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Chapter 8

The Role of Acellular Flowable Matrix in Tissue Regeneration

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Additional information is available at the end of the chapter

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1. Introduction

Wound healing is a complex dynamic biological process which has four partly overlapping phases: hemostasis, inflammation, proliferation and remodeling. These phases involve a large number of cell types, extracellular components, growth factors and cytokines. [1]

The extracellular matrix (ECM) of mammalian tissues has been used as a scaffold to facilitate the repair and reconstruction of numerous tissues. Such scaffolds are prepared in many forms including sheets, powders, and hydrogels. [2]

The ECM is a complex network structure that surrounds and supports cells. It is filled with ECM molecules like proteins and proteoglycans, which are secreted by the cells. Cell receptors bind both soluble and tethered signaling cues from the ECM environment, while simultaneously, cells send out signals to actively construct and degrade their microenvironment for remodeling. Thus, the ECM acts not only as a mechanical scaffold for the cells, but also a bioactive and dynamic environment that mediates cellular functions. [3,4,5]

It is highly desirable to synthesize scaffolds to mimic the structure and biofunctions of the natural ECM. [3,6,7,8]

2. ECM-like scaffolds

A widely-cited challenge in the field of tissue engineering is to provide a blood vessel network to facilitate oxygen, nutrient, biochemical and waste exchange for thick tissues beyond the range of diffusion. In the absence of a blood vessel network, necrosis will quickly occur beyond the surface of any implanted, metabolic tissue. [9,10]

Extracellular matrix (ECM) proteins, such as fibronectin, laminin and collagen IV, play important roles in many cellular behaviors, including cell adhesion and spreading. Understanding their adsorption behavior on surfaces with different natures is helpful for studying the cellular responses to environments. [11]

Various polymers, including natural, synthetic and natural/synthetic hybrid polymers, have been used to make hydrogels via chemical or physical crosslinking. Recently, bioactive synthetic hydrogels have emerged as promising scaffolds because they can provide molecularly tailored biofunctions and adjustable mechanical properties, as well as an extracellular matrix-like microenvironment for cell growth and tissue formation. [3]

Glycosaminoglycans (GAGs) are ubiquitously present at the cell surface and in extracellular matrix, and crucial for matrix assembly, cell-cell and cell-matrix interactions. The supramolecular presentation of GAG chains, along with other matrix components, is likely to be functionally important but remains challenging to control and to characterize, both in vivo and in vitro. [12] The ECM component hyaluronic acid (HA) possesses a non-sulfated glycosaminoglycan (GAG) structure and is widely distributed throughout the ECM of all connective tissues. HA plays an essential role in many biological processes such as tissue hydration, nutrient diffusion, proteoglycan organization and cell differentiation.

Various proteins have been used to make natural-hydrogel tissue-engineering scaffolds. Among them, collagen, the most abundant protein in mammals, is a representative natural polymer to fabricate natural hydrogels. Collagen can be degraded naturally by metallomatrix proteinases (MMPs) – specifically, collagenase – allowing for local degradation controlled by cells present in the engineered tissue. [3]

2.1. Injectable hydrogels

Injectable hydrogels derived from the extracellular matrix (ECM) of decellularized tissues have recently emerged as scaffolds for tissue-engineering applications. [13]

ECM hydrogels provide advantages such as injectability, the ability to fill an irregularly shaped space, and the inherent bioactivity of native matrix. However, material properties of ECM hydrogels and the effect of these properties upon cell behavior are neither well understood nor controlled. [2] The objective of the study, made by Wolf et al. was to prepare and determine the structure, mechanics, and the cell response in vitro and in vivo of ECM hydrogels prepared from decellularized porcine dermis and urinary bladder tissues. Dermal ECM hydrogels were characterized by a more dense fiber architecture and greater mechanical integrity than urinary bladder ECM hydrogels, and showed a dose dependent increase in mechanical properties with ECM concentration. In vitro, dermal ECM hydrogels supported greater C2C12 myoblast fusion, and less fibroblast infiltration and less fibroblast mediated hydrogel contraction than urinary bladder ECM hydrogels. Both hydrogels were rapidly infiltrated by host cells, primarily macrophages, when implanted in a rat abdominal wall defect. Both ECM hydrogels degraded by 35 days in vivo, but UBM hydrogels degraded more quickly, and with greater amounts of myogenesis than dermal ECM. These results show that ECM hydrogel properties

can be varied and partially controlled by the scaffold tissue source, and that these properties can markedly affect cell behavior. [2]

