Chapter 1

Tissue Scarring

Lessons from Wound Healing

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Abstract

Tissue scarring due to abnormal matrix remodeling is an important cause of organ failure, which is a leading cause of morbidity and mortality. Current studies have focused on determination of the molecular basis of controlled wound healing, and uncontrolled tissue scarring. Scarless repair is a unique feature of fetal wounds in early gestation. Our understanding of the molecular basic of fetal response during wound healing may represent a paradigm to modulate incomplete and/or excessive healing (tissue scarring) to an ideal scarless healing. Once the fetal microenvironment that steers scarless wound healing is known, attempts to create a similar artificial environment to modulate abnormal tissue scarring could be accomplished. This brief review addresses the pathogenesis of wound healing and its relevance to tissue scarring.

Wound Healing

A wound is a discontinuity of tissue integrity, while healing is the complex and dynamic process of reconstituting that integrity. Superficial surgical incision causes injury to the lining epithelial cells, disrupts underneath basement membrane, and damages the surrounding connective tissue cells. Such damage induces inflammatory reactions, matrix deposition, and resolution, which are essential components of wound healing. Immediately after the injury, clotted blood containing fibrin and blood cells accumulates in the wound area. In addition, locally generated inflammatory mediators start to recruit neutrophils within 24 hours, with increased proliferating activity in basal epithelial cells. By day 3, most neutrophils are replaced with macrophages. Granulation tissue usually consists of proliferating fibroblasts embedded in the extracellular matrix (ECM) and new blood vessels, and becomes apparent on day 3. The repair process continues, and matrix components in the granulation tissues begin to bridge the wound, which is accompanied by re-epitheliazation. The macrophage has an important role in the healing process. Macrophages are predominant within the injured areas in around 48 to 72 hours after injury. They do not only act as phagocytic cells, but also produce various factors involved in the proliferation and differentiation of matrix-producing fibroblasts to synthesize matrix proteins. Altered macrophage population may result in abnormal healing with poor debridement. A pathogenic role for T cells has also been suggested during the healing process. Experimental studies have suggested that dendritic epidermal T cells (DETCs) that bear a γδ

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T-cell receptor (TCR) play an important role in wound healing. Compared with wild-type mice, a delayed wound closure and reduced epithelial hyperthickening has been observed in TCR$\delta^{-/-}$ mice, which lack γδ T cells, after a full-thickness skin wound.[1]

At about one week after the original wound, although the inflammatory features essentially disappear, fibroblast proliferation and matrix deposition continue. At the end of the first month, the wound is usually healed with scar tissue, covered with a layer of surface epithelium. Every so often, non-surgical wounds are irregular, and the extent of the injury to the surrounding cells and tissues is severe, which makes the healing process difficult; in such cases, healing is accomplished by second intention. Healing by second intention is a complex dynamic process with intensified inflammatory responses, granulation tissue formation, and wound contraction. Usually the pre-injury architecture is not recovered, and original structures are replaced with a scar tissue. The matrix remodeling may continue for a long time with individual variations, which is often influenced by the aging process.

Complex interactions among various cytokines and growth factors regulate the wound healing process. EGF (epidermal growth factor) helps in regeneration of epithelial cells and proliferation of fibroblasts,[2] while PDGF (platelet-derived growth factor) plays a crucial role in proliferation, migration and differentiation of fibroblasts during wound healing.[3] FGF (fibroblast growth factor) and VEGF (vascular endothelial growth factor) exert angiogenic effects on endothelial cells and subsequent neovascularization.[4,5] TGF-β (transforming growth factor-β) helps in granulation tissue formation and subsequent matrix remodeling during the healing process.[6] The replaced scar tissue is rarely as strong as the original tissue. In addition to the above-mentioned factors, certain systemic and local factors influence the complex healing process. For example, vitamin C deficiency impairs healing, by inhibiting collagen synthesis, while, steroid therapy, age, presence of local infections, circulatory state, and genetic background might influence the healing process. Keloid is a scar tissue that is formed as a result of abnormal healing due to excessive accumulation of ECM proteins. The predominant occurrence of keloid in black population is suggestive of a genetic predisposition.[7]

Recent studies have identified the signaling cascade involved in wound healing. For instance, Jun kinase (JNK) signaling pathway plays a crucial role in efficient wound healing in *Drosophila*.[8] The expression of alpha v beta 6 integrin has been reported to be induced in keratinocytes, which is associated with the fusion of the epithelium and initiation of granulation tissue formation during wound healing.[9,10]

