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Acellular Biomaterials: An Evolving Alternative to Cell-Based Therapies

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Abstract

Acellular biomaterials can stimulate the local environment to repair tissues without the regulatory and scientific challenges of cell-based therapies. A greater understanding of the mechanisms of such endogenous tissue repair is furthering the design and application of these biomaterials. We discuss recent progress in acellular materials for tissue repair, using cartilage and cardiac tissues as examples of applications with substantial intrinsic hurdles, but where human translation is now occurring.

Although the promise of cell therapy for tissue regeneration is exciting, troublesome details persist, such as cell selection, delivery, viability, and phenotypic stability, in addition to timing of treatments, regulatory issues, and high costs (1, 2). Indeed, such concerns have led many to consider that effective and readily available cell-based therapies are years—if not decades—away from becoming a cost-effective clinical reality for many applications.

With this in mind, the field of acellular biomaterials is advancing and becoming a feasible alternative to cell-based therapies. Rather than only acting as fillers for tissue defects, materials are now designed to interact with local tissues and cells to alter the normal healing processes after disease or injury. This field has evolved from passive mechanical support to active approaches that truly harness and direct endogenous repair processes. In this Perspective, we briefly cover the evolution of the field of acellular biomaterials, including recent advances that use biomaterials to modulate local cell and tissue responses. This therapeutic concept is then further highlighted in the context of two specific tissues, cartilage and cardiac tissue. Unlike some tissues in the body (such as bone), both of these tissues exhibit a limited propensity for natural tissue regeneration, and new translatable therapies are needed to treat growing patient populations. In both cases, therapies based on the delivery of acellular materials have moved beyond the laboratory and into clinical trials; thus, these examples represent the state of the art in acellular therapies.

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THE HEALING RESPONSE AND MATERIAL EVOLUTION

In most organs, the response to tissue loss or injury is a healing process to maintain the integrity and function of the surviving tissue. However, regeneration of functionally integrated tissue is rarely part of the response to injury in adult mammals, especially under conditions of low cellularity, poor vascular supply, and a reduced size of endogenous progenitor pools, such as with disease or aging. Acellular biomaterials have emerged as an alternative to cell therapy for treating these damaged tissues (Fig. 1). Traditional acellular biomaterials (e.g., metal and plastic joint prostheses) were meant to fill a space and function mechanically without cells. As the field began to conceive of materials as enablers of biologic tissue replacement, biomaterials transitioned toward formulations that could also be infiltrated by cells. Early innovation in this area included the delivery of growth factors to stimulate cellular behavior and matrix production—most notably, collagen delivery vehicles containing bone morphogenetic proteins (BMPs) to enhance bone tissue repair (3). These studies set the stage for synthetic acellular materials, such as porous foams (4) and fibrous scaffolds (5) that guide tissue formation.

These founding principles, along with an ever-advancing understanding of human tissue repair mechanisms, have likewise fomented new classes of emergent acellular biomaterials with advanced functionalities. For example, biologically derived decellularized matrices that retain many of the matrix components and growth factors found in native tissues—yet are acellular in their processed form—are being extensively investigated (6). Indeed, commercial products based on small intestinal submucosa are now used clinically to augment soft tissue repair, and their mechanism of action is being elucidated and optimized (7). These emergent acellular systems act via numerous means, including to endogenously alter the inflammatory cascade, to preserve viable cells after injury, or to recruit and retain progenitor cell populations through chemotactic signals (8).

REPAIRING CARTILAGE TISSUE

Cartilage is an avascular load-bearing tissue in joints that consists of chondrocytes distributed throughout a dense extracellular matrix. Cartilage has a very limited repair capacity in adults, and few treatments have been developed to enhance repair after injury or with disease (9). Current clinical approaches include transfer of tissue (mosaicplasty), delivery of cells [autologous chondrocyte implantation (ACI)], or introduction of endogenous progenitors into the defect site from the underlying bone marrow (microfracture). Each of these methods is limited by damage to native cartilage or in the quality of repair tissue that forms, and many patients will likely progress to total joint replacement.

Cell therapy approaches for cartilage repair have been on the market for more than a decade (pioneered by Genzyme Biosurgery); cells are simply injected into a defect alone or implanted with a biomaterial carrier (10). The major limitations to these approaches are that potentially healthy tissue is damaged to isolate the cells or tissue fragments and most involve substantial costs associated with cell expansion in a GMP facility. For stem cell therapy, our limited understanding of stem cells with respect to terminal differentiation and

hypertrophy (formation of unwanted bonelike phenotypes) and inferior properties of formed tissue are limiting translation (11).

