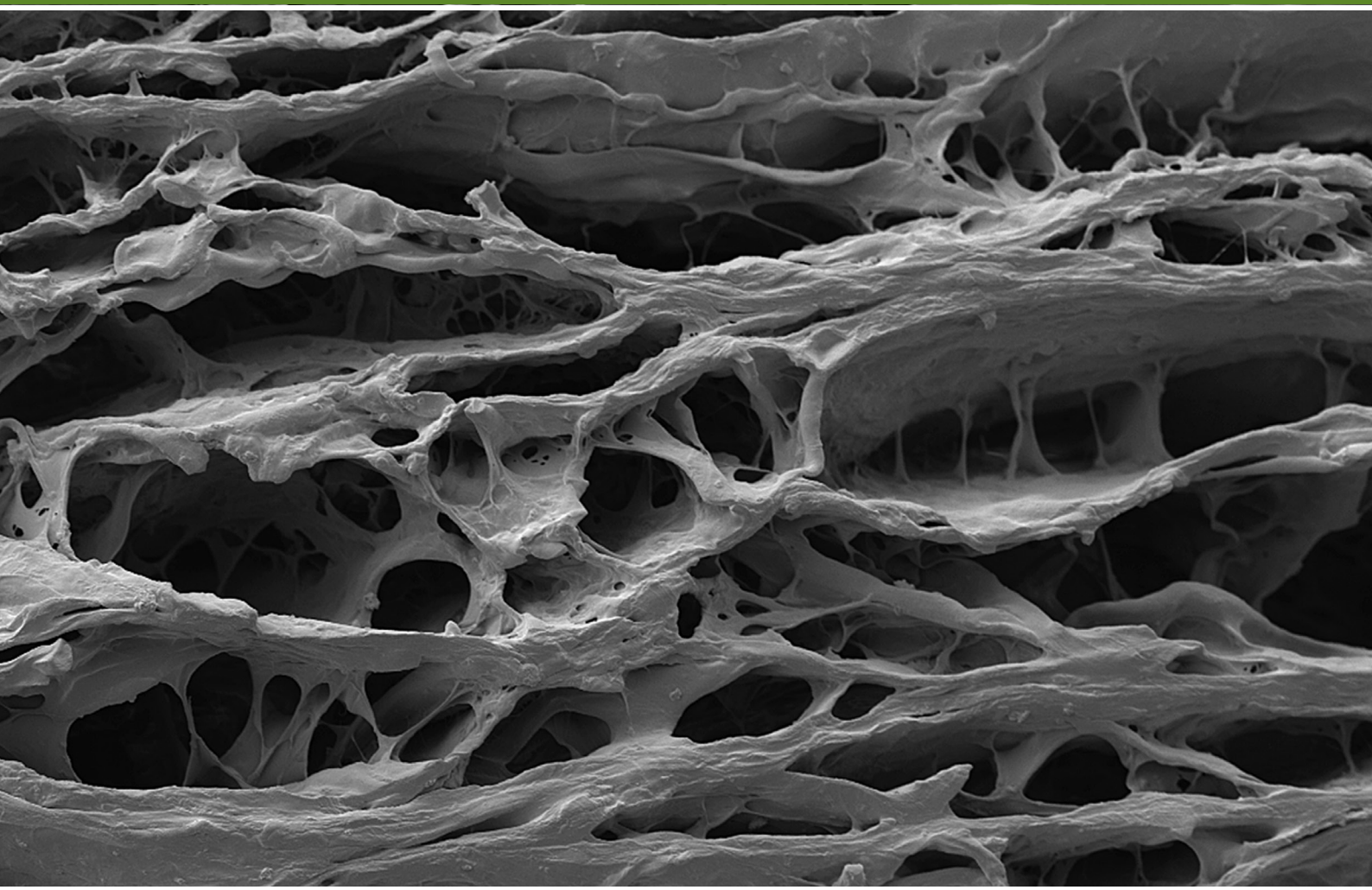
Biodesign®

Scientific monograph series



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Content

The effects of cross-linking in biologic grafts

Natural vs. chemical cross-linking

All biologic grafts are naturally cross-linked, but some are also chemically cross-linked during processing.

