

TOPIC: WOUND HEALING

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INTRODUCTION

[Cytokine](https://www.sinobiological.com/research/receptors/cytokine-receptors) signalling is an important part of the human body regulation. Most cytokines are cell-secreted proteins from glial cells in the nervous system and are necessary for intracellular signalling. Most cytokines are local regulators that alert and activate lymphocytes. Some cytokine-signalling pathways involve hormones such as growth hormones and leptin, the hormone that controls fat storage. The immune system depends on cytokine signalling to keep the human body healthy. Macrophages and dendritic cells engulf foreign particles and send a cytokine signal to nearby dormant lymphocytes. The receptors on the lymphocytes recognize the signal and activate. Those cells are specialized to recognize certain antigens. The combination of the macrophages and activation of lymphocytes through cytokine signalling help keep the body in homeostasis or the proper internal equilibrium. Some cytokine signals are not local but rather travel a long distance throughout the body. These cytokines are sometimes classified as hormones. This classification is changing, however, because cytokines are not secreted from glands. Instead, they are secreted from glial cells of the nervous system. These growth hormones are essential for embryonic development. Cytokines bind to receptors on target cells and activate a cascade of intercellular signals. The most common of these pathways is the protein kinase transduction cascade. After the cytokine binds to the receptor embedded in the membrane of the cell, inactive protein kinases are activated by a process known as phosphorylation.

Cytokine signalling pathway

Cytokine receptors contain one to three chains, one or more of which generally have limited similarity in the membrane-proximal region (often referred to as box1/box2 motifs). According to the nomenclature the ligand-binding subunit of a receptor is referred to as the alpha chain. Other signal transducing subunits are named beta chains, or gamma chains. All cytokine receptors are associated with one or more members of JAKs, which couple ligand binding to tyrosine phosphorylation of various signalling proteins (STATs) recruited to the receptor complex.

Molecular cloning of cytokine receptors and subsequent structure–function studies have revealed that unlike growth factor receptors, cytokine receptors are devoid of catalytic activity. Nevertheless, interaction of a cytokine with its receptor rapidly induces tyrosine phosphorylation of the receptor and a variety of cellular proteins, suggesting that these receptors transmit their signals through cellular tyrosine kinases. During the past 10–15 years, a large amount of experimental data has accumulated to indicate that most cytokines transmit their signals via a distinct family of tyrosine kinases termed *Janus* kinases or JAKs.

Cytokine receptors activate many signalling pathways generally by means of phosphotyrosine residues, which are recognized by SH2 domains on the signalling molecules. The STATs contain a carboxy-terminal SH2 domain, an SH3-like domain and several conserved amino-terminal regions, and a conserved region in the middle of the protein that binds DNA. Tyrosine phosphorylation of a carboxy-terminal site mediates homo- or heterodimerization through the SH2 domains, triggering movement to the nucleus and DNA binding. A native un-liganded receptor in complex with a JAK is in a catalytically inactive latent state. Receptor dimerization/oligomerization due to ligand binding results in the juxta positioning of the JAKs, which are in the vicinity through either homo- or heterodimeric interactions. The recruitment of JAKs appears to result in their phosphorylation, either via autophosphorylation and/or cross phosphorylation by other JAKs or via other families of tyrosine kinases. This activation is presumed to result in increased JAK activity. Activated JAKs then phosphorylate receptors on target tyrosine sites. The phosphotyrosine sites on the receptors can then serve as docking sites that allow the binding of other SH2-domain containing signalling molecules such as STATs, Src-kinases, protein phosphatases and other adaptor signalling proteins such as Shc, Grb2 and phosphatidylinositol 3-kinase (PI3K).



Figure 1. The response to injury is a phylogenetically primitive, yet essential innate host immune response for restoration of tissue integrity.

Tissue disruption in higher vertebrates, unlike lower vertebrates, results not in tissue regeneration, but in a rapid repair process leading to a fibrotic scar. Wound healing, whether initiated by trauma, microbes or foreign materials, proceeds via an overlapping pattern of events including coagulation, inflammation, epithelialization, formation of granulation tissue, matrix and tissue remodelling. The process of repair is mediated in large part by interacting molecular signals, primarily cytokines, that motivate and orchestrate the manifold cellular activities which underscore inflammation and healing.

