Chapter

The Interplay of ECM-Based Graft Materials and Mechanisms of Tissue Remodeling

Jason P. Hodde and Michael C. Hiles

Abstract

Wound healing is a complex natural process that involves the recruitment of cells, the renewal of tissue composition, and the reinforcement of structural tissue architecture. Following ischemic injury or chronic disease, wound healing is delayed, and can often result in chronic inflammation or permanent morbidity. Tissue engineering strategies to harness the wound healing process include the use of naturally derived extracellular matrix (ECM) scaffolds with inherent bioactivity to both passively facilitate and actively direct healing toward a successful resolution. As the body heals, the properly designed ECM scaffold is gradually remodeled and integrated into the body, leaving behind organized tissue that provides long-term strength. Herein we explain the interplay of the ECM (i.e., its complex composition and bioactivity) with the cells of the body throughout the process of tissue remodeling, thus explaining how even a tissue-engineered xenograft material can direct the body to restore itself.

Keywords: wound healing, extracellular matrix, bioactivity, tissue remodeling, xenograft

1. Introduction: extracellular matrix as an implantable graft material

Biologic materials used to repair soft tissue defects must be strong and easy to handle during implantation, but they must also be able to support tissue integration and maturation once implanted. ECM-based biologic grafts have been widely used in surgery over the last two decades. They are a good choice for surgeons because they can be safely implanted in contaminated settings where synthetic materials are contraindicated. Even though synthetic mesh materials continue to be favored in general surgical practice because of their versatility and low cost, they remain susceptible to chemical degradation over time, can create physical tissue erosion due to mismatches in their mechanical properties with the surrounding tissues, and may undergo encapsulation following placement because the body views them as foreign materials [1]. Of critical importance in many applications, synthetics can provide a nidus for microorganism growth; therefore, if they become infected when in the body, they typically need to be removed [2].

ECM biomaterials derived from natural tissue sources, however, have generally provided adequate strength, resistance to infection, and stability over time such that they make adequate materials for soft tissue reconstruction [3].

These materials can be obtained as autografts or allografts, but autografts result in donor site morbidity, while cadaveric allograft tissues may transmit disease, are inherently inconsistent, and are typically quite expensive.

Recent years have seen the advent of multiple off-the shelf tissue-based ECM biomaterials that claim to provide an optimal healing environment for soft tissues. They can be obtained from a wide variety of mammalian tissues, processed using a wide range of chemicals and cross-linking agents, or can be provided in such a way that retains the information-rich scaffold into which adjacent cells migrate to create a replacement tissue (**Table 1**). Many studies have shown constructive, functional tissue remodeling with partial restoration of site-appropriate tissue using these graft materials [4–7], yet this is not always the case. Less favorable outcomes include the accumulation of serous fluid at the implant site, rapid degradation of the graft material with associated mechanical failure, or a lack of biomaterial integration with the patient's tissues, resulting in a foreign body response [8, 9]. These less-than-favorable outcomes typically have been associated with variations in manufacturing methods that result in the failure of the material to maintain nature's natural composition and three-dimensional architecture that makes the extracellular matrix (ECM) the ideal template for tissue repair and regeneration.

Materials that are minimally processed most closely recapitulate the structure and function of the original tissue while providing a safe, biocompatible material for soft tissue reconstruction. The natural ECM, when retained in its complex arrangement of matrix proteins and associated factors, can provide the key extracellular signals and inherent bioactivity needed to restore damaged tissues to their natural state [7]. This complexity allows the naturally occurring biologic graft to completely integrate with the recipient's tissues and cells to ultimately form a vascularized, highly organized tissue structure that resembles the native tissue structure and architecture [4, 7, 10, 11].

Product	Source	Crosslinking agent	Sterilization
Alloderm	Human dermis	N/A	N/A
AlloMax	Human dermis	N/A	Gamma radiation
Biodesign	Porcine small intestine	N/A	EtO
Gentrix	Porcine urinary bladder	N/A	E-beam
GraftJacket	Human dermis	N/A	N/A
Meso BioMatrix	Porcine mesothelium	N/A	EtO
MicroMatrix	Porcine urinary bladder	N/A	E-beam
Miroderm	Porcine liver	N/A	E-beam
OASIS	Porcine small intestine	N/A	EtO
Peri-Guard	Bovine pericardium	Glutaraldehyde	Liquid chemical
Permacol	Porcine dermis	HMDI	Gamma radiation
Strattice	Porcine dermis	N/A	E-beam
Tutoplast	Human pericardium	N/A	Gamma radiation
XenMatrix	Porcine dermis	N/A	E-beam

EtO ethylene oxide, E-beam Electron beam irradiation, HMDI hexamethylene diisocyanate.

Table 1.
Source tissue and post-decellularization processing steps of some common commercially available ECM biomaterials.

2. Extracellular matrix as bioactive structure

The ECM is a three-dimensional network of extracellular macromolecules, such as collagens, glycoproteins, proteoglycans, and glycosaminoglycans, that provides structural and biochemical support to surrounding cells. Because of different structural and mechanical requirements, the composition of ECM varies from tissue to tissue; however, providing a structure for cell adhesion, directing cell-to-cell communication, and regulating cell processes such as growth, migration and differentiation are common functions of the ECM [12].

