived typically from allografts or xenografts. Prosthetic materials have the advantage of ready "off-the-shelf" availability, but frequently have problems related to biocompatibility and the fact that they never become integrated completely into the host. Biologic materials are typically more biocompatible than synthetic prosthetic materials; however, they are still a source of rejection and require treatment with immunosuppressive agents, as in the case of organ transplantation, or they are treated to reduce their immunogenicity and to allow implantation without immunosuppressive agents. This is usually accomplished using either cryopreservation techniques or tissue fixation methods. Alternatively, decellularization methods can also be used. Such treatments either remove the cellular component of the tissue or render the cells nonviable, which worsens the durability of these products. The use of autologous tissue outperforms currently available prosthetic or biologic materials designed for use in surgery and is always preferable when autologous tissue is available in adequate supply.[1]

Tissue engineering is a multidisciplinary science that attempts to create living biomaterials from a patient's own cells. One method of tissue engineering uses a 3-dimensional scaffold that serves as a site for cell attachment and provides space for neotissue formation.[2] The scaffold can serve as a template for neotissue development. Tissue engineering attempts to exploit the cells' reproductive potential and harness the body's innate capacity for healing and regeneration. The goal of tissue engineering is to create living, autologous neotissues that can be used to repair or replace tissues that are diseased, damaged, or congenitally absent.[2] The central hypothesis of tissue engineering is that the tissue-engineered construct will perform more like an individual's own tissue and less like a prosthetic or biologic material.

Departing from more traditional approaches to treat lost organ or tissue function, tissue engineering seeks to replace or restore function to diseased or damaged tissues and organs through implantable devices. From its onset, tissue engineering has been a multidisciplinary field that combines efforts of basic scientists, engineers, and clinicians.[2] Through trial and error, these researchers established 3 major approaches toward tissue engineering implants for regeneration: implanting neotissue derived from cells, implanting engineered matrices, or implanting cells combined within matrices.[3] The first tissue-engineered cells were implanted in the belly of a pig in 1933.[3] Tissue-engineered skin matrices, consisting of cultured epithelial sheets or fibroblast gels seeded onto polymer scaffolds, were created during the late 1970s and the early 1980s.[4-6] During the late 1980s, the first tissue-engineered implantation studies were conducted consisting of the seeding of pancreatic islet cells onto a synthetic polymer implanted subsequently into animals.[7] By the 1990s, tissue engineering had established itself as a recognized field.[2]

Tissue engineering techniques have been used to create a host of tissue types with varying degrees of success. From a translational perspective, dermatologic applications in the form of tissue-engineered skin substitutes are furthest along, and a variety of commercially available products are used commonly in the clinic.[8] Other tissues such as nervous tissues have proved significantly more challenging to create using tissue engineering methodology and are therefore not yet available for clinical use. For the purpose of this review, we focus our discussions on tissue-engineered cardiovascular implants, which provide examples of a variety of tissue engineering applications along the translational spectrum. In this way, we can provide an accurate snapshot of the current state-of-the-art technologies and, during the process, provide an overview of the use of implants in the field of tissue engineering.

The field of tissue engineering is an applied science that approaches complex problems by deconstructing them into multiple, more simple components. The development of most tissue engineering applications uses this paradigm beginning by creating small pieces of tissue, then developing more complex functional tissue components, before finally attempting to create entire bioartificial organs. This "pieces, to parts, to whole organ" experimental design motif is a common thread that runs throughout most tissue engineering projects discussed in this review. It provides a rational framework for designing any tissue engineering application.

Tissue engineering of cardiovascular structures from blood vessels to heart valves, and even whole hearts, has undergone great strides during the past decade. Historically, the foundation for regenerative cardiovascular implants can be traced back to C.C. Guthrie[9] who, in 1919, stated that for repairing a blood vessel "an implanted segment need only temporarily restore mechanical continuity and serve as a scaffolding or bridge for the laying down of an ingrowth of tissue derived from the host."[9(p187)] The defining characteristics of regenerative cardiovascular implants have not

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