Response to injury is frequently modelled in the skin,1 but parallel coordinated and temporally regulated patterns of mediators and cellular events occur in most tissues subsequent to injury. The initial injury triggers coagulation and an acute local inflammatory response followed by mesenchymal cell recruitment, proliferation and matrix synthesis. Failure to resolve the inflammation can lead to chronic nonhealing wounds, whereas uncontrolled matrix accumulation, often involving aberrant cytokine pathways, leads to excess scarring and fibrotic sequelae. Continuing progress in deciphering the essential and complex role of cytokines in wound healing provides opportunities to explore pathways to inhibit/enhance appropriate cytokines to control or modulate pathologic healing.



Figure 2**.** Wound healing is a complex process encompassing a number of overlapping phases, including inflammation, epithelialization, angiogenesis and matrix deposition. During inflammation, the formation of a blood clot re-establishes haemostasis and provides a provisional matrix for cell migration. Cytokines play an important role in the evolution of granulation tissue through recruitment of inflammatory leukocytes and stimulation of fibroblasts and epithelial cells. figure is adapted from (Singer and Clark, 1999)

Most types of injury damage blood vessels, and coagulation is a rapid-fire response to initiate haemostasis and protect the host from excessive blood loss. With the adhesion, aggregation and degranulation of circulating platelets within the forming fibrin clot, a plethora of mediators and cytokines are released, including transforming growth factor beta (TGF-beta), platelet derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), that influence tissue edema and initiate inflammation. VEGF, a vascular permeability factor, influences the extravasation of plasma proteins to create a temporary support structure upon which not only activated endothelial cells, but also leukocytes and epithelial cells subsequently migrate. Angiopoietin-1 (Ang-1), the ligand for Tie-2 receptors, is a natural antagonist for VEGF’s effects on permeability, a key regulatory checkpoint to avoid excessive plasma leakage.

Inflammation

Of the myriad of cytokines that have been investigated in terms of wound healing, TGF- beta (Singer and Clark, 1999) has undoubtedly the broadest effects. Despite the vast number of reports documenting the actions of TGF-beta in this context, both in vitro and in vivo, controversy remains as to its endogenous role. The paradoxical actions of TGF-beta are best appreciated in inflammation, where dependent upon the state of differentiation of the cell and the context of action, TGF-beta acts in a bi-directional manner (Wahl, *et al.,* 1994). Moreover, this understanding of the nature of TGF-beta has led to the hypothesis that it may act as a therapeutic tool in some circumstances, but also a target for therapeutic intervention in others (Wahl, *et al.,*1994). Recent studies, in particular those utilizing genetically manipulated animal models, have highlighted the impact of TGF-beta on various aspects of wound healing, and surprisingly, not all of its effects are conducive to optimal healing. Intriguingly, mutations within the TGF-beta1 gene, or in the cell signalling intermediate Smad (Khalil, *et al.,*1999)., lead to normal or even accelerated cutaneous wound healing responses (Ashcroft, *et al.,*1999). The rate of healing of full-thickness wounds in Smad (Khalil, *et al.,*1999). null mice were significantly greater than in their wild-type counterparts, associated with enhanced epithelialization and keratinocyte proliferation, and a markedly diminished inflammatory response. These observations have broad implications for understanding the role of TGF-beta in the endogenous wound healing response, in that an excess of TGF-beta may be a normal constituent of the response for rapid and optimal protection of the host. In the absence of infection, however, reduction of this overexuberant recruitment, inflammation and keratinocyte suppression may result in a more cosmetically acceptable scar. This knowledge may allow us to optimize the response by modulating selective cell pathways and to tailor therapy to specific cellular defects in pathological conditions such as chronic ulcers and fibrotic processes.

With the initial barrage of mediators, including TGF-beta, a chain reaction is set in motion, with recruitment, proliferation and activation of the cellular participants. Among the first cells to respond are the vascular endothelial cells, which not only respond to cytokines, but release them as well. Cytokine-induced enhancement of adhesion molecules (VCAM-1, ELAM-1, ICAM-1) on the endothelium provides the platform upon which circulating leukocytes expressing counter-adhesion molecules (integrins, selectins, Ig superfamily members) tether, slowing them down to sense the microenvironment and respond to chemotactic signals at the site of tissue injury (Wahl, *et al.,* 1999). Adhesion molecule interactions between blood leukocytes and endothelium enables transmigration from inside to outside the vessel wall in response to multiple chemotactic signals. In addition to the powerful chemotactic activity of TGF-beta1 for neutrophils and monocytes, (Khalil, *et al.,*1999). multiple chemokines are released to entice leukocytes into the site of tissue injury. Chemokines are represented by several families of related molecules based on the spatial location of the cysteine residues. Deletion of genes for chemokines leads to specific alterations in wound healing, underlying their role in this process (Sundy and Haynes, 2000).