Regardless of the source, ECM is a complex three-dimensional scaffold consisting of structural and functional proteins and components arranged in a tissue-specific orientation [12]. The ECM components directly interact with fibroblasts, endothelial cells, and macrophages to maintain a natural and functional homeostatic environment through a process known as dynamic reciprocity (**Figure 1**) [13]. When injury occurs and the natural equilibrium is disrupted, the dynamic environment that exists between the ECM and cells orchestrates acute inflammation, wound healing and tissue remodeling to regain function and restore homeostasis. After injury occurs and the ECM is damaged, a biologic graft can be implanted to provide a surrogate matrix structure that allows dynamic reciprocity to begin immediately, ultimately achieving tissue restoration via the process of constructive tissue remodeling.

Endogenous ECM functions as the intended bioactive structure when normal tissue turnover is taking place or when no significant tissue loss is encountered. The body has a remarkable ability to self-renew, in large part due to the instructional

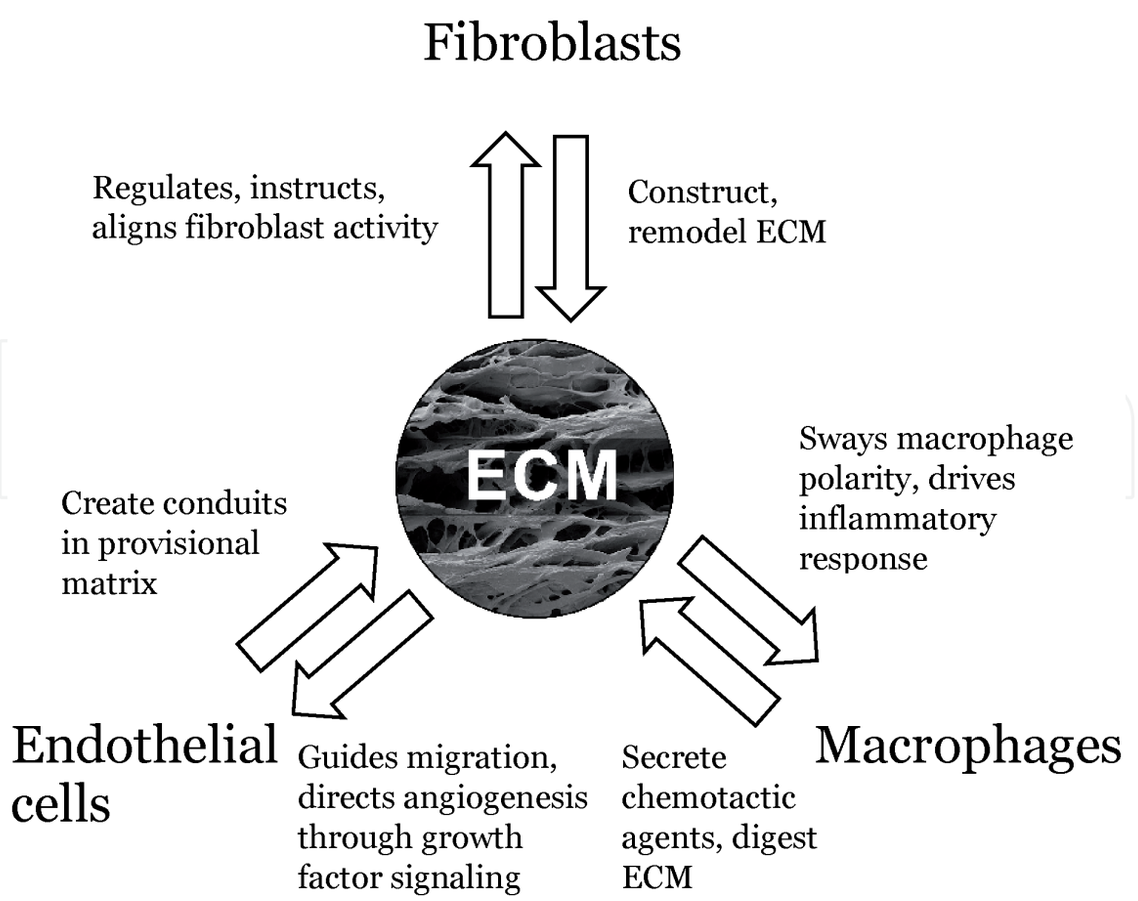

Figure 1.
Examples of dynamic reciprocity of fibroblasts, macrophages, endothelial cells (angiogenesis), and the extracellular matrix (ECM) during wound healing. These interactions occur through signals such as growth factors and/or binding of cells to the ECM.

nature of the ECM, but in the presence of significant tissue loss, large areas of trauma, or surgical reconstructions, there is a need for an exogenous material to augment and to bring order to somewhat chaotic processes. An exogenous ECM can serve as this bioactive, instructive, and even mechanical blueprint for a constructive tissue remodeling process [7, 14, 15].

3. Extracellular matrix and constructive tissue remodeling

Constructive tissue remodeling is more than just another word for wound healing or for tissue repair. The stages of wound healing include initial hemostasis, characterized by clot formation; inflammation, characterized by the deposition of inflammatory and progenitor cells, leading to the formation of granulation tissue; proliferation, where resident cells secrete growth factors and cytokines and collagen deposition occurs; and remodeling, where the newly formed tissue matures and collagen strength increases to meet the demands of the body [16] (**Figure 2**). Tissue repair results in the formation of scar tissue, which is known to be less strong than native tissue and can therefore be more susceptible to reinjury [5].

Unlike the tissue repair process that occurs in the absence of a biologic graft material, the constructive tissue remodeling process that can be directed by an ECM graft leads to a more natural healing process in the recipient that is characterized by the deposition of organized connective tissue, rather than just chaotic scar [17]. The ideal ECM graft is characterized by an open matrix structure to allow for rapid cellular ingrowth. It is also characterized by the presence of structural collagens and non-collagen ECM components (such as messenger nucleic acids, growth factors, glycoproteins, proteoglycans, and glycosaminoglycans), which act to facilitate the renewal of natural dynamic reciprocity [18]. When tissue homeostasis is disrupted, the biologic graft plays the role of the recipient's natural ECM and works to bridge the recipient's cells across the wound to ultimately restore a homeostatic environment. The restoration of homeostasis following injury in the presence of a biologic graft occurs through the constructive process of tissue remodeling.