Natural cross-linking, a common biological reaction joining two or more molecules by a covalent bond, occurs in the mammalian body as connective tissue forms, catalyzed by native enzymes. This normal process provides strength and makes biologic grafts formed from these tissues—such as Biodesign—effective in soft-tissue repair without additional chemical cross-linking, a process used during the manufacture of some other grafts on the market.

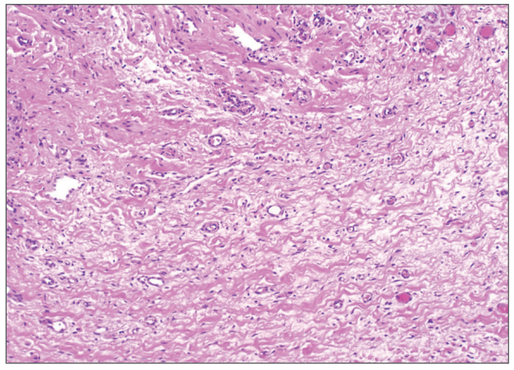
The chemical cross-linking process, sometimes called tanning, mimics natural cross-linking by treating biologic grafts with harsh chemicals, making them resistant to degradation in vivo. However, controlled degradation of the graft is an important step in healing because it signals the surrounding tissue to repair the wound. When degradation is inhibited, cellular attraction is inhibited.[1] Additionally, chemical cross-linking alters the three-dimensional structure of the graft, inhibiting host cell infiltration.[2-4] See Figure 1 below, and notice the degree of cell infiltration in non-cross-linked Biodesign and a cross-linked biologic graft.

The chemicals used in the tanning process can also release cytotoxic residues,[5] induce calcification of the graft,[6] and cause the body to react as if the graft is foreign,[2] provoking inflammation and encapsulation.[7]

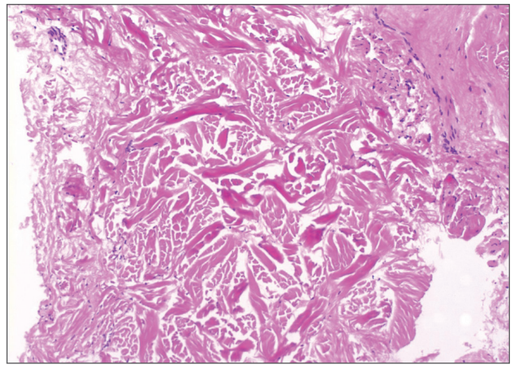
Chemically cross-linked grafts

Some biologic grafts on the market are chemically cross-linked during processing. According to one manufacturer of chemically cross-linked grafts, its grafts are chemically cross-linked for "long-lasting dimensional stability."[8] Published results support this outcome but also demonstrate that this can lead to detrimental results.[2] Chemically cross-linked biologic grafts can remain in the body like synthetic mesh—with the associated unwanted results and risks.

Figure 1: Histologic images showing the extent of cellular infiltration (purple dots) in a Biodesign graft and a cross-linked material.



Biodesign graft at 8 months



Cross-linked material at 26 months.

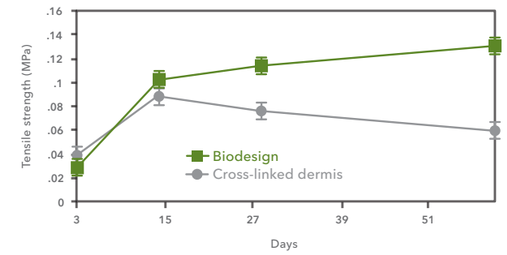
Manufacturers might chemically cross-link biologic devices to decrease the immune response to foreign tissue. However, chemical cross-linking has been shown to result in chronic inflammation,[9] encapsulation, and even a host-versus-graft type of reaction.[2] Lastly, chemical cross-linking might be performed to increase the strength of the biologic device. Yet this is not always the case. At least one study has shown that cross-linked porcine dermis actually decreases in strength of incorporation after two weeks and beyond (Figure 2).[10]