Re-epithelialization

Clearance of debris, foreign agents, and/or infectious organisms promotes resolution of inflammation, apoptosis, and the ensuing repair response that encompasses overlapping events involved in granulation tissue, angiogenesis, and re-epithelialization. Within hours, epithelial cells begin to proliferate, migrate and cover the exposed area to restore the functional integrity of the tissue. Re-epithelialization is critical to optimal wound healing not only because of reformation of a cutaneous barrier, but because of its role in wound contraction. Immature keratinocytes produce matrix metalloproteases (MMPs) and plasmin to dissociate from the basement membrane and facilitate their migration across the open wound bed in response to chemoattractants. The migration of epithelial cells occurs independently of proliferation, and depends upon a number of possible processes including growth factors, loss of contact with adjacent cells, and guidance by active contact. TGF-beta1 stimulates migration of keratinocytes in vitro, possibly by integrin regulation and/or provisional matrix deposition (Wikner *et al.,* 1998). Behind the motile epidermal cells, basal cell keratinocyte proliferation is mediated by the local release of growth factors, with a parallel up-regulation of growth factor receptors including TNF-a, heparin-binding epidermal growth factor (EGF) and keratinocyte growth factor (KGF or FGF-7) Such growth factors are released not only by keratinocytes themselves, acting in an autocrine fashion, but also by mesenchymal cells and macrophages as paracrine mediators (Werner *et al,*,1992). Numerous animal models in which cytokine genes have been deleted or over-expressed have provided further evidence that such factors are involved in the process of epithelialization (Werner *et al.,*1994). TGF-beta1, and -beta2 are potent inhibitors of keratinocyte proliferation, with the Smad3 pathway implicated as the negative modulator. Since epithelialization is significantly accelerated in mice null for the Smad3 gene, with unchecked keratinocyte proliferation, but impaired migration in response to TGF-beta1, the implication is that the early proliferative event is critical to normal epithelialization. Once contact is established with opposing keratinocytes, mitosis and migration stop, and in the skin, the cells differentiate into a stratified squamous epithelium above a newly generated basement membrane. Other factors secreted by keratinocytes may exert paracrine effects on dermal fibroblasts and macrophages. One such factor is a keratinocyte-derived non-glycosylated protein termed secretory leukocyte protease inhibitor (SLPI), which inhibits elastase, mast cell chymase, NF-? B and TGF-beta1 activation. In rodents, SLPI is a macrophage-derived cytokine with autocrine and paracrine activities, but production by human macrophages has not yet been demonstrated. In mice, an absence of this mediator of innate host defense (SLPI null) is associated with aberrant healing (Ashcroft, *et al*., 2000)

Granulation Tissue and Angiogenesis

Granulation tissue forms below the epithelium and is composed of inflammatory cells, fibroblasts and newly formed and forming vessels. This initial restructuring of the damaged tissue serves as a temporary barrier against the hostile external environment. Within granulation tissue, angiogenesis (i.e. the generation of new capillary blood vessels from pre-existing vasculature to provide nutrients and oxygen) is potentiated by hypoxia, nitric oxide (NO), VEGF and fibroblast growth factor 2 (FGF-2) (Conway *et al.*, 2001) and by the chemokines, MCP-1 and macrophage inflammatory protein (MIP-1a).29 VEGF, released from wound epithelium and from the extracellular matrix by endothelial-derived proteases, stimulates endothelial cell proliferation and increases vascular permeability (Ferrara,1999). VEGF may be transcriptionally up-regulated in response to NO, which also influences vasodilatation, an early step in angiogenesis. In a cyclic fashion, VEGF also drives nitric oxide synthase (NOS) in endothelial cells. Endothelial cells express high affinity receptors for VEGF, VEGF R1 (Flt-1) and VEGF R2 (Flk-1), and represent a primary target of this angiogenic and vascular permeability factor (Ferrara,1999) Mice heterozygous for targeted inactivation of VEGF or homozygous for inactivation of its receptors are embryonically lethal, confirming the essentiality of VEGF in angiogenesis (Shibuya, 2001). Besides VEGF, FGFs transduce signals via four protein tyrosine kinase receptors34 to mediate key events involved in angiogenesis. FGFs recruit endothelial cells, and also direct their proliferation, differentiation and plasminogen activator synthesis. Clearly a multifactorial process, the cellular events underlying neovascularization are also impacted by TGF-beta1, EGF, TGF-a, endothelin 1, leptin, and indirectly, TNF-a and IL-1beta.

