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16/mhs03/031

Introduction to Histopathology

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Cytokine biology is now recognized as a fundamental component of immunology and the

actions of cytokines are understood to be essential mechanisms underlying host defense,

immunoregulation, and autoimmunity (John J *et al*..2011).

[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 (Rachel H et al..2016). 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 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 has 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 have 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 juxtapositioning 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).

Platelet Activation and Cytokine Release

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 (Singer.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 (Liekens et al..,2001).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.

Autocrine expression of TGF- beta 1 by leukocytes and fibroblasts, in turn, induces these cells to generate additional cytokines including tumour necrosis factor alpha (TNF-a), interleukin 1 beta (IL-1 beta) and PDGF, as well as chemokines, as components of a cytokine cascade.7 Such factors act to perpetuate the inflammatory cell response, mediating recruitment and activation of neutrophils and monocytes. In response to TGF- beta and other cytokines, which engage their respective cell surface receptors, intracellular signalling pathways are mobilized to drive phenotypic and functional responses in target cell populations (Heldin et al..,2001). Among the upstream signalling cascades engaged in acute tissue injury are NF-?B, Egr-1, Smads, and MAP kinases, which result in activation of many cognate target genes, including adhesion molecules, coagulation factors, cytokines and growth factors (Heldin et al..,2001)

Inflammation

Of the myriad of cytokines that have been investigated in terms of wound healing, TGF- beta 1 has undoubtedly the broadest effects. 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 Smad3, lead to normal or even accelerated cutaneous wound healing responses. The rate of healing of full-thickness wounds in Smad3 null mice was 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. 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. 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, multiple chemokines are released to entice leukocytes into the site of tissue injury (Wahl et al..,1987). 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

 Proteolytic activity is not constitutive, but transcriptionally driven by the cytokines, TGF-beta, IL-1beta and TNF-&alhpa;, released from multiple cellular sources. Neutrophil recruitment typically peaks around 24-48 hours post wounding, followed by an increasing representation of monocytes which are essential for optimal wound healing. Activation of these cells in the context of the wound microenvironment results in enhanced release of chemokines, recruitment of reinforcements, and amplification of the response, with the further release of cytokines, TNF-a, IL-1 and IL-6, that act as paracrine, autocrine and potentially, endocrine mediators of host defense (Clarke et al..,1996). Antigen stimulation drives lymphocytic recruitment and activation, but at a delayed pace compared to the rapid acute response essential to maintain tissue integrity. Beyond the neutrophil, monocyte/macrophage and lymphocyte participants, mast cells have become increasingly recognized as active participants with increased numbers noted at sites of cutaneous injury. Mast cells respond to monocyte chemotactic protein (MCP-1) and TGF-beta1, -beta2 and -beta3, and within the lesion, release mediators (histamine, proteoglycans, proteases, platelet activating factor, arachidonate metabolites) and cytokines, including TGF-beta and IL-4 . Once the inflammatory cells are activated, they become susceptible to TGF-beta1 mediated suppression to reverse the inflammatory process. Moreover, IL-4 may also dampen the inflammatory response as the inciting agent/trauma is dealt with and promote collagen synthesis during the repair phase (McCartney-Francis et al..,2001)

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. 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. TGF-beta1, and -beta2 are potent inhibitors of keratinocyte proliferation, with the Smad3 pathway implicated as the negative modulator (Werner et al..,1994). 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 (Ashcroft et al..,1999). 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 (Ashcroft et al..,1999). 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

The remodelling phase (i.e. re-epithelialization and neovascularization) of wound healing is also cytokine-mediated. Degradation of fibrillar collagen and other matrix proteins is driven by serine proteases and MMPs under the control of the cytokine network. Granulation tissue forms below the epithelium and is composed of inflammatory cells, fibroblasts and newly formed and forming vessels.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) and by the chemokines, MCP-1 and macrophage inflammatory protein (MIP-1a). VEGF, released from wound epithelium and from the extracellular matrix by endothelial-derived proteases, stimulates endothelial cell proliferation and increases vascular permeability (Belperio et al..,2000). VEGF may be transcriptionally up-regulated in response to NO, which also influences vasodilatation, an early step in angiogenesis (Ferrara, N..,1999). 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. 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.