Fetal Wound Healing

The wound repair process in adults is characterized by scar tissue formation, often associated with contracture. Such deformity might be associated with pathological consequences. In contrast to adult wounds, fetal wounds heal without leaving any histological features of scarring during early gestation. Understanding the fetal microenvironment during scarless wound healing will provide important information that might help in creating a similar artificial environment to modulate abnormal scarring. Although the pathomechanism of scarless fetal wound healing is not completely understood, studies have documented that inflammatory mediators, their effects on fetal dermal fibroblasts, subsequent downstream signaling cascade, and composition of matrix proteins are different than those of adult wound healing. Accelerated healing process, and a relative lack of an acute inflammatory response distinguishes fetal wound healing from adult wound healing. Increased monocytic infiltration with relatively less neutrophilic activity is associated with fetal wound healing.[11] Similarly, relatively less amount of interleukin (IL)-6, IL-8, TGF-β and FGF have been detected during scarless fetal wound healing, compared with the adult healing.[11-16] The exogenous addition of TGF-β1 in fetal wounds resulted in healing with scar tissue formation.[14,15] Likewise, lower level of IL-6

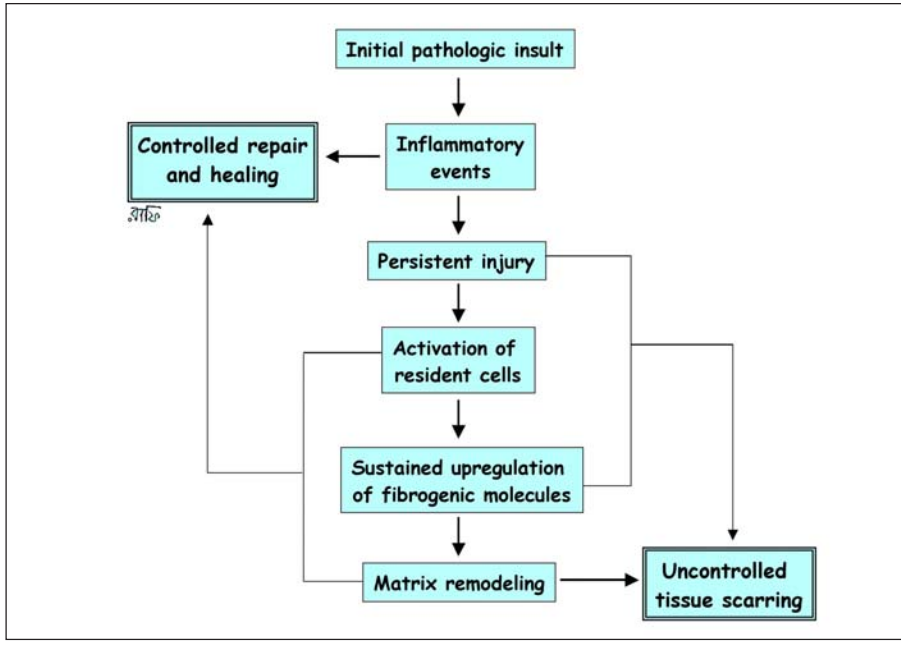

Figure 1. Simplified diagram showing various events during controlled wound healing and uncontrolled tissue scarring.

expression has been detected during fetal wound healing, while exogenous addition of IL-6 resulted in fetal wound healing with scar formation.[16] Furthermore, compared with adult wound healing process, relatively lower levels of bone morphogenetic proteins (BMPs), members of TGF-β superfamily, and BMP receptors have been detected during fetal wound healing.[17] On the other hand, the fetal wound contains higher amounts of hyaluronic acid, and consists of less tightly cross-linked ECM components. During the first 3 days, hyaluronic acid was detected at high levels in the adult wound, but was not detected by day 7. Adult wound healing is mostly achieved by accumulation of collagen, which is the main component of scar tissue. In contrast, the level of hyaluronic acid remains elevated for 21 days during fetal wound healing,[18] while collagen deposition is rapid and not excessive. Rapid upregulation of epidermal integrin receptors specific for fibronectin and other matrix proteins during human fetal wound healing might facilitate the migration of keratinocytes and subsequent re-epithelialization, thereby limiting inflammatory responses, and fibrogenic activities.[19] Fetal fibroblasts do not only have greater migratory abilities, but also have greater ability to induce formation of dermal appendages. Further studies are needed to determine the molecular mechanisms of relatively less differentiated cells in the fetal wound bed, and the reasons for less tightly cross-linked ECM accumulation during scarless fetal wound healing. The understanding of the molecular basis of fetal wound healing might help in designing therapeutic strategies to help avert tissue scarring in adults.