Of necessity, angiogenesis is a tightly controlled process. It is characterized not only by the presence of endogenous inducers, but also inhibitors which mediate a decline in the process as the granulation tissue, named for the granular appearance of the blood vessels in the wound, matures and scar remodelling continues. Among the identified endogenous inhibitors of re-vascularization are thrombospondin (TSP-1), IFN-? IP-10, IL-12, IL-4 and the tissue inhibitors of MMPs (TIMPs), in addition to the recently recognized activities of angiostatin and endostatin. Since loss of angiogenic control may have negative consequences as evident in tumors, rheumatoid arthritis, and endometriosis, identification of potential endogenous and therapeutic modulators continues.

Matrix Production and Scar Formation

With the generation of new vasculature, matrix-generating cells move into the granulation tissue. These fibroblasts degrade the provisional matrix via MMPs and respond to cytokine/growth factors by proliferating and synthesizing new extracellular matrix (ECM) to replace the injured tissue with a connective tissue scar. Although the stage is being set for tissue repair from the beginning (provisional matrix, platelet release of PDGF and TGF-beta, cytokine reservoir), fibroblasts migrate into the wound and matrix synthesis begins in earnest within a couple of days, continuing for several weeks to months. TGF-beta contributes to the fibrotic process by recruiting fibroblasts and stimulating their synthesis of collagens I, III, and V, proteoglycans, fibronectin and other ECM components.4, TGF-beta concurrently inhibits proteases while enhancing protease inhibitors, favoring matrix accumulation. In vivo studies have confirmed that exogenous TGF-beta1 increases granulation tissue, collagen formation, and wound tensile strength when applied locally or given systemically in animal models. Increased levels of TGF-beta are routinely associated with both normal reparative processes, as well as fibro pathology. In Smad3 null mouse wounds, matrix deposition (fibronectin) could be restored by exogenous TGF-beta, implying a Smad3-independent pathway, whereas collagen deposition was not restored, suggesting a dichotomous Smad3-dependent regulation. The progressive increase in TGF-beta3 over time and its association with scarless fetal healing have implicated this member of the TGF-beta family in the cessation of matrix deposition.36 Other members of the TGF-beta superfamily may also contribute to the wound healing response. Activin A when over-expressed in basal keratinocytes stimulates mesenchymal matrix deposition, whereas BMP-6 over-expression inhibits epithelial proliferation (Blessing *et a*l.,1996)

PDGF, released at the outset by degranulating platelets, represents a family of cytokines consisting of two polypeptide chains (A and B) which form the dimers PDGF-AA, AB and B. In addition to platelets, PDGF is released by activated macrophages, endothelial cells, fibroblasts and smooth muscle cells and is a major player in regulating fibroblast and smooth muscle cell recruitment and proliferation through PDGF specific receptor-ligand interactions (Claesson-Welsh, 1996). Beyond its role in fibroblast migration and matrix deposition, PDGF-A and -B also up-regulate protease production, in contrast to the anti-protease activity of TGF-beta. PDGF represents the only FDA approved cytokine/growth factor for the clinical enhancement of delayed wound healing. Also central to repair are the FGFs, which signal mitogenesis and chemotaxis, underlying granulation tissue formation, and the production of MMPs. FGF-1 (acidic FGF) and FGF-2 (basic FGF) have been the most intensely studied, but the additional members of this family may also support tissue repair and/or have clinical application. The role of FGF-2 has been confirmed in the FGF-2 null mouse which shows not only retarded epithelialization but also reduced collagen production (Ortega *et al*.,1998).

With many overlapping functional properties with FGFs, epidermal growth factor (EGF) orchestrates recruitment and growth of fibroblasts and epithelial cells in the evolution of granulation tissue. EGF and TGF-a, which share sequence homology, enhance epidermal regeneration and tensile strength in experimental models of chronic wounds (Andresen and Ehlers, 1998). TNF-a and IL-1beta, key mediators of the inflammatory process, also contribute to the reparative phase either directly by influencing endothelial and fibroblast functions or indirectly, by inducing additional cytokines and growth factors. IL-6 has also been shown to be crucial to epithelialization and influences granulation tissue formation, as shown in the wound healing studies of mice null for the IL-6 gene (Gallucci *et al.,* 2000) As repair progresses, fibroblasts display increased expression levels of adhesion molecules and assume a myofibroblast phenotype, mediated in part by TGF-beta and PDGF-A and -B, to facilitate wound contraction (Grinnell, 1994)