Tissue remodeling is a process of tissue restoration that improves upon the scar tissue outcome typically achieved by tissue repair. It can be divided into three separate phases: 1) Cell recruitment; 2) Tissue renewal; and 3) Tissue reinforcement.

During cell recruitment, the remodeling process starts when the body's inflammatory and progenitor cells populate the biologic graft and release cytokines and growth factors that bind to the graft and recruit collagen-secreting fibroblasts [18, 19]. In this phase, the graft primarily acts as a scaffold material to support the population of the open ECM structure by the patient's own cells.

As remodeling progresses, the patient's macrophages and fibroblasts in the newly populated matrix work together with matrix-bound signaling factors to renew the tissue through the complementary processes of phagocytosis, collagen deposition, and angiogenesis. In this phase, the biologic graft is gradually replaced by the patient's own tissue and cells [18, 19].

Over the medium to long term, the resident fibroblasts secrete cytokines and growth factors to signal reinforcement of the deposited tissue through the processes of additional collagen deposition and maturation, resulting in a strong, repaired tissue [10, 20–22]. In this phase, the biologic graft is no longer needed as the patient's own collagen has gradually matured into a stable structure that has long-term strength but is entirely the patient's own [20–22]. The resulting tissue structure is mature, organized and strong, and can withstand (and is even driven by) the natural physiological forces that it encounters [17, 23].

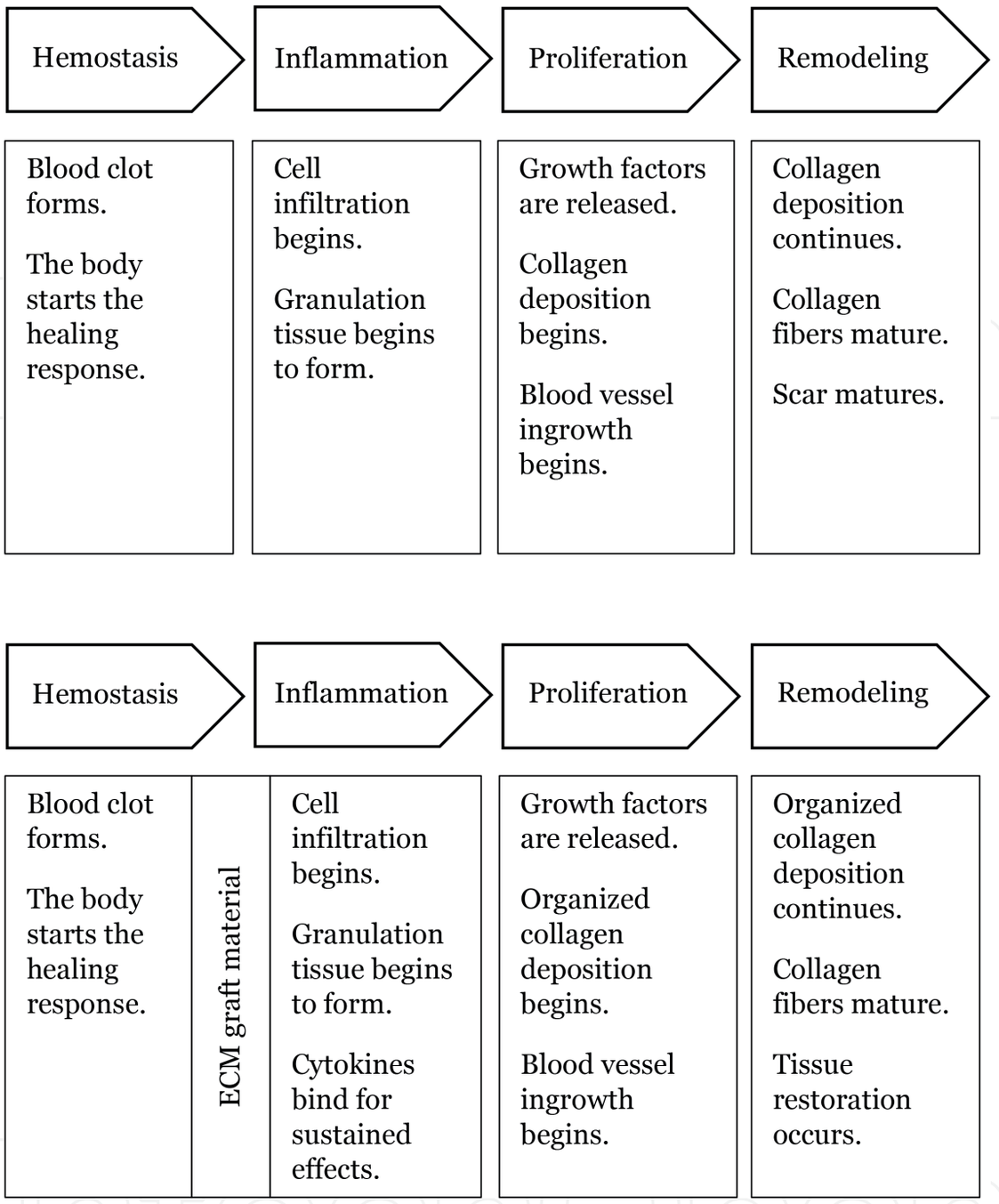

Figure 2.
The phases of wound healing and the processes involved in each stage. The addition of an ECM graft material shortly after the injury occurs results in a more natural wound healing response than in its absence.