Seif-Naraghi et al. introduce the potential for using a decellularized ECM-derived hydrogel for the improved delivery of heparin-binding growth factors. Immobilization of growth factors on a scaffold has been shown to increase their stability and activity. This can be done via chemical crosslinking, covalent bonding, or by incorporating natural or synthetic growth factor-binding domains similar to those found in vivo in sulfated glycosaminoglycans (GAGs). Many decellularized ECM-derived hydrogels retain native sulfated GAGs, and these materials may therefore provide an excellent delivery platform for heparin-binding growth factors. In his study, the sulfated GAG content of an ECM hydrogel derived from decellularized pericardial ECM was confirmed by Fourier transform infrared spectroscopy and its ability to bind basic fibroblast growth factor (bFGF) was established. Delivery in the pericardial matrix hydrogel increased retention of bFGF both in vitro and in vivo in ischemic myocardium compared to delivery in collagen. In a rodent infarct model, intramyocardial injection of bFGF in pericardial matrix enhanced neovascularization by approximately 112% compared to delivery in collagen. Importantly, the newly formed vasculature was anastomosed with existing vasculature. Thus, the sulfated GAG content of the decellularized ECM hydrogel provides a platform for incorporation of heparin-binding growth factors for prolonged retention and delivery. [13]

2.2. Acellular flowable matrix

In recent years development of new technologies and therapies aimed to treat hard-to-heal wounds. The formation of a sinus tract complicates these difficult-to-treat diabetic wounds even further. In the lower extremity, sinus tract wounds are a significant risk for osteomyelitis. Typical treatment includes extensive surgical debridement with radical dissection, cavity packing, and occlusive dressing. Cellular and acellular bioengineered grafts have demonstrated some promise as alternatives for the treatment of such wounds. [14,15,16,17]

However, these grafts are provided as sheets in planar form. As such, they are harder to use and less effective in sinus tract wounds because of the irregularly shaped tunnels or extensions in these wounds. Ideally, the matrix material is capable of conforming to the wound area and providing the necessary bulk and scaffold to support the woundhealing process. [17]

An injectable form of an acellular human dermal regenerative tissue matrix Graftjacket® Xpress Flowable Soft Tissue Scaffold was designed to treat difficult tunneling wounds in a minimally invasive manner. This injectable matrix is a micronized form of a human acellular dermal regenerative tissue matrix. The injectable human matrix is composed of a micronized or powdered version of the graftjacket membrane. The matrix membrane is a human acellular scaffold derived from human dermal tissue. It is biocompatible and biologically permissive. This dermal matrix retains its native extracellular matrix proteins such as collagens I, III, IV, and VII; elastin; and proteoglycans in cell-friendly forms.

Although the sheet form of the scaffold does demonstrate intact vascular channels that allows for rapid angiogenesis, those channels are destroyed in the micronization process. The

flowable matrix allows for nutritional diffusion and cell attachment to facilitate cell migration as well as proliferation. These properties result in the rapid revascularization and cellular repopulation of the matrix scaffold. [17]

Graftjacket® Xpress FSTS supports the body's repair of damaged or inadequate integumental tissue, such as deep dermal wounds or diabetic ulcers. Graftjacket® FSTS is supplied as a dried, acellular dermal particulate in a syringe, before aplication it is reconstituted through syringe adapter with sterile saline solution and applied directly into the debrided, clean wound through a flexible applicator tip. The product is recomended for burns, chronic wounds as diabetic foot ulcers, pressure ulcers, surgical wounds ans venous ulcers.