Tissue integration with Biodesign grafts

Because they are not chemically cross-linked during the careful treatment process, Biodesign grafts provide a natural scaffold that allows the body to restore itself through site-specific tissue remodeling. As healing occurs, Biodesign grafts initially act as scaffold material to support the population of the ECM with patient-derived cells. Over time, Biodesign grafts are gradually remodeled and integrated into the body, leaving behind organized patient tissue that provides long-term strength.[11] Biodesign grafts are not cytotoxic, are resistant to infection and encapsulation, and become strong, vascularized tissue that functions naturally. As shown in Figure 2, Biodesign grafts result in a repair that becomes stronger over time.[10]

This revolutionary tissue-repair technology is available for use in many parts of the body. As of June 2020, more than 1,600 journal articles have been published about the technology on which Biodesign grafts are based, including long-term data.[11] The technology behind Biodesign grafts is a breakthrough advancement in the evolution of tissue repair—a whole new category.

Figure 2: Strength of incorporation (SOI)



Strength of incorporation of explanted grafts. Days post-implantation versus tensile strength in megapascals (MPa). Error bars = SEM, N=6.[10]

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The effects of elastin in biologic grafts

Elastin in dermis-based biologic grafts

Elastin is a structural protein that gives body tissues their elasticity. Normal elastin content varies widely across different tissue types. For instance, the aorta contains 37-57% elastin, dermis contains between 4-10%, and many tissues, like liver, spleen, or intestinal submucosa, contain none or very little.[1-3]

Many dermis-based biologic grafts are harvested from human cadaveric tissue. Although tissue banking regulations ensure that they are carefully tested for their disease transmission potential, they may not be screened for the donor's age, smoking history, or sun exposure history. Both smoking and sun exposure have been shown to dramatically increase the appearance and size of elastic fibers in the skin. This apparent increase is due primarily to elastin damage.[4] Thus, many of these harvested dermis-based biologic grafts may contain damaged elastin.[5]

Elastin and collagen ratios in tissues affect their function.[6] For dermis-based biologic grafts, the elastin contributes elasticity, significantly affecting the graft's mechanical characteristics following implant. Because the turnover rate of elastin in humans is exceptionally slow, with an average residence time in tissues of approximately 74 years,[7] grafts made from dermis never completely remodel and remain within the patient, stretching over time. This laxity, also termed "diastasis," is a significant side effect of hernia repair that impacts patient quality of life and can lead to the appearance of a hernia recurrence.[8]

Complete tissue graft remodeling requires that all parts of the implant be replaced by newly formed patient tissue over time. Because elastin is stable within tissues and, unlike collagen, is not rapidly metabolized, the elastin from the graft remains in the patient throughout the process of tissue remodeling, contributing to the late-term laxity that is seen when dermis-based products are implanted.[8]

Properties of collagen and elastin

Collagen and elastin are both structural proteins. They are arranged together within tissues to provide the appropriate strength (collagen) and elasticity (elastin) the tissue needs for its required function.[6] A review of the mechanical properties of elastin and collagen demonstrates that collagen is nearly 100 times stronger and about 1,000 times stiffer than elastin (Table 1).[9] Additionally, collagen has one-tenth the strength of steel, while elastin is very weak.[9]

Table 1: Material Properties[9]

Material	Strength σ_{max} (GPa)	Stress in use (MPa)	Stiffness E_{init} (GPa)
Elastin	0.002	0.55	0.0011
Collagen	0.12	60	1.2
Spring steel	1.5	600	200

The ratio of collagen to elastin in biologic grafts can affect the ability of the device to completely remodel. Animal studies and human studies out to 2.5 years post-implantation demonstrate that elastin remains present in the tissue after non–cross-linked dermis-based biologic grafts are used.[10,11] If elastin is still present in the repaired tissue, the ability of the implant site to stretch over time remains.