A biologic graft with the correct composition and three-dimensional architecture directs the patient's body to replace itself – to completely remodel – rather than to heal through a tissue repair process that results in chaotic, weak, and ineffective scar tissue formation [20–22]. By providing the correct cues to help the body restore itself, the graft provides both an essential temporary structure and the local tissue instructions to lead the patient to achieve a natural repair (**Figure 3**).

4. Mechanisms of action for ECM-directed tissue remodeling

An ECM-based biologic graft that has been optimally processed to harness the tissue remodeling properties of nature acts more than just a mechanical tissue reinforcement device. While mechanical reinforcement is still the primary mechanism of action

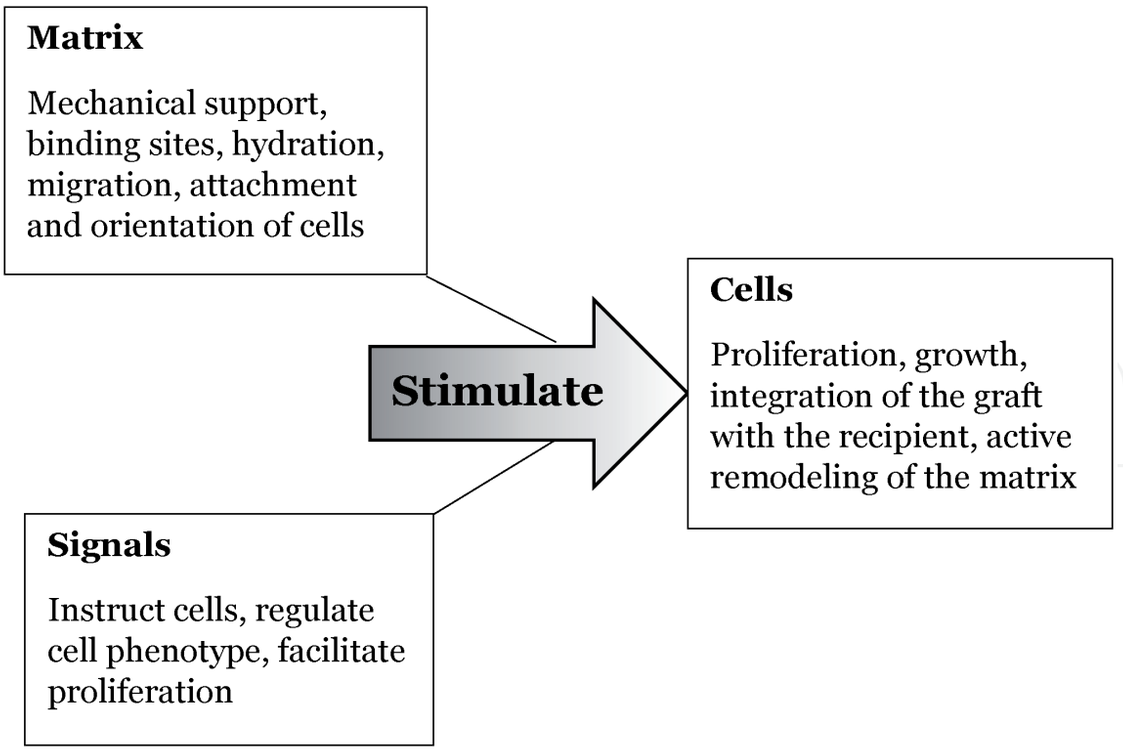

Figure 3.
Mechanisms of action for ECM-directed tissue remodeling. The ECM graft initially provides for a direct mechanical tissue repair that has inherent strength. It also provides a matrix structure for the support, attachment, and orientation of cells. The ECM graft has the ability, through its inherent composition, to modulate the local wound environment to have a direct effect on endogenous growth factors and cytokines. The graft can provide signals of its own, which may include growth factors, binding sequences on extracellular matrix proteins, or other endogenous factors provided by the recipient. Signals control and modify cells and other elements. Together the ECM and signals stimulate cell division, proliferation, growth, and integration of the ECM graft with the recipient.

for these materials, additional mechanisms of action include: providing a porous tissue scaffold matrix structure to allow for fibroblast infiltration and population; altering the surrounding wound environment by modulating local cytokine activity; and, optimally, acting as a reservoir for growth factors and signaling molecules that can be used by the patient as tissue renewal and reinforcement progress (**Table 2**).

4.1 Mechanical reinforcement during surgical repair

Poor wound healing after trauma, surgery, or due to chronic disease is the consequence of a poorly regulated tissue repair response that directly effects the processes of inflammation, angiogenesis, matrix deposition, and cell recruitment [24]. As a result, tissue healing typically takes a significant time to achieve in patients with advanced age or with comorbidities. Prolonged mechanical reinforcement is often needed to get proper approximation of the wound edges and to bolster the anatomy until tissue ingrowth is sufficient to achieve the required strength to maintain tissue integrity. This mechanical reinforcement mechanism is the primary (and often only) means by which most implantable devices achieve their effect. For example, synthetic mesh materials, such as polypropylene or polytetrafluoroethylene, derive their reinforcement benefit from the strength of their fibers at implant but never completely integrate with the patient's tissues over time [25]. Synthetic materials are often recognized as foreign by the body – as a material that needs to be removed or expunged [26]. When this occurs, an inflammatory response is initiated by the patient's immune system, setting up a chronic inflammatory state that never resolves and can result in chronic pain and fibrosis [26].