Remodelling Phase

The remodelling phase, during which collagen is synthesized, degraded and dramatically reorganized (as it is stabilized via molecular crosslinking into a scar), is also cytokine-mediated. Although repaired tissue seldom achieves its original strength, it provides an acceptable alternative. Degradation of fibrillar collagen and other matrix proteins is driven by serine proteases and MMPs under the control of the cytokine network. MMPs not only degrade matrix components, but also function as regulatory molecules by driving enzyme cascades and processing cytokines, matrix and adhesion molecules to generate biologically active fragments. TIMPs provide a natural counterbalance to the MMPs and disruption of this orderly balance can lead to excess or insufficient matrix degradation and ensuing tissue pathology (Birkedal-Hansen, 1995). Similarly, there exists a naturally occurring inhibitor of elastase and other serine proteases (i.e. SLPI). The coordinated regulation of enzymes and their inhibitors ensures tight control of local proteolytic activity. In physiologic circumstances, these molecular brakes limit tissue degradation and facilitate accumulation of matrix and repair.

Aberrant Healing

Rapid clearance of the inciting agent and resolution of inflammation during healing minimizes scar formation, whereas persistence of the primary insult results in continued inflammation and chronic attempts at healing. Prolonged inflammation and proteolytic activity prevent healing as evident in ulcerative lesions. On the other hand, continued fibrosis in the skin leads to scarring and potentially, disfigurement, whereas progressive deposition of matrix in internal organs such as lungs, liver, kidney or brain compromises not only their structure, but also function, causing disease and death. Inhibitors of TGF-beta (e.g. antibodies, decorin, Smad, antisense oligonucleotides) reduce scarring, as does local administration of exogenous TGF-beta336 or systemic delivery of TGF-beta1. (Song *et al.,* 1999) IFN-? is a natural antagonist of fibrogenesis through its ability to inhibit fibroblast proliferation and matrix production and has been shown to have clinical efficacy (Duncan, *et al.,* 1985) IL-10 may be considered anti-fibrotic via its anti-inflammatory activities, (Akdis, *et al.,* 2001) as are inhibitors of TNF-a. (Wahl, *et al.,* 2001)

Wound healing is a complex process encompassing a number of overlapping phases, including inflammation, epithelialization, angiogenesis and matrix deposition. Ultimately these processes are resolved or dampened leading to a mature wound and macroscopic scar formation. Although inflammation and repair mostly occur along a proscribed course, the sensitivity of the process is underscored by the consequences of disruption of the balance of regulatory cytokines. Consequently, cytokines, which are central to this constellation of events, have become targets for therapeutic intervention to modulate the wound healing process. Depending on the cytokine and its role, it may be appropriate to either enhance (recombinant cytokine, gene transfer) or inhibit (cytokine or receptor antibodies, soluble receptors, signal transduction inhibitors, antisense) the cytokine to achieve the desired outcome.

The body's response to tissue injury in a healthy individual is an intricate, sequential physiologic process that results in timely healing with full re-epithelialization, resolution of drainage, and return of function to the affected tissue. Chronic wounds, however, do not follow this sequence of events and can challenge the most experienced clinician if the underlying factors that are impairing wound healing are not identified. The purpose of this article is to present recent information about factors that impair wound healing with the underlying pathophysiological mechanism that interferes with the response to tissue injury. These factors include co-morbidities (diabetes, obesity, protein energy malnutrition), medications (steroids, non-steroidal anti-inflammatory drugs or NSAIDs, anti-rejection medications), oncology interventions (radiation, chemotherapy), and life style habits (smoking, alcohol abuse). Successful treatment of any chronic wound depends upon identification and management of the factors for each individual.

The body's response to tissue injury in a healthy individual is an intricate sequential physiologic process that results in timely healing with full re-epithelialization, resolution of drainage, and return of function to the affected tissue. Chronic wounds, however, do not follow this sequence of events and stall in some phase of wound healing, usually inflammation, without progression to the next phase. The lack of progression may be a result of inability to recruit the necessary cells, the lack of “materials” to build the tissue needed to fill and/or cover the wounded area, or pathological cellular dysfunction as a result of harmful products introduced into the body.