Recent studies have focused on the potentials of bone marrow derived stem cells in controlled tissue repair. In experimental studies, when mouse bone marrow cells from nondiabetic and diabetic mice were enriched with putative stem cells and injected under skin wounds of nondiabetic or type 2 diabetic Lepr^{db} mice, exogenous nondiabetic bone marrow–derived cells increased vascularization and improved wound healing in Lepr^{db} diabetic mice with little effect

on nondiabetic controls.[20] In clinical set up, autologous corneal stem cell grafting in patients with unilateral chemical burns was successful in restoring vision, reducing irritation with regeneration of regular corneal epithelium replacing the conjunctival overgrowth.[21] Similarly, in patients with partial limbal stem cell deficiency, amniotic membrane transplantation was effective in restoring a stable corneal epithelium.[22] Preliminary studies are projecting a promising role for stem cells in regeneration and healing process. Ongoing studies will help us understand the therapeutic potentials of stem cells in modulating tissue scarring.

Tissue Scarring

Irreversible end-stage tissue scarring continues to be a leading cause of morbidity and mortality, and to date no specific therapeutic agents are available to treat scarring of various tissues in mostly irreversible progressive diseases. Inflammatory reactions, matrix deposition, and resolution are important pathological events of the wound healing (Fig. 1). In contrast to the regular wound healing, no true resolution occurs during tissue scarring. It is the prolonged activation of the genes encoding for fibrogenic molecules that distinguishes controlled wound repair from uncontrolled pathologic tissue scarring, where accumulation of matrix proteins often continues in spite of apparent resolution and/or disappearance of the initial triggering factors. Activated fibroblasts and myofibroblasts mostly produce increased levels of matrix proteins, which eventually replace the normal tissue with scar tissue, leading to loss of function of the affected tissues or organs.[23]

Various factors and/or disorders are associated with tissue scarring. For instance, certain physical or chemical injuries and immunological disorders are associated with cutaneous fibrosis such as keloids, hypertrophic scars and scleroderma. Even a simple incision during a routine surgery may heal with scarring with unanticipated pathologic consequences. Often abdominal surgeries are associated with fibrous intraperitoneal adhesion with resultant mechanical obstruction of the intestine. Post-surgical strictures are encountered in the anastomotic sites like bowel, blood vessels, trachea, ureter, or bile duct, due to abnormal regulation of matrix metabolism. Similarly, metabolic diseases (diabetes mellitus), systemic diseases (hypertension), immunological diseases (glomerulonephritis), and even prolonged urinary protein leaking may lead to the development of renal scarring.[24,25] The clinical use of a significant number of useful drugs have been restricted for their tissue scarring effects, which includes bleomycin, cisplatin, cyclosporin, and gentamicin.[26-29] Prolonged alcohol consumption and chronic viral infections are usually associated with liver fibrosis,[30] while, toxic vapors, and certain drugs can induce pulmonary fibrosis. Although pulmonary fibrosis is triggered by diverse known and unknown factors including exposure to inorganic dusts or radiation, not all exposed individuals develop fibrosis, suggesting a possible genetic predisposition.[31,32] Identifying genetically susceptible population by genetic profiling might allow early detection, and early intervention.

The process and progression of tissue scarring can be broadly divided in to three phases and/or events: initial triggering events, leading to inflammatory events, which are usually followed by fibrotic events. These phases usually overlap, and are regulated by a wide range of phase-specific cytokines, chemokines, growth factors, and signaling molecules.[33] Details of the molecular and cellular interactions among some of these molecules during the progression of fibrosis/sclerosis in the lung, liver, heart, blood vessels, and kidney are described in the accompanying chapters. In general, there are similarities in tissue scarring in various organs, although the natures of the initial insults are diverse, and are not always detectable. In most fibrotic diseases, the initial insults trigger damage to the affected tissues or organs, which is accompanied by inflammatory reactions. Induction of various mitogenic and fibrogenic factors by inflammatory cells and activated resident cells results in activation of matrix-producing cells causing their proliferation, differentiation (to myofibroblasts), and eventual production of

excessive matrix proteins, or scar tissue, in response to the injury.[23,33,34] Furthermore, the antioxidant defense system is thought to be impaired during fibrogenesis, and the pathologic role of reactive oxygen species (ROS) has been demonstrated in the early stage of various human and experimental fibrotic diseases. For instance, high levels of myeloperoxidase and low levels of glutathione, an important antioxidant, have been detected in the alveolar epithelial lining fluid of patients with idiopathic pulmonary fibrosis, suggesting the role of oxidant-mediated injury in pulmonary fibrosis.[35,36] Similarly, overproduction of ROS, and down-regulation in the expression of cellular antioxidants enzymes have been suggested in mediating renal injuries; the protective effects of antioxidants, including vitamin E and α-lipoic acid in modulating renal injuries provide evidence of oxidant-mediated injuries in the pathogenesis of scarring renal diseases.[37,38]