	Mechanical Surgical Repair	Tissue Scaffold Matrix Structure	Modulation of Endogenous Cytokines	Delivery of Exogenous Cytokines
Synthetic mesh implant	✓	×	×	×
Bio-synthetic mesh implant	✓	×	×	×
Cross-linked ECM biologic graft	✓	✓/×	×	×
Purified ECM biologic graft	✓	✓	×	×
Naturally complex ECM biologic graft	✓	✓	✓	✓

Table 2.
Mechanisms of action for different types of implantable graft materials. While all implantable materials serve a mechanical function to reinforce soft tissue, synthetic and biosynthetic materials fail to provide a matrix structure and complex composition that is designed to positively interact with the wound healing environment and lead to constructive tissue remodeling that is seen with naturally complex ECM biologic graft materials.

For a well-designed biologic ECM graft, the mechanical means of tissue support remains its primary mechanism of action. The ECM graft must allow the passage of suture and reinforce the area of weakness under significant pull-out force. It must also provide tensile strength and mechanical compliance commensurate with the surrounding tissues. Unlike synthetic or even many biosynthetic materials, such as poly-4-hydroxybutyrate (P4HB), ECM-based biologic devices are not meant to be static implants but are designed to fully integrate with the patient over time. Their mechanical properties change after implant as they undergo interaction with the patient's cells, tissues, and the local wound environment [27] and must therefore be designed to retain their mechanical integrity even while actively participating in the process of tissue renewal. The dynamic process of tissue remodeling is a balance of ECM graft degradation with the formation of new patient-derived collagen, meaning that an ECM graft must be designed with known strength requirements and degradation rates to keep the repair intact during all phases of tissue remodeling: 1) Cell recruitment; 2) Tissue renewal; and 3) Tissue reinforcement (**Figure 4**) [20, 28].

4.2 Providing a tissue scaffold matrix structure

When foreign materials are implanted into the body, they are quickly recognized by the immune system as something either to rapidly destroy or to compartmentalize [29]. The body accomplishes these activities by secreting inflammatory enzymes and pH modifiers or by recruiting an army of macrophages to form a scarified wall around the implant. While permanent synthetic materials and crosslinked biologic grafts are typically walled off by the recipient because they are resistant to degradation [30], biosynthetic matrices are often hydrolyzed or otherwise degraded over time without allowing complete tissue integration and permanent reinforcement to occur [31].

Purified biologic ECM grafts typically contain few of the naturally occurring macromolecules of the complex ECM because they have been deconstructed with chemicals and then "purified" into single-component constructs or reconstituted into single-component implants. While this type of graft material can still act as a matrix structure to support cell ingrowth, the lack of complex signaling macromolecules from the natural ECM and its susceptibility to matrix-degrading enzymes, such as collagenases, limits its ability to actively promote fibroblast and endothelial cell proliferation and secretion of new ECM [32, 33].

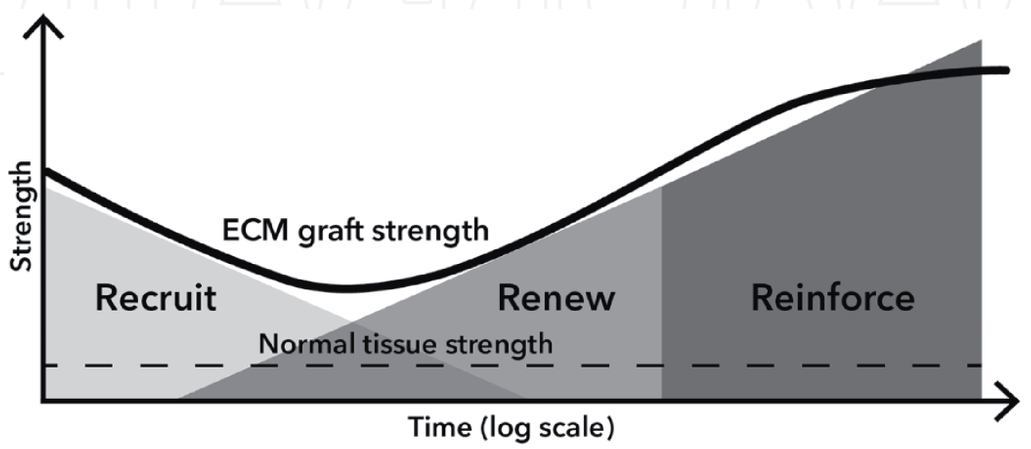

Figure 4.
ECM-based graft materials must be designed to withstand physiologic forces while undergoing the active processes of tissue remodeling and tissue integration following implant. The overall repair strength must be maintained well above the normal tissue strength required to keep the repair intact while facilitating cell recruitment, tissue renewal, and tissue reinforcement.

Non-crosslinked biologic ECM grafts that have been processed to retain the composition and architecture of healthy ECM are neither encapsulated nor degraded upon implant [7]. Instead, they contain the complex information of the natural ECM that makes them an ideal scaffold environment upon which cells can move and proliferate, allowing for colonization of fibroblasts and endothelial cells, the eventual secretion of growth factors, and the deposition of a collagen matrix [10]. The porous nature of the ECM scaffold provides not only the structure and interstices for ingrowth but also the recognition and binding sites that facilitate cellular attachment and migration [10]. During the process of tissue renewal, the porous matrix structure of the non-crosslinked ECM graft allows for angiogenesis and ultimately the removal of byproducts of cellular metabolism, facilitating the process of tissue remodeling that is essential to obtaining a long-lasting, strong, and permanent repair [10, 34].