While the principles of standard wound care (including debridement, treating infection, moisture appropriate dressings, and off-loading or pressure-redistribution if indicated) are applicable to all wounds, identification and treatment of the impeding factors is a necessary part of the patient assessment and plan of care. These factors can be classified into the following categories: co-morbidities, medications, oncology interventions, and life style habit.

Co-morbidities

Diabetes

Diabetes is present in 8.3% of the United States' population and is becoming an increasingly prevalent issue in modern-day health care (ADA, 2012). One complication of diabetes is ulceration of the foot secondary to neuropathic involvement (Vairamon *et al.,2013*). Peripheral neuropathy leads to decreased protective sensation and foot deformities (Vairamon *et al.,2013*). The deformities then lead to a redistribution of pressure during gait and can result in ulceration at high pressure areas (Vairamon *et al.,2013*). Further, autonomic neuropathy results in trophic changes to the skin which can leave it vulnerable to cracking and breakdown, thus increasing the risk of infection (Vairamon *et al.,2013*). For patients with wounds of other etiologies (e.g. surgical incisions, pressure ulcers, or infected wounds) diabetes with poorly-controlled blood sugars results in cellular dysfunction that impedes all phases of wound healing. During hemostasis, there is decreased platelet-derived growth factor (PDGF) receptor expression on endothelial and epithelial cells, resulting in delayed transition to inflammation. An increase in the number of wound-activated macrophages (WAMs) causes increased and prolonged expression of inflammatory cytokines, thereby prolonging the inflammatory phase.

The proliferative phase is affected by impaired fibroblast signalling resulting in poor granulation tissue formation, fibrotic extracellular matrix resulting in stalled keratinocyte migration and delayed re-epithelialization, elevated metallomatrix proteinases and reactive oxygen species (ROS) resulting in ECM instability, and altered sensitivity to VEGF resulting in decreased angiogenesis and poor vascularization. lists the values recommended for diabetes markers in order to facilitate healing and prevent complications to all systems.

Obesity

Obesity is prevalent in one third of the United States' adult population (CDC, 2012). A major concern of obesity is the increased workload of the heart to supply oxygenated blood to body tissues. If the heart is unable to perfuse these tissues, ischemia can occur and thus contribute to necrosis and impaired wound healing. An obese person has a tendency to hyperventilate because the diaphragm is unable to fully descend due to the large amount of adipose tissue. Hyperventilation and decreased chest expansion then result in decreased vital capacity and decreased oxygenation of blood, thereby negatively impacting tissue oxygenation (Goldman, 2009). If tissue near a wound is not adequately oxygenated, fibroblasts cannot form collagen and oxygen-dependent cellular repair processes cannot occur (Goldman, 2009).

Once an obese patient develops a wound, the risk for infection is higher partly due to the avascularity of the surrounding adipose tissue (Goldman, 2009). Avascularity decreases the body's ability to defend against infection because the lack of oxygen prevents neutrophils from effectively phagocytizing bacteria, thus increasing the bacterial load of the wound (Goldman, 2009). Decreased blood supply to the wound prevents the necessary cells, e.g. neutrophils and macrophages, from reaching the wound site to protect against infection.

On a cellular level, researchers have shown that obesity can impair wound closure via the effects on circulating blood cells. Normally, vasculogenic progenitor cells (PC), derived from adult bone marrow, respond to peripheral injury by traveling through the circulatory system to the wound site and contributing to wound angiogenesis. In a recent study by Wagner et al, PCs of 25 non-diabetic and obese subjects (BMI > 30) and 17 non-obese subjects (BMI < 30) were harvested, cultured, and assessed for their ability to adhere, migrate and proliferate. PCs of obese subjects were significantly less adherent to collagen, had significantly decreased ability to migrate, and were unable to proliferate effectively. As a result, Wagner et al demonstrated that obesity is associated with impaired vasculogenic PC function which results in delayed wound closure.

Protein Energy Malnutrition

Malnutrition is a common problem in the elderly population and can result in delayed wound healing. Protein intake can result in decreased collagen production, angiogenesis and fibroblast proliferation, all of which negatively impact wound healing. In addition, ingested proteins are metabolized into amino acids and peptides that serve as enzymes, hormones, cyotokines, growth factors, and components of antibodies. Inadequate numbers of these protein substances impede both tissue maintenance and wound healing.