Another interesting commercially available product is Integra® Flowable Wound Matrix. It is an advanced wound care device comprised of a granulated Integra® Wound Matrix, which consists of collagen and glycosaminoglycan. Collagen is of bovine origin. The Integra® Flowable Wound Matrix is hydrated with saline prior to application. It is designed for use in deep soft tissue or tunneling wounds. Gel-like consistency allows intimate contact between the grafting material and wound bed, composition and method of administration allows for complete coverage in deep crevice wounds. It provides a resorbable scaffold on which cells can attach, migrate, proliferate and differentiate.

Integra® Flowable Wound Matrix is indicated for the management of wounds including: partial-and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds.

3. Review of recent clinical experience with acellular matrix

Schmidt et al. in his retrospectively study concluded, that acellular porcine dermal collagen matrix is a feasible and reliable biological patch material for reconstruction of the thoracic wall. Excellent wound healing and long-term stability were achieved even in large defects or complete sternal replacements. Biological collagen matrixes have emerged as an alternative to the routinely used synthetic materials by major thoracic wall resections. Histological examination showed integration, neovascularization, and long-term persistence of the collagen matrix on late reoperation of one patient. [18]

The results of the multicenter prospective study from Kavros et al. demonstrate that the use of fetal bovine acellular dermal matrix (PriMatrix) integrated with standard-of-care therapy is a successful treatment regimen to heal diabetic foot ulcers (DFUs). In the study were included patiets with chronic DFU that ranged in area from 1 to 20 cm and failed to heal more than 30% during a 2-week screening period when treated with moist wound therapy. For qualifying subjects, PriMatrix was secured into a clean, sharply debrided wound; dressings were applied to maintain a moist wound environment, and the DFU was pressure off-loaded. Wound area measurements were taken weekly for up to 12 weeks, and PriMatrix was reapplied at the

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discretion of the treating physician. 55 patiets were enrolled at 9 US centers with 46 subjects progressing to study completion. Ulcers had been in existence for an average of 286 days, and initial mean ulcer area was 4.34 cm. Of the subjects completing the study, 76% healed by 12 weeks with a mean time to healing of 53.1 ± 21.9 days. The mean number of applications for these healed wounds was 2.0 ± 1.4, with 59.1% healing with a single application of PriMatrix and 22.9% healing with 2 applications. For subjects not healed by 12 weeks, the average wound area reduction was 71.4%. [19]

Goyal et al. evaluate in the study the degree of patient acceptance with acellular dermal matrix (ADM) allograft in the treatment of buccal gingival recession and compare it with subepithelial connective tissue graft. Obtaining predictable and aesthetic root coverage has become an important part of periodontal therapy. The search for the appropriate root coverage techniques has resulted in many different approaches. In the study thirty patients with Miller's class II recessions were treated and randomly assigned to the test group (ADM) and control group (subepithelial connective tissue graft). All patients underwent full periodontal evaluation and pre-surgical preparation, including oral hygiene instructions and scaling and root planing. The exposed roots were thoroughly planed and covered by a graft without any further root treatment. Results were evaluated based on the parameters measuring patient satisfaction and clinical outcome after 6 months of the surgical procedure. Postoperatively, significant root coverage, reduction in probing depth, gain in clinical attachment level, and increase in widths of keratinized tissue and attached gingiva were observed on intra-group comparison. There was no significant difference in any of the parameters between test and control groups. The subepithelial connective tissue graft and ADM graft were able to successfully treat gingival recession defects; however, the ADM showed better patient acceptance than the connective tissue graft. [20]