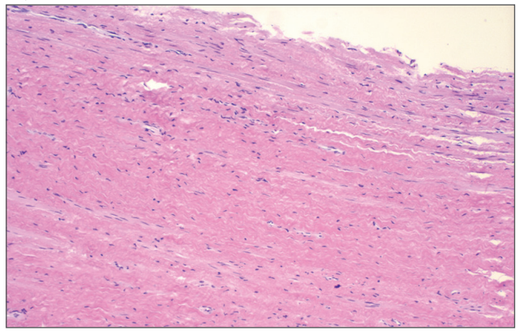
Long-term outcomes with Biodesign grafts

One dermis-based biologic graft has been shown histologically to retain elastin in the patient tissue, even 2.5 years after implant.[11] Clinical evidence demonstrates that the use of dermis-based biologic grafts results in diastasis and/or hernia recurrence even with "pre-stretching" of the graft.[8,12,13] At least one manufacturer of human dermis-based biologic grafts advocates suturing the graft under significant tension at the time of implant in order to minimize laxity as much as possible.[14] Even so, placing a highly elastic tissue in a low-elasticity site is inadvisable because the graft will still relax over time when placed under tension. As one group states, "[Human acellular dermis] should not be used as an interposition graft because of unacceptably high recurrence rates."[13] The requirement of a follow-up operation to repair laxity is not an insignificant consequence.[8]

A 2016 study comparing outcomes of various dermis-based biologic grafts in hernia repair demonstrated failure rates as high as 59% at 18 months.[15] This is significant, as hernia recurrence rates tend to increase over time. Conversely, recurrence rates as low as 13.6% after 3 years have been reported when the Biodesign Hernia Graft, an advanced tissue-repair graft made from small intestinal submucosa, is used in open ventral hernia repair procedures.[16]

Biodesign Advanced Tissue Repair products provide a natural scaffold that allows the body to restore itself through site-specific tissue remodeling.[17,18] As healing occurs, Biodesign grafts initially act as scaffold materials to support the population of the extracellular matrix with patient-derived cells.[17] Over time, Biodesign grafts are gradually remodeled and integrated into the body, leaving behind organized tissue that provides long-term strength.[19] The final result is completely remodeled, strong, vascularized patient tissue within 3-6 months, without the presence of a permanent material or significant residual elastin (Figure 1).[20]

Figure 1



Biodesign grafts completely remodel, creating complex tissues appropriate for the site of repair after only a few months. (Biopsy courtesy of Dr. Henry Flournoy, Coastal Associates of Obstetrics & Gynecology, Brunswick, Georgia).

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BIODESIGN® ADVANCED TISSUE REPAIR

Constructive tissue remodeling in tissue repair

Biologic grafts made from natural tissues, when processed correctly for clinical use, have unique properties that are not found in synthetic materials, bioresorbable materials, or highly processed and cross-linked graft materials.

These unique properties allow 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.[1,2]

Dynamic reciprocity

More than just allowing tissue repair to occur, these unique biomaterials directly interact with the recipient in a process known as "dynamic reciprocity" to orchestrate the complex process of tissue remodeling. Dynamic reciprocity is the bidirectional interaction between the acellular part of the body, known as extracellular matrix (ECM), and the body's cells.[3] In a natural environment void of injury, the ECM and the cells communicate with each other and respond dynamically to each other to maintain homeostasis. After injury occurs and the ECM is damaged, a biologic graft can be implanted to restore the matrix structure and allow dynamic reciprocity to begin anew, ultimately achieving tissue restoration via the process of constructive tissue remodeling.[4]

Tissue repair vs. remodeling

Tissue remodeling is more than just another phrase 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.[5] Wound healing, or 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.[6]

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 the correct 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.[7] The correct 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 growth factors, glycoproteins, proteoglycans, and glycosaminoglycans), which act to facilitate the renewal of natural dynamic reciprocity.[8] 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.

Phases 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: **cell recruitment, tissue renewal, tissue reinforcement**.