Insufficient protein intake can be assessed utilizing hematological markers such as albumin and pre-albumin or total lymphocyte count. Other diagnostic tools, namely the Rainey MacDonald nutritional index (RMNI) or the Mini-nutritional assessment (MNA), are useful in assessing risk or presence of protein malnutrition. A study by Guo et al utilized the RMNI, MNA and total lymphocyte counts to assess the impact of protein levels on wound healing for 207 patient’s status post hip fracture surgery (Guo, 2010). The authors determined that total lymphocyte count levels and MNA scores were significantly predictive for determining a patient's risk of delayed wound healing.

Protein malnutrition is important to assess for patients with chronic wounds of all etiologies. Forty-one patients with chronic venous insufficiency ulcers underwent a wound evaluation and nutritional assessment at both baseline and 12 weeks after start of care (Legendre, 2008). These patients were compared to a control group of 43 patients attending an outpatient dermatology clinic. Protein deficiency, marked by a serum albumin level less than 35 g/L, was independently related to increased wound size at 12 weeks follow-up. Also, researchers found that wound complications, such as infection or hospitalization, were associated with the presence of an inflammatory syndrome, as evidenced by the C-reactive protein level. Therefore, protein deficiency has a large impact on chronic wounds and can be associated with a poor prognosis.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to have a depressant effect on wound healing while simultaneously decreasing the granulocytic inflammatory reaction. NSAIDs inhibit the production of PGE2, an inflammatory mediating prostaglandin, and can thereby reduce pain (Guo, 2010). The suppression of PGE2 also occurs with excessive wound scarring and therefore NSAIDs may increase scar formation, especially if they are used during the proliferative phase of healing (Guo, 2010). NSAIDs have an anti-proliferative effect on blood vessels and skin, thereby delaying healing rate. NSAIDs may be prescribed post soft-tissue injury or post-surgery to assist with pain control management and to diminish inflammation; however, due to their negative effects on wound healing, their use is controversial.

Platelets, inflammatory cells, fibroblasts and epithelial cells produce nitric oxide (NO), partially in response to inflammatory cytokines that are released with injury. Subsequently nitric oxide assists in angiogenesis and inflammation mediation. If the nitric oxide enzymes necessary for this cascade are inhibited by either medication or disease, wound healing is impaired. Kaushal et al attempted to determine if by linking NO to ibuprofen, the anti-inflammatory effect could be retained while preventing its negative impact on healing (Legendre, 2008). The study compared ibuprofen alone with ibuprofen linked to NO on incisional wounds of rats. Ibuprofen linked to NO encouraged collagenation and epithelialization, as well as promoted wound contraction (Legendre, 2008). The results suggest that ibuprofen with NO may prevent the healing depressant effect of NSAIDs while maintaining the anti-inflammatory effects.

Another study by (Krischak *et al*., 2006) analysed the effects of NSAIDs on incisional wound healing after surgery using a rat model. Of 20 rats given incisions, 10 rats were given the NSAID diclofenac and 10 rats were given a placebo. Histologically, although all wounds closed, the rats treated with NSAIDs had a significant reduction in fibroblasts, thereby inhibiting proliferation (Legendre, 2008). Therefore, the results suggest that short-term use of NSAIDs after surgery is beneficial for its analgesic effect, but that patients with chronic wounds or diabetes could be more dramatically affected by NSAID's effect on fibroblast inhibition (Legendre, 2008). Thus, in these conditions, NSAIDs should be used with caution.

Steroids

Steroids are used in diagnoses such as asthma, cancer, or autoimmune disorders. An example of a commonly used steroid is dexamethasone, an anti-inflammatory drug and immunosuppressant glucocorticoid. Despite the beneficial effects of glucocorticoids in rheumatoid arthritis and bronchospasms, the anti-inflammatory and immunosuppressant actions of these steroids can result in delayed healing. Another at-risk patient population is transplant recipients who are placed on anti-rejection medications (e.g. Prednisone and Cellcept) after transplant surgery. The negative impact on wound healing results from the tendency of steroids to impede wound contraction and decrease tensile strength.

Even in the best of conditions, wound healing is an intricate process that requires timely communication of cellular and acellular components to complete the process in order to restore optimal function of both the injured tissue and the individual patient. Any pathophysiologic interruption in the process results in delayed or halted healing and presents conundrums that result in frustrating and expensive care and therefore does not achieve patient and provider goals. An astute clinician will explore all aspects of the patient medical history, psychosocial habits, potential undiagnosed disorders, and medications to determine the cause of wound chronicity and to develop the optimal plan of care.

