

# The Extracellular Matrix in Wound Healing

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Clinician understanding of pathophysiological event processes in wound healing must include knowledge of normal structure and function. Such information enables appropriate application of replacement products or adjunctive therapies that assist in restoring the normal healing process. For example, a matrix is more than a construct of collagen that acts as a scaffold for tissue re-growth (the common, basic perception) — it is a complex, highly organized three-dimensional structure that serves not only as a scaffolding, but also as a signaling, binding, and activating substrate that interacts with the highly organized wound healing process. A matrix is important at all stages of wound repair from homeostasis to healing; it may promote communication between the keratinocyte and the fibroblast. In the past few years, technology has allowed a better understanding of the events of wound healing. Peer-reviewed clinical data are now available on matrix replacement options in chronic wounds. This article provides an overview of the extracellular matrix and its role in wound healing.

## What is the Extracellular Matrix?

The extracellular matrix (ECM) is a complex structure that surrounds cells in all tissues of the body. Its exact biochemical composition varies somewhat from tissue to tissue. In healthy skin, the ECM helps support cells and comprises key components of the basement membrane that anchor and help replenish epidermal cells.

## Extracellular Matrix Components

Extracellular matrix components are integral to each phase of wound healing, interacting with cells and growth factors in a dynamic give-and-take that eventually results in wound closure. More specifically, components of the ECM play key roles in stimulating cell proliferation and differentiation, guiding cell migration, and modulating cellular responses.<sup>1-3</sup> When the ECM is dysfunctional, wound healing is slowed or stalled — eg, in difficult-to-heal or chronic wounds. The following sections describe the components of the dermal ECM and their roles in wound healing.

**Structural proteins.** Under normal, non-wound conditions, the ECM consists primarily of collagens, the most abundant proteins in the body. There are at least 19 different types of collagens, many encoded by different genes.<sup>4</sup> Collagen in the skin is primarily type I and type III and provide structure, strength, and integrity. Type IV collagen is a component of epidermal and endothelial basement membranes.<sup>5</sup>

Elastin, another protein found in the ECM, gives skin and other tissue elasticity by assuming an elongated, linear organization when stretched and returning to a more coiled structure when released.

**Cell-adhesive glycoproteins.** These molecules include fibronectin, laminin, and vitronectin. Cell-adhesive glycoproteins bind to cells and multiple components of the ECM and serve as modulators for growth factor activity.<sup>6</sup> Cells bind to adhesive glycoproteins via cell surface receptors called *integrins*.



**Glycosaminoglycans and proteoglycans.** These straight polysaccharide chains include hyaluronic acid, dermatan sulfate, chondroitin sulfate, heparin, heparan sulfate, and keratan sulfate. Glycosaminoglycans draw large amounts of water into their structures, allowing them to resist compression forces. Glycosaminoglycans are also somewhat rigid, which, combined with their high water content, permits migration of cells, nutrients, and other substances through their structures. Most glycosaminoglycans are bound to a protein core to form proteoglycans. An exception is hyaluronic acid, which does not form a proteoglycan.<sup>7</sup>

Glycosaminoglycans interact with proteins (such as the adhesive protein fibronectin) in the ECM. Through this interaction, glycosaminoglycans anchor proteins at specific locations and affect their biological activity.<sup>7</sup> Proteoglycans also serve as co-receptors for growth factors, participate in cell signaling, and help regulate the activity of many other molecules.<sup>9</sup> These activities enable glycosaminoglycans and proteoglycans to play key roles in cell adhesion and migration.

**Matricellular proteins.** These proteins include thrombospondins, osteopontin, tenascins, and secreted protein acidic and rich in cysteine (SPARC), which modulate cell-matrix interactions and help regulate inflammation and the response to certain growth factors. Additionally, matricellular proteins help promote keratinocyte migration and formation and contraction of matrix.<sup>9</sup>

## Extracellular Matrix and Wound Healing

In normally healing wounds, the ECM directs an organized response characterized by the four phases of hemostasis, inflammation, proliferation, and remodeling. The effects exerted by the various ECM components vary with wound stage and are influenced by their interactions with cells and growth factors in a dynamic, reciprocal process.<sup>1</sup>

When the dermis is wounded, damaged collagen fibrils and other proteins serve as signals for platelets to form a clot at the wound site.<sup>5</sup> Collagen also interacts with myofibroblasts and keratinocytes to effect wound contraction via interaction with integrins.