Given limitations in cell-based approaches, a newer focus in cartilage repair is promoting the activity of endogenous progenitor cell sources through acellular biomaterials (Fig. 2). In particular, autologous matrix-induced chondrogenesis (AMIC) is the combination of the original microfracture technique (the release of blood and marrow from the subchondral tissue into the defect) with acellular scaffolds (12). The majority of these scaffolds are the same as those being used for cell-delivery approaches, including collagen membranes or scaffolds (VeriCart by Histogenics, Chondro-Gide by Geistlich, Chondromimetic by TiGenix), hyaluronan meshes (Hyalofast by Anika Therapeutics), and porous synthetic scaffolds (TrueFit by Smith & Nephew). These materials are designed to attract cells through chemotaxis to degradation products and to structurally stabilize the clot to initiate a more robust repair response when compared with microfracture alone. It is acknowledged that this approach may not produce tissue that is identical to that of native cartilage; however, the formed tissue may forestall further damage, resulting in clinical success for the patient.

One formulation, Chondrotissue (Bio- Tissue AG), incorporates biological components, such as serum and hyaluronic acid, which may participate in the recruitment of cells to the site (for example, homing of bone marrow cells) in addition to those that are released with microfracture (13). Alternatively, a variety of hydrogels are now being explored for AMIC procedures, where gels fill the defect after mixing with either whole blood or bone marrow released during the microfracture procedure. The gels include biologic compositions such as chitosan (BST CarGel by Piramal Healthcare), synthetic compositions such as photopolymerized poly(ethylene glycol) (PEG) (Chondux by Biomet), and mixed compositions such as PEG with fibrinogen (GelrinC by Regentis Biomaterials).

In the above procedures, pain relief and some functional restoration of the joint have been documented in humans, and the regenerated tissue is generally superior in matching components and organization of native tissue to that seen with microfracture alone (14). In the laboratory stage of development, materials are being modified to incorporate growth factors and other molecules so as to improve the repair process through enhanced recruitment and differentiation of endogenous progenitor cell pools (15, 16). In one application, transforming growth factor- β 3 was combined with a collagen-infiltrated porous biodegradable scaffold in order to chemoattract endogenous stem cells to resurface an entire joint surface in a rabbit (16). Similarly, such materials are designed to direct cell behavior after migration into the wound site or to attenuate local inflammation (8, 16). It should be noted that the addition of biologics, such as growth factors, may slow the regulatory process and undergo greater scrutiny than would approaches that deliver materials alone. Thus, the benefits of adding soluble factors need to outweigh the time and costs associated with development and translation.

TREATING PATIENTS AFTER MYOCARDIAL INFARCTION

Another clinical area in need of new materials-based treatment options is cardiac repair. The past decade witnessed mounting enthusiasm for cell-based therapies to treat myocardial loss resulting from acute myocardial infarction (MI) (17). However, early spectacular results in small animal models (18) have been difficult to reproduce, and regeneration of electromechanically integrated myocardium has never been achieved in humans or large animal models. Despite increasing research activity and funding, the ability to regenerate functional myocardium after MI is likely decades away. Thus, it is important to acknowledge other directions that may lead to functionally relevant therapies more quickly.

The therapeutic merit of regenerating myocardium as a treatment for MI seems obvious; but is it really? Of the more than one million Americans who suffer from MI each year, the vast majority of patients survive and initially have adequate cardiac function (19). Only with time do patients experience progressive ventricular dilatation and symptoms of heart failure, a maladaptive phenomenon termed ventricular remodeling (20). Immediately after MI, the affected region of myocardium stops contracting and experiences paradoxical bulging and stretching while the rest of that heart contracts. These phenomena alter myocardial stress distributions, perpetuate adverse ventricular remodeling, and may lead to heart failure. If the post-MI ventricle could be stabilized and functional loss prevented, there would be little need for myocardial regeneration in all but the largest infarcts.

Acellular biomaterials have been investigated to influence the post-MI remodeling process by altering infarct properties or by delivering therapeutics (Fig. 2) (21, 22). Materials tested to date have included both natural and synthetic hydrogels (alginates, fibrin, hyaluronic acid, decellularized tissues) and have been able to reduce infarct stretching and bulging, leading to normalization in myocardial stress distribution and attenuated ventricular remodeling (23). Many types of materials with wide-ranging properties and degradation behavior have been investigated, so a mechanistic understanding of the influence of these materials is still being developed, as well as translation into clinically relevant models of MI. However, interest in this therapeutic approach is high owing to the potential for developing percutaneous therapies to limit ventricular remodeling and prevent the onset of congestive heart failure. One example is the use of acellular alginate hydrogels injected into infarcted myocardium, which has translated into ongoing clinical trials (Ikaria, Clinical-Trials.gov Identifier: NCT01226563).