Accumulation of inflammatory cells, including neutrophils, lymphocytes, mast cells, monocytes, and macrophages is a consistent histological feature of the early stage of tissue scarring. Of these, macrophages are not only actively involved in the inflammatory events by producing high levels of IL-8 to facilitate neutrophil trafficking into the affected sites,[39] but also exert mitogenic and fibrogenic effects by secreting various cytokines, chemokines, and growth factors, including PDGF and TGF-β1. These factors in turn can act on fibroblasts and myofibroblasts to produce excessive amount of matrix proteins. Certain macrophage regulating molecules, including macrophage colony-stimulating factor (m-CSF) and macrophage migration inhibitory factor (MIF), by inducing increased accumulation and local proliferation of macrophages determine macrophage population in the injured tissues, which eventually develop tissue scarring.[40,41] Studies have convincingly demonstrated that the release and activation of certain transcriptional factors [e.g., activating protein (AP-1) and nuclear factor-kappaB (NF-κB)], chemokines [e.g., monocyte chemoattractant protein-1 (MCP-1), regulated on activation normal T-cell expression and secreted (RANTES)] cytokines (e.g., IL-1, IL-4, IL-8), and growth factors [e.g., PDGF, TGF-β1, tumor necrosis factor (TNF)-α], by infiltrating inflammatory cells could intensify both the inflammatory and fibrotic events in the affected organs.[42-44] Moreover, ECM-derived signals may exert chemotactic effects on a number of matrix-producing cells, which are involved in transcriptional activation of AP-1 and NF-κB to produce inflammatory cytokines, such as IL-1 and TNF-α and thereby exacerbate the fibroproliferative process.[45] In early stage of tissue scarring, inflammatory infiltration of lymphocytes and macrophages, with induction of adhesion molecules, such as vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) by resident cells has been detected.[46] Both VCAM-1 and ICAM-1 are ligand for receptors expressed on memory-activated T cells and monocytes, and thus could create a microenvironment for the interaction of inflammatory cells and with resident cells. Change in the microenvironments due to altered composition of matrix proteins during tissue scarring may activate adjacent cells to produce factors that may influence both inflammatory responses and matrix remodeling. For instance, a type I collagen-rich microenvironment could activate matrix-producing hepatic stellate cells,[47] and these activated cells express increased levels of collagen receptors α1β1 and α2β1 integrins.[48] Some of these collagen receptors of integrins are also involved in the signal transduction, and may participate in transcriptional regulation of genes that might regulate proliferation, migration and adhesion of matrix-producing cells, and thus influence and contribute to tissue scarring. Heat shock protein 47 (HSP47) is a collagen-specific molecular chaperon, and is involved in the biosynthesis and secretion of procollagens.[49] Recent studies have documented a fibrogenic role for HSP47 in excessive accumulation of collagens during tissue scarring.[50-55]

An imbalance in the level of production and rate of degradation of matrix proteins could determine the extent of tissue scarring, in the involved tissues and organs. Accumulation of ECM is mostly achieved through the production collagenous and non-collagenous proteins.

The degradation of ECM is mostly regulated by proteolytic enzymes, including MMPs (matrix metalloproteinases) and ADAMs (a disintegrin and metalloproteinase domain).[56,57] In addition, tissue inhibitors of metalloproteinases (TIMPs) also play an active role in matrix remodeling by neutralizing activities of MMPs. For instance, high expression levels of MMP-1, -2, and -9 have been detected during pulmonary fibrogenesis,[58] which was associated with increased levels of their inhibitory enzymes, TIMPs -1 and -2.[59] It is likely that the expression of TIMPs could neutralize the collagenolytic effects of MMPs, and thereby could facilitate matrix accumulation. Recent studies have suggested that TGF-β1 could induce a number of matrix remodeling molecules, including MMPs and plasminogen activator inhibitor-1 (PAI-1) during tissue scarring.[60,61] The reversibility of scarring in affected organs may be partly determined by the proteolytic activities of the relevant enzymes.

Conclusion

The basic science is meaningful, consequential and far-reaching when the hard, and often the difficult work of scientists is applied to minimize patient's sufferings, by clinical control of disease progression. The detailed understanding of the molecular mechanisms of scarless fetal wound healing might allow basic scientists and clinicians to influence the outcome of the scarring process, by preventing and/or delaying the progression of excessive tissue scarring. In this respect, it has been convincingly demonstrated that a similar type of injury elicits different responses by adult and fetal dermal fibroblasts, resulting in healing with scar formation in adults and healing without scar in fetus.[62] In this book, individual chapters do not only describe in detail the up-to-date information on fibrogenesis in various tissues and organs, but also discuss the implications of this information in developing new therapeutic strategies to treat progressive fibrotic diseases.

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