Wang et al. made an interesting prospective randomized multi-center study with comparison of two differently processed acellular dermal matrix products for root coverage procedures. They have compared 2 acellular dermal matrix (ADM) materials produced by different processing techniques, freeze-dried (FDADM) and solvent-dehydrated ADM (SDADM), in their ability to correct Miller's Class I and II recession defects. Eighty subjects from four study centers, each with a single maxillary anterior Miller's class I or II recession defect were enrolled. Subjects were randomly assigned and treated with coronally advanced flap (CAF)+FDADM (N=42) or CAF+SDADM (N=38). Gingival thickness, recession depth, recession width, probing pocket depth, clinical attachment level, Gingival index, Plaque index, patient discomfort and wound healing index were recorded before surgery, immediately post surgery, and over 2, 4, 12, 24 and 52 weeks postoperatively. When evaluating the clinical parameters after one year, both groups showed significant ($P<0.05$) improvement for most of the parameters evaluated when compared to baseline (Day 0). For example, percentage of root coverage was 77.20% ± 29.10% for CAF+FDADM and 71.01% ± 32.87% for CAF+SDADM. On the other hand, no significant differences were observed between the two materials for any clinical parameter tested or for patient satisfaction except for PD on the mesial side of the defects ($p=0.03$). As a conclusion both ADM materials, freeze-dried or solvent-dehydrated, can be used successfully

to correct Miller's class I or II recession defects. There were no statistically significant differences between groups for any of the clinical parameters tested. [21]

In a prospective, randomized study made in 2004 by Brigido and colleagues, Graftjacket tissue matrix, an acellular regenerative tissue matrix, has been used for wound closure. He studied the efficacy of this tissue product in wound repair compared with conventional treatment. Therefore, researchers used diabetic foot ulcers to evaluate the efficacy of GraftJacket tissue matrix in wound repair. Only a single administration of the tissue matrix was required. After 1 month of treatment, preliminary results demonstrate that this novel tissue matrix promotes faster healing at a statistically significant rate over conventional treatment. Because wounds in this series of patients are deep and circulation around the wound is poor, the preliminary results suggest that this tissue matrix could be applicable to other types of orthopedic wounds. [22]

Another multicenter, retrospective study from Winters el al. presents the use of a human acellular dermal regenerative tissue matrix (Graftjacket regenerative tissue Matrix) as an alternative treatment for 100 chronic, full-thickness wounds of the lower extremity in 75 diabetic patients. Wound locations included the foot (86.0%), ankle (8.0%), and lower extremity (6.0%). Mean wound age was 20.4 weeks (1.3-191.4 weeks). University of Texas (UT) wound classifications included 15 (15.0%) 1A, 1 (1.0%) 1B, 1 (1.0%) 1C, 2 (2.0%) 1D, 18 (18.0%) 2A, 8 (8.0%) 2B, 5 (5.0%) 2C, 3 (3.0%) 2D, 3 (3.0%) 3A, 7 (7.0%) 3B, 3 (3.0%) 3C, and 34 (34.0%) 3D. The mean time to matrix incorporation, 100% granulation, and complete healing was 1.5 weeks (0.43-4.4 weeks), 5.1 weeks (0.43-16.7 weeks), and 13.8 weeks (1.7-57.8 weeks), respectively. The overall matrix success rate, as defined by full epithelialization, was 90.0%. One failed wound subsequently healed approximately 7 weeks after matrix reapplication. The healing rate was 91.0%, as 91 of the 100 wounds healed. No statistically significant differences were observed between UT classifications and time to matrix incorporation, 100% granulation, and complete healing. Absence of matrix-related complications and high rates of closure in a wide array of diabetic wounds suggest that this matrix is a viable treatment for complex lower extremity wounds. Lack of any statistically significant differences between UT grades and wound outcome end points lends further support to the universal applicability of this matrix, with successful results in both superficial diabetic wounds and in wounds penetrating to the bone or joint. [23]

Integra bilayer wound matrix (IBWM) is a bilayer skin replacement system composed of a dermal regeneration layer and a temporary epidermal layer. It is used to treat various types of deep, large wounds via an inpatient procedure in an operating room. Prospective pilot study with Integra bilayer wound matrix (IBWM) in the treatment of diabetic foot ulcers was made by Yao and colleagues. They sought to determine ease of use and effectiveness of IBWM in an outpatient clinical setting when treating diabetic foot ulcers. In addition, no epidermal autografting was performed in conjunction with the IBWM after silicone release, as is common in the inpatient setting. Eleven patients with diabetic foot ulcers were enrolled. One patient was discontinued from the study owing to noncompliance leading to a serious adverse event. Therefore, ten patients who received the study intervention were included in the per-protocol population reported herein. The mean patient age was 60.6 years, with an average 11-year

history of diabetes mellitus. Each ulcer was located on the plantar aspect of the foot. No infection was reported during the study. Patients treated with IBWM showed progressive wound healing over time: the greatest mean wound reduction was approximately 95% in week 12. Seven of ten patients (70%) achieved complete wound closure by week 12. No recurrent ulcers were reported during follow-up. These results are consistent with the hypothesis that IBWM is easy to use, safe, and effective when used on diabetic foot ulcers in an outpatient clinical setting without the secondary procedure of autografting for closure. [24]

