Strategies for functional bioscaffold-based skeletal muscle reconstruction

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Abstract: Tissue engineering and regenerative medicine-based strategies for the reconstruction of functional skeletal muscle tissue have included cellular and acellular approaches. The use of acellular biologic scaffold material as a treatment for volumetric muscle loss (VML) in five patients has recently been reported with a generally favorable outcome. Further studies are necessary for a better understanding of the mechanism(s) behind acellular bioscaffold-mediated skeletal muscle repair, and for combination cell-based/bioscaffold based approaches. The present overview highlights the current thinking on bioscaffold-based remodeling including the associated mechanisms and the future of scaffold-based skeletal muscle reconstruction.

Keywords: Tissue engineering; regenerative medicine; bioscaffolds; extracellular matrix (ECM); volumetric muscle loss (VML); skeletal muscle reconstruction

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Introduction

The results of a clinical cohort study published in *Science Translational Medicine* (*STM*) described positive clinical outcomes following surgical implantation of an acellular bioscaffold-based approach for skeletal muscle reconstruction following volumetric muscle loss (VML) (1). A recent review of this study discussed potential mechanisms responsible for the constructive remodeling response (2). The overview presented herein expands upon these potential mechanisms and discusses next steps in scaffold-based skeletal muscle reconstruction.

Mechanisms of extracellular matrix (ECM) bioscaffold-based skeletal muscle reconstruction

Although the mechanisms responsible for ECM bioscaffold-based skeletal muscle remodeling following VML injury are only partially understood, the key processes involve fundamental concepts of mammalian physiology, tissue homeostasis, and the response to injury. Among these processes are the cell-signaling effects that result from ECM degradation including the concomitant release of embedded growth factors, cytokines and chemokines, and the release of bioactive matricryptic peptides (3-5). The products of ECM scaffold degradation serve to recruit stem/progenitor cells and induce a regulatory and constructive innate immune response (1,3-9). Each of these processes is discussed below.

ECM bioscaffold degradation

Bioscaffolds composed of ECM that are not chemically crosslinked typically degrade rapidly *in vivo*; i.e., within 75-90 days (10). Specifically, studies show that surgically placed ECM scaffolds derived from tissue such as porcine small intestinal submucosa and porcine urinary bladder become 60% degraded by 30 days post implantation and completely degraded by 90 days, though this rate is likely dependent upon factors including the source tissue from which the scaffold was derived, the form of scaffold (i.e., sheet, powder-pillow construct, hydrogel) and the use of crosslinking agents (10,11). During the degradation period, the scaffold becomes populated by host-derived

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mononuclear cells which facilitate the formation of site-specific functional host tissue that is histologically indistinguishable from native tissue. Scaffold degradation is mediated by, in fact dependent upon, the infiltrating macrophages which produce proteolytic enzymes that degrade the scaffold material (11-13).

ECM scaffolds have been degraded *ex vivo* by chemical and physical methods (14). Recent findings suggest that the degradation products of ECM are bioactive (4,15-17) and include antimicrobial activity (14,16), osteogenic activity (4), and chemotactic activity for progenitor and adult cell populations (3,15,17-20). These degradation products also strongly influence the host innate immune response (6,16,21-24). Stated differently, ECM bioscaffold degradation is desirable and necessary to realize the full potential of biologic processes that can support functional tissue reconstruction.