4.3 Modulating endogenous cytokine activity

The local wound environment is characterized by a dynamic milieu of signaling factors designed to shepherd an injury through the four phases of wound healing and to ultimately restore tissue strength and homeostasis [16]. In most instances this occurs in a well-defined series of events leading to complete tissue restoration that is modulated directly by the local ECM. Because the ECM is laden with macromolecules that explicitly bind cytokines and alter their half-lives, bioactivities, and concentrations, the presence of a healthy ECM in the local wound environment is essential for tissue remodeling to occur. When the ECM is corrupt, it cannot support tissue restoration and chronic inflammation results [35].

Chronic, non-healing wounds are characterized by increased levels of pro-inflammatory cytokines, increased levels of MMPs, and low levels of growth factors known to stimulate wound closure [36, 37]. They are highly inflamed and proteolytic, have become stalled in the inflammation stage of wound healing, and cannot support fibroblast function [38]. In cases such as this, replacing the damaged ECM with a healthy ECM-based biologic graft can alter the local wound environment by modulating the endogenous cytokine profile of the injured area and stimulating normal fibroblast and endothelial cell function [39].

This tertiary mechanism of action for ECM-directed tissue remodeling, endogenous cytokine modulation, harnesses the natural structure and composition of the ECM to direct tissue remodeling down a productive pathway [37]. Unlike synthetic and biosynthetic materials that contain no ECM-binding sites and cannot directly influence the composition of the natural wound environment; unlike crosslinked ECM biologic graft materials which have had their binding sites obscured by the crosslinking process; and unlike purified biologic ECM grafts that are limited in the types of cytokines that can interact with them; well-designed, non-crosslinked, biologic ECM graft materials have been shown to positively alter the local environment and lead to constructive tissue remodeling and wound healing [10, 37, 39, 40].

4.4 Acting as a cytokine reservoir

Matrix biologists have long regarded the ECM as a repository for latent bioactivity in the form of growth factors, cytokines, and more recently, messenger nucleic acid depots. Even in their dehydrated state, these factors retain their potency and structure because they are tightly bound to proteins that protect them from degradation [41, 42]. Also, recently, science has uncovered the remarkable ability for these embedded matrix molecules to modulate cellular activity across species and after long periods of dormancy. Porcine growth factors can activate human cells,

and vice-versa, with predictable potency and expected effects, even after dehydration and sterilization [41, 42]. It is this growth factor and cytokine repository that separates a complex biologic ECM graft from other types of non-instructional implant materials.

After implantation, a complex biologic ECM graft plays the role of the innate ECM, interacting with the patient's cells through dynamic reciprocity to direct tissue repair down a positive, active state of wound healing and toward an organized repair that resembles native tissue structure and architecture rather than scar tissue. When its role has been fully realized, an ECM graft becomes completely replaced by patient tissue and removed from the body through the normal process of matrix turnover, leaving no graft components behind [43]. In many ways it is the repository of latent bioactivity that allows the well-designed ECM graft to stimulate transformation of itself, by the patient's cells, into a new, complex and complete, functional tissue.

5. Summary: extracellular matrix past, present, and future

ECM graft materials have been used surgically for decades, but historically they have been enzymatically stripped of their biological information, chemically cross-linked to enhance their durability (while quite effectively silencing their biological activity), or otherwise adulterated in such a way as to act much more like synthetic mesh than a truly instructive matrix [34, 44]. A more modern approach to ECM graft design can capitalize on the inherent complexity and instructiveness of natural ECM to build an implant with multi-factorial mechanisms of action that harmonize with healing, serve as a surrogate ECM in the wound, and stimulate the processes of dynamic reciprocity toward renewed homeostasis. Such an implant can guide the patient's cells through a series of cellular recruitment, renewal of lost matrix structures, and reinforcement of tissue strength while undergoing complete turnover and disappearance of the original implant.

The current state of the art for ECM grafts has been described. These materials have shown remarkable success in a wide variety of clinical applications [3, 7]. However, there is still room for improvement. Naturally occurring biologic ECM graft materials can be enhanced or fortified to accelerate some of these biological functions, stimulate cellular phenotype selection, or even create inherent antimicrobial activities that will better withstand infection. Ultimately, the goal of such "next generation" implants must be one of synergizing with natural biology and improving upon the complex interaction of the graft with the patient to allow tissue repair, remodeling, and regenerative processes to proceed unhindered.

Acknowledgements

The authors thank Susan Erb and Samantha Stevenson for their review and edits of the final manuscript.

Conflict of interest

Jason P. Hodde and Michael C. Hiles are employees of Cook Biotech Incorporated and hold multiple patents covering ECM-based biomaterials.

DOI: http://dx.doi.org/10.5772/intechopen.96954

Author details

Jason P. Hodde* and Michael C. Hiles
Cook Biotech Incorporated, West Lafayette, IN, USA

*Address all correspondence to: jason.hodde@cookbiotech.com

References

[1] Gavlin A, Kierans AS, Chen J, Song C, Guniganti P, Mazzariol FS. Imaging and treatment of complications of abdominal and pelvic mesh repair. Radiographics. 2020;40:432-453. DOI: 10.1148/rg.2020190106.

[2] Schneeberger SJ, Kraft CT, Janis JE. No-touch technique of mesh placement in ventral hernia repair: Minimizing postoperative mesh infections. Plast Reconstr Surg. 2020;145:1288-1291. DOI: 10.1097/PRS.0000000000006767.

[3] Cramer MC, Badylak SF. Extracellular matrix-based biomaterials and their influence upon cell behavior. Ann Biomed Eng. 2020;48:2132-2153. DOI: 10.1007/s10439-019-02408-9.