**Hemostasis.** During the hemostasis phase, the primitive or provisional ECM of fibrin and fibronectin is formed. This provisional or temporary matrix acts as a scaffold for contact guidance of leukocytes and fibroblasts.<sup>1</sup> Integrin binds endothelial cells to adhesion proteins such as fibronectin and vitronectin, a requirement for angiogenesis in wound healing, and activates vascular endothelial growth factor (VEGF).<sup>9,10</sup>

**Inflammatory phase.** During the inflammatory phase, leukocytes bind to ECM proteins through integrins as they leave the circulation and enter the extracellular space.<sup>11</sup> Extracellular matrix proteins stimulate the activity of monocytes/macrophages,

increasing the efficiency with which they clear neutrophils and debris from the wound site.<sup>12</sup> Binding to the ECM components also stimulates differentiation of monocytes into macrophages, which then produce various cytokines and chemoattractants for fibroblasts.<sup>13</sup>

**Proliferative phase.** Granulation tissue develops during the proliferative phase, characterized by a dynamic reciprocity among fibroblasts, growth factors, and the ECM.<sup>1</sup> After binding to the ECM, macrophages release growth factors that stimulate angiogenesis, collagen synthesis, and fibroblast proliferation; endothelial cells must exhibit integrins, which bind ECM proteins, in order for angiogenesis to proceed.<sup>14</sup> In turn, fibroblasts deposit matrix that further supports migration of cells, including macrophages, endothelial cells, and fibroblasts.<sup>1</sup>

**Remodeling phase.** During the remodeling phase, wound contraction continues as fibroblasts become myofibroblasts through their interactions with ECM proteins and growth factors.<sup>1,15</sup> Myofibroblasts then interact with collagen, vitronectin, and other proteins to contract the wound.<sup>16</sup> As the remodeling phase proceeds, fibronectin and hyaluronic acid are replaced by collagen bundles that lend strength to the tissue.<sup>1</sup>

## Implications for Difficult-to-Heal or Chronic Wounds

In difficult-to-heal or chronic wounds (eg, venous, diabetic, and pressure ulcers), the normal healing process is slowed or stalled due to underlying systemic dysfunction. These wounds exhibit deficiencies or dysfunction in the ECM — such wounds are characterized by a corrupt ECM that cannot support healing.<sup>17</sup> For instance, chronic wound fibroblasts are unresponsive to growth factors and other signals,<sup>18</sup> contain aberrantly high levels of metalloproteinases,<sup>19</sup> and lack the integrin receptor for fibronectin binding and keratinocyte migration.<sup>20</sup> These well-documented abnormalities possibly may be developing in difficult-to-heal wounds (ie, wounds still proceeding through the wound healing stages but at an exceedingly slow rate), although such wounds have not been well studied.

Chronic wounds presumably develop these characteristic biochemical abnormalities over some period of time. When wounds become chronic, they typically are non-responsive to most treatments. For these reasons, it may be most advantageous to intervene with aggressive healing strategies early in wound management to prevent progression to a chronic state. This may be particularly important in patients at high risk of developing chronic wounds, which includes those with diabetic, venous, or pressure ulcers who do not respond adequately to several weeks of standard care.

Because of the consequences of a corrupt ECM, wound healing strategies that replace the missing or dysfunctional ECM may be

beneficial. Ideally, such a replacement would closely approximate the components and structure of the normal dermal ECM, given its multifaceted and interactive nature.

## Conclusion

The ECM comprises many components that interact with cells and growth factors in a dynamic give-and-take that results in wound healing. Extracellular matrix components are central to every phase of wound healing — without them, healing would not proceed. Chronic wounds exhibit a dysfunctional or corrupt ECM; in difficult-to-heal wounds, these ECM deficits may be developing. For this reason, ECM replacement treatments may be an appropriate part of the management strategy for difficult-to-heal or chronic wounds.