In addition to mechanical effects, biomaterials may be used for the local delivery of molecules that influence specific biologic processes associated with ventricular remodeling, such as apoptosis and angiogenesis, as well as for the recruitment of cells associated with wound healing and tissue repair (23). In one example, decellularized cardiac tissue, which has been reported to improve cell viability and promote differentiation, was delivered as a hydrogel into MI models in both rats and pigs to improve function, including using a percutaneous catheter delivery approach in a pig model (24). Toward the preservation of viable cells, self-assembling hydrogels have been designed to deliver factors such as platelet-derived growth factor (PDGF). Controlled delivery of PDGF in a rat MI model led

to improvements in ventricular function and a reduction in ventricular expansion when compared with that in untreated animals or with delivery of hydrogel alone (25).

In addition to providing structural support, acellular materials can enhance vascularization in ischemic myocardium through the release of angiogenic factors or attract stem cells through the local delivery of homing factors. As an example, combinations of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) have been delivered from alginate hydrogels in rats (26). VEGF alone has been delivered from nanofibrous scaffolds to alter local vascularization and improve functional outcomes in large-animal models (27). Toward the recruitment of stem cell and progenitor cells, molecules including stromal-derived factor-1 α (SDF-1 α) have been delivered from peptide-based hydrogels and have enhanced left ventricular (LV) function in rats (28). Additionally, hyaluronic acid (HA) gels have been used to deliver SDF-1 α locally to infarcted cardiac tissue in mice, and both the released molecule and the HA degradation product stimulated recruitment of mobilized stem cells (29).

The delivery of molecules to recruit stem cells from endogenous tissues could also play a major role in cardiac repair in humans, avoiding the complications associated with identifying and characterizing the appropriate cell source for translation. Yet, future clinical trials will be needed to confirm translation of these observations from animals to human.

TRANSLATING ACELLULAR TECHNOLOGIES

It is not a simple process to translate any preclinical therapeutic strategy to safe and effective treatment modalities for human patients. As with any new therapy, this challenge is manifest in biomaterial-related tissue repair studies by the difficulty in predicting clinical success with preclinical data; reproducing findings in small animals in more clinically relevant, large-animal models; balancing innovation with risk; and ensuring that the appropriate intellectual property and business model are considered (30). Additionally, the ease of translation depends on various factors in the therapy, such as prior use of the biomaterial in people, and the incorporation of various biologics, such as growth factors (29).

However, unlike cell therapy, the therapeutic goals of acellular biomaterial therapies are of en more clearly understood. As reviewed recently by Pashuck and Stevens, there are numerous routes to translation and navigation of regulatory hurdles (31). Most of the acellular therapies covered here would fall under the Center for Devices and Radiological Health of the Office of Combination Products at the U.S. Food and Drug Administration, but it depends on the primary mechanism of action. Additionally, biomaterial-based therapies are likely to enter the market through premarket notification and the 510(k) approval process if they are similar to previously approved devices or through premarket approval if considered potentially high-risk, a route with added costs and scrutiny. Regardless, the translation path should be considered in any new therapy development (30).

EVOLUTION CONTINUES

The work presented in this Perspective only represents a fraction of the advances that have been accomplished and are currently being developed in this field. It is important to note

that cell-based therapies that regenerate tissues may ultimately be needed, particularly in patients with systemic pathologies that compromise native tissue repair responses (such as diabetes and other diseases that limit wound repair) or those who suffer from extensive tissue loss. However, in many applications in which the goal is to improve patient outcomes (such as limiting joint pain and preventing the onset of congestive heart failure) and eliminate the need for invasive surgical procedures (such as total joint replacements and heart transplants), acellular approaches may provide the clinical solution. As this field continues to evolve, including our understanding of how biomaterials alone may play a role in the healing cascade, new therapies are likely to move from the laboratory to the clinic.

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Fig. 1. The evolving roles of acellular biomaterials in tissue repair

The application of acellular biomaterials ranges from traditional approaches of promoting tissue formation through mechanical support or the delivery of growth factors, to current/ongoing approaches to vascularize and organize tissues, and to emerging techniques that modulate endogenous cellular processes and recruitment.

Fig. 2. Cartilage and cardiac tissues exemplify advances in acellular materials

Tissues damaged through traumatic and disease processes undergo adverse responses if left untreated. **(A)** In cartilage tissue, small lesions can progress to large areas of joint erosion and be accompanied by pain. Acellular, injectable gels and implantable scaffolds that recruit stem cells may improve tissue repair. In cardiac tissue, myocardial infarction initiates a cascade of events that leads to LV dilatation. **(B)** Acellular biomaterials can be used to alter the local stress profiles and to deliver therapeutic molecules.