Endogenous cell recruitment by ECM bioscaffolds

Biologic scaffolds composed of mammalian ECM have been shown to be chemotactic for a variety of stem/progenitor cells. For example, $Sox2^+$ cells were shown to be present at the site of ECM implantation in an adult mammalian model of digit injury (3,18). This primitive stem cell population was found present only in digits that had been treated with ECM. ECM bioscaffolds also recruit multipotential cells. For example, bone-marrow derived cells were shown to participate in the remodeling of ECM mediated Achilles tendon repair (25). Specifically, in the preclinical Achilles tendon injury model, ECM scaffold explants promoted chemotaxis of progenitor cells after 3, 7, and 14 days of *in vivo* remodeling (20,26). ECM bioscaffolds recruit myogenic progenitor cells to sites of skeletal muscle injury. Host $CD133^+$ myogenic progenitor cells were found present at the site of ECM implantation in a canine model of musculotendinous junction reconstruction (27). The results of the study showed greater migration of progenitor cells towards tendons repaired with ECM scaffolds compared to tendons repaired with autologous tissue and uninjured normal contralateral tendon. ECM bioscaffolds recruit myogenic progenitor cells to sites of skeletal muscle injury. Degradation products from ECM bioscaffolds have been shown to be chemotactic for cells with myogenic potential including bone-marrow mesenchymal stromal cells (BM-MSCs), skeletal muscle myoblasts, and perivascular stem cells (PVSCs) *in vitro* (3,4,25,28,29). Myogenic perivascular stem cells (PVSC) were found at the site of ECM bioscaffold implantation in both mice and humans following VML (1). Degradation products of ECM bioscaffolds were also shown to induce mitogenic and chemotactic effects upon neural stem cell populations, a phenomenon that is of particular importance for the reconstruction of functionally innervated skeletal muscle tissue (30). Taken together these results suggest that ECM bioscaffolds are capable of recruiting a variety of cell-types, including those capable of contributing to myogenesis, to the site of implantation for skeletal muscle constructive tissue remodeling.

Modulation of the host innate immune response by ECM bioscaffolds

The host innate immune system, especially macrophages, plays a pivotal role in the host response to biomaterial implantation. In fact, macrophage depletion prevents the degradation of ECM biologic scaffolds *in vivo* (24). Macrophages have been shown to respond to many different implanted biomaterials, including those composed of polymers (31) and biologic proteins such as collagens and xenogeneic ECM (24,32). Non-degradable or synthetic biomaterials are typically associated with activation of the foreign body reaction including macrophage mediated foreign body giant cell formation and pro-inflammatory cytokine production (33,34). However, several recent studies suggest that regulatory macrophages can facilitate constructive and site-appropriate tissue remodeling in response to ECM bioscaffold implantation (8,9,24,35). Specifically, surgically placed ECM bioscaffolds have been associated with a constructive macrophage phenotype.

Macrophages within the context of the innate immune response have typically been regarded as mononuclear phagocytes responsible for propagating a pro-inflammatory response, antigen presentation, and the removal of cellular debris following acute tissue injury (36-38). However, macrophages are now recognized to have a much broader role in tissue development, homeostasis, and repair. These cells show remarkable phenotypic diversity and play a key role in immune regulation and tissue repair (12,39-45). Specifically, macrophages have been categorized according to their functional properties as either M1-like or M2-like (41,42). M1-like or "classically activated" macrophages propagate a pro-inflammatory response while M2-like or "alternatively activated" macrophages promote immunomodulation, anti-inflammatory effects, and regulate constructive tissue remodeling. The phenotype of responding macrophages has been found to be an important determining factor in

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the host response to an implanted biomaterial scaffold and its ultimate remodeling outcome (6,23). Surgically placed ECM bioscaffolds have been consistently associated with the constructive and regulatory M2-like macrophage phenotype (6,9,23). In fact, a recent study showed that degradation products of ECM bioscaffolds are able to directly promote the M2-like phenotype *in vitro* (8). The same study went on to show that ECM-polarized macrophages exert myogenic paracrine effects upon skeletal muscle myoblasts similar to traditional M2-like macrophages. Furthermore, ECM degradation products were shown to augment the chemotactic paracrine effects of macrophages for PVSCs and skeletal muscle myoblasts (8). This series of studies suggest that ECM bioscaffolds promote the M2-like macrophage phenotype, which is known to be essential for the promotion of efficient skeletal muscle regeneration in response to injury.