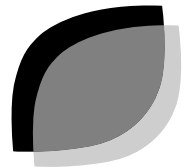
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**CLINICAL PHARMACOLOGY:** Papain, the proteolytic enzyme derived from the fruit of carica papaya, is a potent digestant of nonviable protein matter, but is harmless to viable tissue. It has the unique advantage of being active over a wide pH range, 3 to 12. Despite its recognized value as a digestive agent, papain is relatively ineffective when used alone as a debriding agent, primarily because it requires the presence of activators to exert its digestive function. Urea is combined with papain to provide two supplementary chemical actions: (1) to expose by solvent action the activators of papain (sulfhydryl groups) which are always present, but not necessarily accessible, in the nonviable tissue or debris of lesions, and (2) to denature the nonviable protein matter in lesions and thereby render it more susceptible to enzymatic digestion. In pharmacologic studies involving digestion of beef powder, Miller<sup>1</sup> showed that the combination of papain and urea produced twice as much digestion as papain alone. Chlorophyllin Copper Complex Sodium adds healing action to the cleansing action of the proteolytic papain-urea combination. The basic wound-healing properties of Chlorophyllin Copper Complex Sodium are promotion of healthy granulations, control of local inflammation and reduction of wound odors.<sup>2</sup> Specifically, Chlorophyllin Copper Complex Sodium inhibits the hemagglutinating and inflammatory properties of protein degradation products in the wound, including the products of enzymatic digestion, thus providing an additional protective factor.<sup>1,2</sup> The incorporation of Chlorophyllin Copper Complex Sodium in PANAFIL SE permits its continuous use for as long as desired to help produce and then maintain a clean wound base and to promote healing.

**INDICATIONS AND USES:** PANAFIL SE is suggested for treatment of acute and chronic lesions such as venous, diabetic and decubitus ulcers, burns, postoperative wounds, pilonidal cyst wounds, carbuncles and miscellaneous traumatic or infected wounds. PANAFIL SE is applied continuously throughout treatment of these conditions (1) for enzymatic debridement of necrotic tissue and liquefaction of fibrinous, purulent debris, (2) to keep the wound clean, and simultaneously (3) to promote normal healing.

**CONTRAINDICATIONS:** Do not use if you are allergic to or have known or suspected hypersensitivity to any ingredient in this product.

**PRECAUTIONS:** See Dosage and Administration. Not to be used in eyes.

**ADVERSE REACTIONS:** PANAFIL SE is generally well-tolerated and non-irritating. A small percentage of patients may experience a transient "burning" sensation on application of the spray. Occasionally, the profuse exudate resulting from enzymatic digestion may cause irritation. In such cases, more frequent changes of dressings until exudate diminishes will alleviate discomfort.

**DOSAGE AND ADMINISTRATION:** Cleanse the wound with ALLCLENZ<sup>®</sup> Wound Cleanser or saline. Avoid cleansing with hydrogen peroxide solution as it may inactivate the papain. Note: Papain may also be inactivated by the salts of heavy metals such as lead, silver and mercury. Contact with medications containing these metals should be avoided. In accordance with good wound care practices, protect the periwound with a skin protectant of choice to prevent and/or reduce maceration and irritation due to drainage from the wound. When practicable, daily or twice daily changes of dressings are preferred. Longer intervals between redressings (two or three days) have proved satisfactory, and PANAFIL SE may be applied under pressure dressings.

**INSTRUCTIONS FOR USE:** Hold the PANAFIL SE spray bottle 2"–4" from wound. Upon first use, depress the nozzle gently to break seal. Apply drug in a single layer to cover wound bed. Note that application of cover dressing (gauze or appropriate dressing of choice) should cause drug to disperse for additional coverage. Wipe nozzle with clean gauze after each use.

It is not necessary to shake or prime the bottle.

**HOW SUPPLIED:** 34 mL bottle.

Store at controlled room temperature 20–25° C (68–77° F).

**REFERENCES:** 1. Miller, J.M.: The Interaction of Papain, Urea and Water-Soluble Chlorophyll in a Proteolytic Ointment for Infected Wounds, *Surgery* 43:939, 1958. 2. Smith, L.W.: The Present Status of Topical Chlorophyll Therapy, *New York J. Med.* 55:2041, 1955. 3. Barnard, R.D.: Elucidation of Chemically Defined Haptens For Competitive Inhibition of Aggressin Activity, *Immunol.* 8:78, 1954.

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