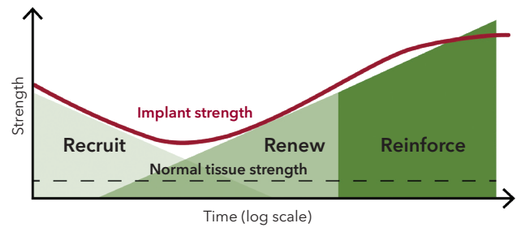
During **cell recruitment**, the remodeling process starts when the body's inflammatory and progenitor cells populate the biologic graft and release cytokines and growth factors that bind to the graft and recruit collagen-secreting fibroblasts.[8,9] In this phase, the graft primarily acts as a scaffold 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 proteins to **renew the tissue** through the complementary processes of phagocytosis, collagen deposition, and angiogenesis (blood vessel formation). In this phase, the biologic graft is gradually replaced by the patient's own tissue and cells.[8,9]

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.[1,2,10,11] 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 (Figure 1).[1,2,11] The resulting tissue structure is mature, organized and strong, and can withstand (and is even driven by) the natural physiological forces that it encounters.[12]

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.[1,2] By providing the correct matrix 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 1: Biodesign graft remodeling



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Constructive inflammation in wound healing

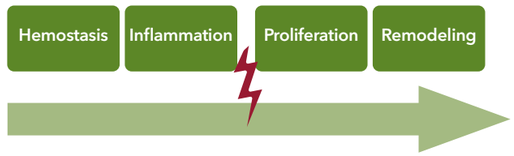
Wound healing is a dynamic process occurring after injury that is characterized by a careful orchestration of events occurring in a well defined order. The stages of wound healing include initial **hemostasis**, characterized by clot formation; **inflammation**, characterized by the deposition of inflammatory and progenitor cells, leading to the formation of granulation tissue; **proliferation**, where resident cells secrete growth factors and cytokines, collagen deposition occurs, and neovascularization begins; and **remodeling**, where the newly formed tissue matures and collagen strength increases to meet the demands of the body.[1]

Inflammation

Inflammation is an essential step in the wound healing process, as it both helps control bleeding and reduce the likelihood of infection. During inflammation, resident macrophages promote the influx of neutrophils. Neutrophils initiate the inflammatory response while secreting chemoattractants that promote the infiltration of additional immune cells like eosinophils, mast cells, and additional macrophages. Bacteria in the wound are phagocytosed, and damaged extracellular matrix (ECM) and dead cells are removed to clean up the area of injury. Growth factors are also released to stimulate angiogenesis (blood vessel formation) and direct the influx of progenitor cells to the area, eventually signaling the fibroblasts to form granulation tissue.[2,3]

In a healthy individual, the stages of wound healing occur in a sequential, yet overlapping order.[2] In patients with severe trauma or multiple comorbidities, however, wound healing often gets stalled in the inflammatory stage and fails to proceed down the ordered path, leading to chronic inflammation and impairment (Figure 1). Chronic inflammation is caused by the hyper and continued influx of immune cells and the overexpression and release of local proteases and enzymes. This leads to continued and repeated breakdown of newly deposited ECM and tissue, preventing the wound from progressing into the proliferation stage.[3]

Figure 1: Wound-healing stages



Chronic wounds fail to progress through the stages of wound healing, often getting stuck in the inflammation stage.

Graft materials following tissue loss

Controlling the inflammatory response and preventing the onset of chronic inflammation in the presence of multiple comorbidities and/or following major trauma are essential to successful wound healing. Because inflammation is partially directed by the ECM environment and the signaling factors contained within it,[4] implanting a naturally occurring graft material that replaces the damaged ECM can be an effective strategy for restoring a normal progression of healing and allowing tissue remodeling to occur.

The key to using a biologic graft material as a replacement for damaged tissue lies in the composition and structure of the graft material itself, largely due to its source and the processing methods used during its manufacture. The patient's immune system needs to accept the graft and the role it plays in tissue restoration, rather than recognizing the graft as foreign and mounting an assault on it, which leads to a rejection response and can create a chronic inflammatory environment.

BIODESIGN® ADVANCED TISSUE REPAIR

Foreign-body response due to overprocessing

While synthetic meshes and cross-linked biologic grafts can be engineered to have the adequate mechanical properties to support the primary function of soft tissue reinforcement, these materials have also been shown to have negative effects on inflammation.[5,6] These materials can be highly processed in ways that are not well accepted by the body. They have been shown to be associated with a rejection-type Th1-dominant lymphocyte response; the release of cytokines, such as IL-6, TNF-α, and IFN-γ, that lead to macrophage activation; and the polarization of macrophages into the cytotoxic (M1) phenotype.[5-7] These materials are viewed by the body as foreign, as something that needs to be removed. As a result, the body sets up a response designed to rid the material before returning to the normal progression of healing.