[4] Sandusky GE, Badylak SF, Morff RJ, Johnson WD, Lantz GC. Histologic findings after in vivo placement of small intestinal submucosal vascular grafts and saphenous vein grafts in the carotid artery in dogs. Am J Pathol. 1992;140:317-324.

[5] Liang R, Woo SL, Takakura Y, Moon DK, Jia F, Abramowitch SD. Long-term effects of porcine small intestine submucosa on the healing of medial collateral ligament: A functional tissue engineering study. J Orthop Res. 2006;24:811-819. DOI: 10.1002/jor.20080.

[6] Badylak SF. The extracellular matrix as a biologic scaffold material. Biomaterials. 2007;28:3587-3593. DOI: 10.1016/j.biomaterials.2007.04.043.

[7] Hodde JP. Use of small intestinal submucosa dECM in tissue engineering and regenerative medicine. In: Yamaoka T, Hoshiba T, editors. Decellularized Extracellular Matrix: Characterization, Fabrication and Applications. London, England: The Royal Society of Chemistry; 2020. p. 181-198. DOI: 10.1039/9781788015998.

[8] Ho KL, Witte VMN, Bird ET. 8-ply small intestinal submucosa tension-free sling: Spectrum of postoperative inflammation. J Urol. 2004;171:268-271. DOI: 10.1097/01.ju.0000098680.60020.32.

[9] Soler JA, Gidwani S, Curtis MJ. Early complications from the use of porcine dermal collagen implants (Permacol) as bridging constructs in the repair of massive rotator cuff tears. A report of 4 cases. Acta Orthop Belg. 2007;73:432-436.

[10] Nihsen ES, Johnson CE, Hiles MC. Bioactivity of small intestinal submucosa and oxidized regenerated cellulose/collagen. Adv Skin Wound Care. 2008;21:479-486. DOI: 10.1097/01.ASW.0000323561.14144.19.

[11] Nguyen KP, Zotos V, Hsueh EC. Long-term outcome of biologic graft: A case report. J Med Case Rep. 2014;8:255. DOI: 10.1186/1752-1947-8-255.

[12] Kular JK, Basu S, Sharma RI. The extracellular matrix: Structure, composition, age-related differences, tools for analysis and applications for tissue engineering. J Tissue Eng. 2014;5:2041731414557112. DOI: 10.1177/2041731414557112.

[13] Schultz GS, Davidson JM, Kirsner RS, Bornstein P, Herman IM. Dynamic reciprocity in the wound microenvironment. Wound Rep Regen. 2011;19:134-148. DOI: 10.1111/j.1524-475X.2011.00673.x.

[14] Zhu M, Li W, Dong X, Yuan X, Midgley AC, Chang H, Wang Y, Wang H, Wang K, Ma PX, Wang H, Kong D. In vivo engineered extracellular matrix scaffolds with instructive niches for oriented tissue regeneration. Nat Commun. 2019;10:4620. DOI: 10.1038/s41467-019-12545-3.

[15] Hodde J, Hiles M. Transforming surgery through biomaterial template technology. Br J Hosp Med (Lond). 2016;77:162-166. DOI: 10.12968/hmed.2016.77.3.162.

[16] Lin PH, Sermersheim M, Li H, Lee PHU, Steinberg SM, Ma J. Zinc in wound healing modulation. Nutrients. 2017;10:16. DOI: 10.3390/nu10010016.

[17] Woo SL, Takakura Y, Liang R, Jia F, Moon DK. Treatment with bioscaffold enhances the fibril morphology and the collagen composition of healing medial collateral ligament in rabbits. Tissue Eng. 2006;12:159-166. DOI: 10.1089/ten.2006.12.159.

[18] Hodde JP. Extracellular matrix as a bioactive material for soft tissue reconstruction. ANZ J Surg. 2006;76:1096-1100. DOI: 10.1111/j.1445-2197.2006.03948.x.

[19] Badylak SF, Park K, Peppas N, McCabe G, Yoder M. Marrow-derived cells populate scaffolds composed of xenogeneic extracellular matrix. Exp Hematol. 2001;29:1310-1318. DOI: 10.1016/s0301-472x(01)00729-9.

[20] Badylak S, Kokini K, Tullius B, Whitson B. Strength over time of a resorbable bioscaffold for body wall repair in a dog model. J Surg Res. 2001;99:282-287. DOI: 10.1006/jsre.2001.6176.

[21] Franklin ME Jr, Trevino JM, Portillo G, Vela I, Glass JL, Gonzalez JJ. The use of porcine small intestinal submucosa as a prosthetic material for laparoscopic hernia repair in infected and potentially contaminated field: a long term follow-up. Surg Endosc. 2008;22:1941-1946. DOI: 10.1007/s00464-008-0005-y.

[22] Stelly M, Stelly TC. Histology of CorMatrix bioscaffold 5 years after pericardial closure. Ann Thorac Surg. 2013;96:e127-e129. DOI: 10.1016/j.athoracsur.2013.06.114.

[23] Hodde JP, Badylak SF, Shelbourne KD. The effect of range of motion on remodeling of small intestinal submucosa (SIS) when used as an Achilles tendon repair material in the rabbit. Tissue Eng. 1997;3:27-37.

[24] Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: mechanisms, signaling, and translation. Sci Transl Med. 2014;6:265sr6. DOI: 10.1126/scitranslmed.3009337.