Five patient cohort study and limitations

The recently published cohort study showed that acellular ECM bioscaffolds promote stem cell mobilization and myogenesis concomitant with improved force production and functional task performance in patients suffering from VML (1). Ultrasound guided tissue biopsies taken from sites of ECM bioscaffold surgical placement showed the formation of myosin heavy chain positive skeletal muscle within the implant site. Histomorphology suggested that most of this skeletal muscle was present in discontinuous small islands of cells separated from adjacent healthy tissue by collagenous connective tissue. However, the distribution of these cells throughout both the center of the scaffold implantation site and near the interface with normal muscle tissue combined with the associated motor evoked potentials and/or improved force production suggests that the resulting remodeled tissue contributed to the improved functional outcomes. Histomorphology also showed the presence of collagenous connective tissue contiguous with all edges of the defect which could arguably contribute to, or interfere with, overall muscle function. The term "functional fibrosis" has been proposed (46), but any functional contribution would likely have to include a physical/mechanical continuity between proximal and distal remnants of normal muscle while simultaneously excluding inadvertent adhesion and attachments to surrounding muscle bodies, adjacent bone, and connective tissue.

The positive outcomes in the aforementioned study are partially attributed to an aggressive, targeted physical therapy regimen prescribed to all patients, which was implemented within 24-48 h after ECM bioscaffold implantation. The application of physiologic mechanical load (i.e., concomitant physical rehabilitation) during the ECM-remodeling period has been shown to promote favorable pre-clinical and clinical outcomes including an increased cellular infiltrate, more rapid and extensive neovascularization, more organized and aligned connective tissue matrix, and influence upon gene expression and cellular behavior (47,48). VML patients treated with ECM bioscaffolds were subjected to exhaustive physical therapy prior to bioscaffold implantation during which time they achieved a plateau in their performance. Physical therapy was resumed immediately following implantation, and strength and functional outcomes were shown to improve from 0% to 1,820% above the preoperative maximum values by 24-28 weeks after implantation (1). Physical rehabilitation has also been shown to promote progenitor cell proliferation and immunomodulation (49,50), both of which are key mechanisms of ECM-mediated remodeling.

While the present acellular ECM bioscaffold-based approach did not produce fully mature organized skeletal muscle tissue, the *de novo* formation of skeletal muscle islands could potentially be augmented by simultaneous delivery of myogenic stem/progenitor cell populations for the formation of continuous skeletal muscle fibers. Such a combination approach is worthy of investigation.

Future of scaffold-based skeletal muscle reconstruction

In addition to associated strict FDA regulatory restrictions, cell-based tissue engineering approaches are typically limited by chronic pro-inflammatory activation of the host immune system and failure of the cells to incorporate within host tissue, among others (51-55). Injected cells, lacking a scaffold material, are typically unable to redistribute throughout the injection site and do not migrate more than 200 μm *in vivo* (56). Intravenous (IV) cell delivery frequently results in unintentional cell engraftment within tissues such as the liver and spleen (57). Cell that are able to be adequately delivered to intended tissues are typically unable to engraft. In fact, it is widely accepted that myogenic stem/progenitor cell transplantation typically does not result in a significant engraftment of donor cells within host tissue. Favorable outcomes associated with cell-based skeletal muscle tissue engineering approaches are most likely associated with a paracrine effect of the donor

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cells upon the host injured microenvironment rather than by direct myogenesis from the delivered cells (58-63).

Recent preclinical rodent studies have shown that skeletal muscle progenitor cells delivered in concert with an ECM bioscaffold have the potential to obviate the above limitations (64,65). Specifically, the studies combine allogeneic muscle-derived cells (MDCs) and bladder acellular matrices (BAMs) which are then subjected to a period of ex vivo bioreactor mediated preconditioning prior to surgical placement. The most recent study showed that acellular BAMs were able to promote a 26% functional improvement while MDC seeded BAMs showed a 61% functional improvement in a rodent model of tibialis anterior (TA) VML (65). These studies suggest that although ECM bioscaffolds facilitate endogenous cell recruitment, it may be possible to augment this response with exogenous cell delivery.

Summary

Tissue engineering and regenerative medicine-based strategies for the reconstruction of functional skeletal muscle tissue have included cellular and acellular approaches. Recent clinical results in a small cohort patient study using an acellular bioscaffold-based approach showed positive clinical outcomes associated with significant functional improvements, but was limited by incomplete myogenesis as identified by histologic methods. Recent rodent studies have shown the ability of similar bioscaffolds to serve as a substrate for myogenic cells prior to, and following surgical implantation. Although optimal strategies for successful functional tissue engineering have yet to be identified, they likely will be a combination of cell-based and bioscaffold-based techniques.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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