Biodesign grafts in inflammation

In contrast to synthetic materials or cross-linked biologic grafts, Biodesign grafts manufactured from porcine small intestinal submucosa (SIS) not only have adequate mechanical strength for the primary function of soft tissue reinforcement, they have also been shown to be more accepted by the body's immune system and do not lead a rejection response.[8] They do not cause the activation of the complement cascade, nor are they acutely rejected following implant.[8] They are associated with a Th2-dominant lymphocyte response (a response associated with transplant acceptance[9]) that does not adversely affect the patient's ability to overcome viral or bacterial infections.[10,11] They have also been associated with an M2 macrophage phenotype response[5]—a macrophage phenotype that promotes immunoregulation, tissue repair, and constructive tissue remodeling.[12] In a 2020 publication, an *ex vivo* model of peritoneal inflammation demonstrated that Biodesign grafts did not stimulate peritoneal tissue anti-healing gene expression or cytokine production.[13] Taken together, these findings demonstrate that the implantation of Biodesign grafts aids in the successful resolution of the inflammatory stage of wound healing and allows for progression into the proliferation stage, leading to complete tissue remodeling.

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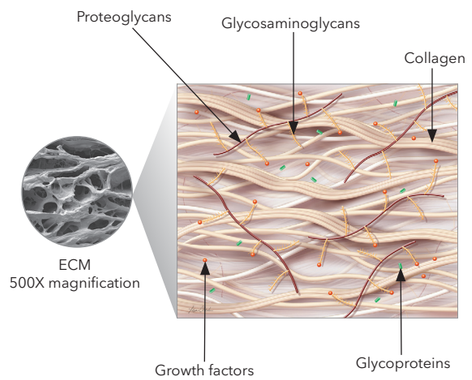
Biology of the Extracellular Matrix (ECM)

The extracellular matrix (ECM) is a fundamental component of biological tissues and is composed of an intricate network of complex protein and carbohydrate-based macromolecules that are organized in a tissue-specific manner (Figure 1).

Figure 1: Extracellular matrix components



Components of the ECM interconnect with each other to form a stable scaffold structure that contributes to the mechanical properties of tissues, provides a reservoir for growth factors and cytokines, and directly interacts with, and controls, many fundamental cell functions, including cell migration and blood vessel formation.[1]

Major structural ECM components

Collagens are formed by three polypeptide chains that wrap around each other to form a triple helical structure. There are at least 28 different types of collagens that can be separated into fibril-forming, network-forming, and fibril-associated forms.[2] In mature dermis, the most common fibril-forming collagen is collagen type I; in early phases of wound healing, collagen type III prevails. The composition of the fibril-forming collagenous backbone dictates tissue architecture, shape, and organization,[1] including that of dermis. Network-forming collagens, such as collagen type IV in the basement membrane of skin, are essential to maintaining normal epidermis function and restoring wound closure following injury.[3]

Proteoglycans are macromolecules containing a core protein with one or more covalently bound **glycosaminoglycan** (GAG) chains.[4] GAGs are linear, anionic polysaccharides made of repeating disaccharide units. There are four groups of GAGs: hyaluronic acid, keratan sulfate, chondroitin/dermatan sulfate, and heparan sulfate, including heparin. The highly negatively charged GAG chains allow the proteoglycans to retain water, providing natural lubrication to the ECM.[1] Proteoglycans also interact with **growth factors** and other ECM components to modulate signal transduction, ECM organization, and skin architecture.[5]

Glycoproteins consist of a large protein core with a polysaccharide chain attached. The laminin family of glycoproteins consists of approximately 20 different variants that assemble into a cross-linked web structure in combination with collagen type IV to form the stable basement membrane in skin.[1,3] Fibronectin is critical for the attachment and migration of cells, functions at many stages of the wound healing process, and acts as a "biological glue" of the ECM. Fibronectin contains binding sites to other fibronectin dimers, collagen, heparin, and cell surface receptors. These interactions between components are essential for normal skin integrity and play various important roles in wound healing after injury.[6-8]

Overview of general ECM functions

Constant Renewal. The ECM is a dynamic structure that is perpetually undergoing remodeling as its components are deposited, modified, or degraded.[1] It responds to external stimuli, such as mechanical stretch or pressure,[9] and the functions of additional matricellular components, such as growth factors, matrix metalloproteases (MMPs), and cytokines.