Purpose of retrospective comparative study from Papa et al in 2014 was to evaluate the results of reconstruction of diabetic feet by split thickness skin graft (STSG) and by dermal substitute Integra® covered by STSG in terms of vascularity of the reconstructed wound-bed by measurements of tissue oxygenation (TcPO2). 23 patients were included into the study (12 were reconstructed by STSG only and 11 with Integra® and STSG three weeks later). Wound beds reconstructed by Integra® showed on average 10 mmHg higher TcPO2. The study estimated in an objective way, by TcPO2 value measurements, the oxygenation of the wound bed in diabetic feet after reconstruction by STSG only and after adding dermal substitute Integra® to the wound bed before final STSG coverage. During first month after reconstruction no statistically significant differences were found. After 3 months TcPO2 studies revealed statistically significant higher oxygen tissue pressure in diabetic feet covered by Integra® plus STSG. These findings endorse in an objective way the clinical findings already reported while using the dermal substitute. It remains to explain the role of this increase of oxygen tissue pressure in redefine the indications for the use of dermal substitutes in reconstruction of poor vascularized regions. [25]

3.1. Review of most recent clinical experience with acellular flowable tissue matrix

Retrospective study from Brigido et al. about an acellular flowable dermal replacement scaffold used on lower extremity sinus tract wounds showed successful treatment potencial. Injectable human dermal matrix has been developed for the treatment of complex diabetic sinus tract wounds. In this retrospective series, 12 patients with deep tunneling wounds were treated with GRAFTJACKET Xpress Scaffold and followed for 12 weeks. Complete wound healing was achieved in 10 of 12 patients within the 12-week evaluation. The average time to complete healing was 8.5 weeks, whereas the average time to depth healing was 7.8 weeks. The data from the study suggest that this injectable human dermal matrix has unique properties that allow it to facilitate healing of complex tunneling diabetic foot ulcers. The material was easy to prepare and inject into the wound, thereby preventing the necessity of extensive surgical exposure. The matrix supports neo-subcutaneous tissue formation and allows the body to rapidly repair these wounds. [17]

We treated two patients with lower limb chronic wounds of different etiology: unhealed ulcer off the stump following transmetatarsal amputation of the foot in a patient with diabetes and a patient with foot ulcer after traumatic foot amputation. Both patients were previously treated for two years with modern wound dressings, that were changed according to the appearance of the bottom of the wound and the amount of exudate. Despite optimal choice of dressing ulcers persisted. After appropriate preparation of the wound bed and removal of hypercera-

totic edges we applied Integra ™ Flowable Wound Matrix, which was covered with a non-adhesive silicone dressing and polyurethane foam. After seven days, we measured the the perimeter and the surface of the wound. The extent of the wound in the first patient was reduced by 40% and the surface by 61%. In the second patient, the treatment was less effective, with reduction of the perimeter by 7% and surface area by 11%. We hope to offer the new treatment option to a larger number of patients and gather more representable data.

4. Conclusions

This review provides an outlook on some of the advanced wound healing options and summarizes established treatment strategies of using acellular matrix and acellular flowable wound matrix. Due to high rates of morbidity and mortality, chronic ulcers pose a global health problem requiring substantial resources. Conventional methods of treatment are insufficient when dealing with complex and non-healing ulcers. Advanced regenerative methods should be considered in patients with delayed healing of ulcers, that did not reduce in size after conventional standard 4-week treatment. The regenerative treatment should be used additonally to the conventional methods, maintaining the gold standards of appropriate debridement, infection control and moist wound healing.

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