[25] Korzinskas T, Jung O, Smeets R, Stojanovic S, Najman S, Glenske K, Hahn M, Wenisch S, Schnettler R, Barbeck M. In vivo analysis of the biocompatibility and macrophage response of a non-resorbable PTFE membrane for guided bone regeneration. Int J Mol Sci. 2018;19:2952. DOI: 10.3390/ijms19102952.

[26] Farmer ZL, Domínguez-Robles J, Mancinelli C, Larrañeta E, Lamprou DA. Urogynecological surgical mesh implants: New trends in materials, manufacturing and therapeutic approaches. Int J Pharm. 2020;585:119512. DOI: 10.1016/j.ijpharm.2020.119512.

[27] Harth KC, Blatnik JA, Anderson JM, Jacobs MR, Zeinali F, Rosen MJ. Effect of surgical wound classification on biologic graft performance in complex hernia repair: an experimental study. Surgery. 2013;153:481-492. DOI: 10.1016/j.surg.2012.08.064.

[28] Ayubi FS, Armstrong PJ, Mattia MS, Parker DM. Abdominal wall hernia repair: a comparison of Permacol and Surgisis grafts in a rat hernia model. Hernia. 2008;12:373-378. DOI: 10.1007/s10029-008-0359-z.

[29] Jordan SW, Fligor JE, Janes LE, Dumanian GA. Implant porosity and the foreign body response. Plast Reconstr Surg. 2018;141:103e-112e. DOI: 10.1097/PRS.0000000000003930.

[30] Todros S, Pavan PG, Natali AN. Synthetic surgical meshes used in abdominal wall surgery: Part I-materials and structural conformation. J Biomed Mater Res B Appl Biomater. 2017;105:689-699. DOI: 10.1002/jbm.b.33586.

[31] Fatkhudinov T, Tsedik L, Arutyunyan I, Lokhonina A, Makarov A, Korshunov A, Elchaninov A, Kananykhina E, Vasyukova O, Usman N, Uvarova E, Chuprynin V, Eremina I, Degtyarev D, Sukhikh G. Evaluation of resorbable polydioxanone and polyglycolic acid meshes in a rat model of ventral hernia repair. J Biomed Mater Res B Appl Biomater. 2019;107:652-663. DOI: 10.1002/jbm.b.34158.

[32] Capella-Monsonís H, Tilbury MA, Wall JG, Zeugolis DI. Porcine mesothelium matrix as a biomaterial for wound healing applications. Mater Today Bio. 2020;7:100057. DOI: 10.1016/j.mtbio.2020.100057.

[33] Sun WQ, Xu H, Sandor M, Lombardi J. Process-induced extracellular matrix alterations affect the mechanisms of soft tissue repair and regeneration. J Tissue Eng. 2013;4:2041731413505305. DOI: 10.1177/2041731413505305.

[34] Badylak S, Kokini K, Tullius B, Simmons-Byrd A, Morff R. Morphologic study of small intestinal submucosa as a body wall repair device. J Surg Res. 2002;103:190-202. DOI: 10.1006/jsre.2001.6349.

[35] Clark RA. Fibrin and wound healing. Ann N Y Acad Sci. 2001;936: 355-367. DOI: 10.1111/j.1749-6632.2001.tb03522.x.

[36] Lazaro JL, Izzo V, Meaume S, Davies AH, Lobmann R, Uccioli L. Elevated levels of matrix metalloproteinases and chronic wound healing: an updated review of clinical evidence. J Wound Care. 2016;25:277-287. DOI: 10.12968/jowc.2016.25.5.277.

[37] Hodde JP, Hiles MC, Metzger DW. Characterization of the local wound environment following treatment of chronic leg ulcers with SIS wound matrix. J Tissue Viability. 2020;29:42-47. DOI: 10.1016/j.jtv.2019.12.003.

[38] Przekora A. A concise review on tissue engineered artificial skin grafts for chronic wound treatment: Can we reconstruct functional skin tissue in vitro? Cells. 2020;9:1622. DOI: 10.3390/cells9071622.

[39] Nihsen ES, Zopf DA, Ernst DM, Janis AD, Hiles MC, Johnson C. Absorption of bioactive molecules into OASIS Wound Matrix. Adv Skin Wound Care. 2007;20:541-548. DOI: 10.1097/01.ASW.0000294756.97425.c9.

[40] Witherel CE, Graney PL, Freytes DO, Weingarten MS, Spiller KL. Response of human macrophages to wound matrices in vitro. Wound Repair Regen. 2016;24:514-524. DOI: 10.1111/wrr.12423.

[41] Hodde JP, Ernst DMJ, Hiles MC. An investigation of the long-term bioactivity of endogenous growth factor in Oasis Wound Matrix. J Wound Care. 2005;14:23-25. DOI: 10.12968/jowc.2005.14.1.26721.

[42] McDevitt CA, Wildey GM, Cutrone RM. Transforming growth factor-b1 in a sterilized tissue derived from the pig small intestine submucosa. J Biomed Mater Res. 2003;67A:637-640. DOI: 10.1002/jbm.a.10144.

[43] Record RD, Hillegonds D, Simmons C, Tullius R, Rickey FA, Elmore D, Badylak SF. In vivo degradation of 14C-labeled small intestinal submucosa (SIS) when used

for urinary bladder repair. Biomaterials. 2001;22:2653-2659. DOI: 10.1016/s0142-9612(01)00007-2.

[44] De Silva GS, Krpata DM, Gao Y, Criss CN, Anderson JM, Soltanian HT, Rosen MJ, Novitsky YW. Lack of identifiable biologic behavior in a series of porcine mesh explants. Surgery. 2014;156:183-189. DOI: 10.1016/j.surg.2014.03.011.