Wound infection is one of the most common reasons for delayed wound healing (WHO, 2013). When a wound is contaminated or becomes infected, the immune system marshals energy to fight the bacteria, leaving little for healing. The bacteria produce toxins that also interfere with healing and cause cell death.

Conditions that reduce blood flow and oxygenation are common causes of poor wound healing. Advanced age, diabetes, peripheral vascular disease and high blood pressure can all affect circulation and interfere with healing. Anaemia and chronic lung disease impair oxygenation, and obesity slows wound healing because fatty tissue has fewer blood vessels. Tobacco also impairs wound healing because it reduces circulation.

Causes of slow wound healing. There are a number of things that can delay or complicate the healing of wounds, including: Diabetes mellitus. Low HGH (human growth hormone) Rheumatoid arthritis. Vascular or arterial diseases. Zinc deficiency.

Oxidative stress in normal and impaired wound repair.

A large percentage of the population suffers from wound healing abnormalities, in particular aged individuals, patients with diabetes, and those treated with immunosuppressive drugs, chemo- or radiotherapy. The mechanisms underlying the impaired healing response are still poorly understood. Recent studies provided strong evidence for a role of oxidative stress in the pathogenesis of non-healing ulcers. Therefore, it is of major importance to identify and functionally characterize the factors involved in the generation and detoxification of reactive oxygen species (ROS). This will provide the basis for the development of new strategies for therapeutic intervention. In this review we summarize the current information about the roles of low molecular weight antioxidants and ROS-detoxifying enzymes in normal and impaired wound repair, and we report on the consequences of their modulation at the wound site.

The production of various reactive oxidant species in excess of endogenous antioxidant defense mechanisms promotes the development of a state of oxidative stress, with significant biological consequences. In recent years, evidence has emerged that oxidative stress plays a crucial role in the development and perpetuation of inflammation, and thus contributes to the pathophysiology of a number of debilitating illnesses, such as cardiovascular diseases, diabetes, cancer, or neurodegenerative processes. Oxidants affect all stages of the inflammatory response, including the release by damaged tissues of molecules acting as endogenous danger signals, their sensing by innate immune receptors from the Toll-like (TLRs) and the NOD-like (NLRs) families, and the activation of signaling pathways initiating the adaptive cellular response to such signals. In this article, after summarizing the basic aspects of redox biology and inflammation, we review in detail the current knowledge on the fundamental connections between oxidative stress and inflammatory processes, with a special emphasis on the danger molecule high-mobility group box-1, the TLRs, the NLRP-3 receptor, and the inflammasome, as well as the transcription factor nuclear factor-Κb

The thematic issue addresses the role of oxidative stress in the development of diabetes and its related complications. Diabetes is a growing pandemic of the 21st century that has reached 1 in every 11 people worldwide (WHO, 2013). Changes in lifestyle such as unhealthy diet and physical inactivity are strongly associated with the growing prevalence of this disease. Chronic hyperglycemia, the common outcome of all diabetes types, may negatively influence the structure and function of many organ systems, particularly the cardiovascular, nervous, and renal systems. These diabetic complications are associated with increased rate of morbidity and mortality. The role of oxidative stress has been an important piece of the puzzle for the understanding of the complex mechanism by which diabetes and its complications are developed. In this context, numerous research groups have focused on the characterization of the reactive oxygen species (ROS) source, its triggered pathway, scavenging and antioxidant substances in diabetes. The multifaceted effects of oxidative damage in diabetes have been well addressed in the current issue and it provides a bigger picture of complication in a single platform. Therefore, this special issue includes 8 research articles focusing on the role of oxidative stress and antioxidant defense on the development of diabetes and its associated diseases. The guest editors are pleased to present a compendium of these cutting-edge original research and review articles as follows.

Astragalus membranaceus and Panax notoginseng, the Novel Renoprotective Compound, Synergistically Protect against Podocyte Injury in Streptozotocin-Induced Diabetic Rats,” ever since the diabetic complications have been understood and oxidative injury has been established as a cause, many compounds/plant extracts that attenuate oxidative damage and cell death have been researched upon. Adding to this field, one article in this issue showed the renoprotective role of treatment with Astragalus membranaceus (AG) and Panax notoginseng (NG). Treatment significantly reduced albuminuria and improved renal histopathology and podocyte foot process effacement in STZ-induced diabetic rats. AG and NG synergistically attenuated the structural and functional abnormalities in the kidney, and in the future, it may provide treatment combination for diabetic nephropathy and other kidney diseases.

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