Reservoir for bioactive molecules. The ECM serves as a reservoir for growth factors and cytokines. In particular, the fibroblast growth factor family strongly binds to the heparan sulfate chains of heparan sulfate proteoglycan.[10] Transforming growth factor-β, secreted in its latent form, is stored in the ECM attached to its binding protein and remains inactive until activated by MMP-dependent proteolysis.[11] Both of these growth factors are important players in the wound healing process following injury.[12,13]

Providing chemical and physical cues. The ECM directly interacts with the local cells through their surface receptors. Chemical cues provided by ECM components, such as fibronectin, integrin receptors, and growth factors, can trigger distinct cellular responses.[14] Physical properties of the ECM, such as its rigidity, density, porosity, and topography, provide physical cues to the cells that can direct cellular differentiation down different phenotypical paths.[15] These direct ECM/cell interactions, first named "dynamic reciprocity" by Bornstein and colleagues in 1982[16] to describe the effects of the ECM on endothelial cell function, and later elaborated by Bissell and colleagues,[17] explain how the ECM and the cells communicate with each other and respond dynamically to each other to maintain homeostasis.

Summary

The ECM is a dynamic, three-dimensional scaffold composed of an interacting network of collagens, proteoglycans, and glycoproteins. It provides the structural support and the chemical and physical cues that, through direct ECM/cell interactions, regulate cell growth, differentiation, and behavior. Cells produce, secrete, deposit, and remodel ECM to mediate ECM composition. The ECM, in turn, provides a favorable local environment that influences cell characteristics and activities.[1] This feedback mechanism is critical for rapid and appropriate cellular responses to surrounding environmental changes and to the process of wound healing following injury.

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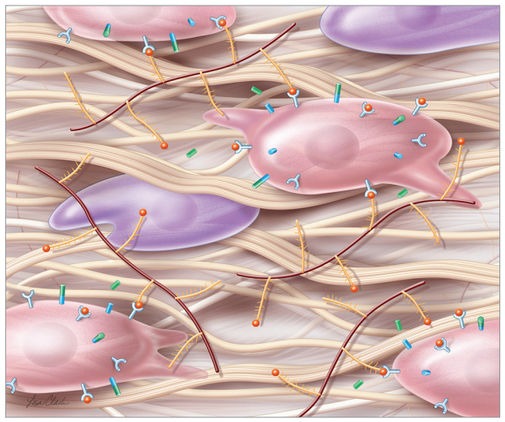
Dynamic reciprocity and wound healing

Dynamic reciprocity

Normal wound healing is characterized by a well-coordinated, progressive series of events designed to restore the barrier function and mechanical integrity of the skin. It involves interactions between cells and their microenvironment, of which the extracellular matrix (ECM) is the primary component. It is through these interactions that cells are directed to differentiate or dedifferentiate, proliferate or remain quiescent, and assume the architecture and function of the skin.[1]

Figure 1



Cells directly interact with their local ECM environment in a process called "dynamic reciprocity."

This direct ECM/cell interaction is a process that has been termed "dynamic reciprocity" (Figure 1).[2] In a natural environment void of injury, the ECM and the cells communicate with each other and respond dynamically to each other to maintain homeostasis. After injury occurs and the ECM is damaged, cells need to restore the local tissue structure by removing the debris from the damaged ECM and replacing it with healthy ECM, ultimately achieving tissue restoration via the process of constructive tissue remodeling.[3]

Dynamic reciprocity and normal wound healing

The stages of normal wound healing include initial hemostasis, characterized by clot formation; inflammation, characterized by the deposition of inflammatory and progenitor cells, leading to the removal of bacteria and devitalized tissue; proliferation, where resident cells secrete growth factors and cytokines and collagen deposition occurs to rebuild the ECM, resulting in granulation tissue formation; and remodeling, where the newly formed tissue matures and collagen strength increases to meet the demands of the body.[4]

Dynamic reciprocity is an essential mechanism by which the well-coordinated, progressive series of events of wound healing occurs. Examples can be found in each stage. During hemostasis, the direct interaction between platelets and the exposed ECM collagen triggers a series of events that leads to eventual thrombus formation and the stabilization of the fibrin clot.[5] During inflammation, monocytes bind to fibronectin, which increases their phagocytic capacity and leads to increased breakdown of damaged ECM and removal of cellular debris—essential steps if wound healing is going to proceed to the proliferation stage.[6] During the proliferation stage of wound healing, fibroblast binding to fibronectin stimulates their secretion of matrix-degrading enzymes, which in turn enhances endothelial cell migration and blood vessel formation (angiogenesis).[7] As angiogenesis progresses, endothelial cells form tubes, which involves the recruitment of pericytes in response to endothelial cell-derived basic fibroblast growth factor (FGF-2) and platelet-derived growth factor (PDGF).[8] Finally, as an example of dynamic reciprocity in the remodeling stage of wound healing, fibroblasts bound to fibronectin through integrin receptors migrate and proliferate in response to PDGF.[9] When this interaction occurs in the presence of TGF-β1, the fibroblasts are directed to preferentially secrete collagen type I instead of collagen type III, and a fraction of them are instructed to differentiate into myofibroblasts.[10] Myofibroblasts are then able to interact with collagens in the ECM to stabilize and remodel the wound.

The above are only discrete examples of dynamic reciprocity that occur in different stages of wound healing. In reality, each wound healing stage requires the coordinated effects of many different cell types and ECM components to lead the wound through the normal wound healing process.

Dynamic reciprocity and non-healing wounds

While most wounds heal in a timely and orderly pattern, the process can be stalled or stopped completely in patients with diabetes mellitus, venous insufficiency, suppressed immune systems, or following immobility that leads to prolonged pressure. Chronic wounds may develop in these cases, potentially leading to pain, immobility, hospitalization, and/or amputation.

Non-healing wounds fail to exhibit the normal sequence of actions and reactions between cells and the ECM that characterizes acute wound healing because of changes in the physiological environment resulting from the underlying disease. The normal, sequential pattern of these interactions does not occur, and the disruption of these interactions leads to downstream effects on other cell-ECM interactions that ultimately delay or prevent healing.[1]

Disease-related abnormalities that lead to the occurrence of chronic wounds include changes in cellular responsiveness, elevated proteolytic environments, and microvascular abnormalities. For example, diabetes is associated with deficits in the bactericidal action of granulocytes,[11] glycation of collagen and fibronectin that interferes with epithelial cell adherence,[12] and a decreased vasodilatory response.[13] Chronic wounds are characterized by the presence of elevated levels of various metalloproteases (MMPs) and decreased levels of tissue inhibitors of metalloproteases (TIMPs);[14] studies have found a correlation between elevated MMP levels, chronic inflammation, and non-healing wounds.[15,16]

Excessive degradation of the ECM and growth factors by MMPs deprives cells of attachment sites and signals required for migration, differentiation, and proliferation. The result is that cells can no longer respond to the normal cues in their environment, thus preventing the sequential series of changes in the matrix composition needed for wound healing to progress.[1]

Harnessing dynamic reciprocity to achieve healing

The presence of a natural, intact ECM in the local wound environment is essential for successful wound healing.

Restoring the natural ECM environment using tissue-engineered products has been shown to be an effective treatment strategy for a wide variety of acute and chronic wounds.[3] These materials can positively alter the local environment and lead to constructive tissue remodeling.[3,17,18] Due to dynamic reciprocity, the patient's cells remodel the biomaterial into the patient's own local tissue with local tissue properties. Rather than relying on the patient's cells to generate their own ECM or ECM attachment sites in a suboptimal healing environment, direct application of intact ECM may be an effective strategy for optimizing wound healing outcomes and improving patients' quality of life.

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