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. TGF-beta concurrently inhibits proteases while enhancing protease inhibitors, favouring matrix accumulation. 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 scar less fetal healing have implicated this member of the TGF-beta family in the cessation of matrix deposition (Niesler et al..,2001). 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,37 whereas BMP-6 over-expression inhibits epithelial proliferation (Blessing et al..,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 (Ross et al..,1990) .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 Claesson-Welsh 1996). PDGF represents the only FDA approved cytokine/growth factor for the clinical enhancement of delayed wound healing (Laiho et al..,1987). Also central to repair are the FGFs, which signal mitogenesis and chemotaxis, underlying granulation tissue formation, and the production of MMPs (Ornitz et al..,1996). 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 (Payne et al..,2001). 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 S. et al..,1998)

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.

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 reduce scarring, as does local administration of exogenous TGF-beta336 or systemic delivery of TGF-beta1 (Wahl et al..,1993). 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 (Song et al., 1999). (Ghosh et al..,2001), IL-10 may be considered anti-fibrotic via its anti-inflammatory activities, (Akdis..,2001) as are inhibitors of TNF-a.

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.

2) Impaired wound healing — A wound is a disruption of the normal structure and function of the skin and underlying soft tissue (Taylor PT et al.,2004) . Acute wounds in normal, healthy individuals heal through an orderly sequence of physiologic events. The overlapping intricacy of the wound healing pathway serves to prevent a single primary factor from disrupting the process. As examples, local tissue ischemia and neuropathy can impair chemotaxis during the haemostasis and inflammatory stages, tissue necrosis and infection alter the balance of inflammation and compete for oxygen, and uncontrolled periwound edema and wound instability disrupt myofibroblast activity, collagen deposition, and cross-linking. Impaired wound healing often occurs in the setting of multiple, smaller contributing issues to stall the healing process; however, infection or ischemia alone can impair wound healing. When the healing process is stalled, a chronic wound may develop, and this is more likely to occur in patients with underlying medical disorders. Chronic ulceration commonly affects the lower extremities with a prevalence that ranges between 0.18 and 1.3 percent in the adult population (Ling et al.., 2003). The most common nonhealing wounds affecting the lower extremities are associated with chronic venous insufficiency, peripheral artery disease, and diabetes mellitus (Taylor PT et al.,2004; Ling et al.., 2003)

3)Oxygen is important for cell metabolism, especially energy production by means of ATP, and is critical for nearly all wound-healing processes. It prevents wounds from infection, induces angiogenesis, increases keratinocyte differentiation, migration, and re-epithelialization, enhances fibroblast proliferation and collagen synthesis, and promotes wound contraction ([Bishop, 2008](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2903966/#bibr5-0022034509359125); [Rodriguez et al., 2008](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2903966/#bibr81-0022034509359125)). In addition, the level of superoxide production (a key factor for oxidative killing pathogens) by polymorphonuclear leukocytes is critically dependent on oxygen levels.

Due to vascular disruption and high oxygen consumption by metabolically active cells, the microenvironment of the early wound is depleted of oxygen and is quite hypoxic. Several systemic conditions, including advancing age and diabetes, can create impaired vascular flow, thus setting the stage for poor tissue oxygenation. In the context of healing, this overlay of poor perfusion creates a hypoxic wound. Chronic wounds are notably hypoxic; tissue oxygen tensions have been measured transcutaneously in chronic wounds from 5 to 20 mm Hg, in contrast to control tissue values of 30 to 50 mm Hg ([Tandara and Mustoe, 2004](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2903966/%22%20%5Cl%20%22bibr95-0022034509359125)).

In wounds where oxygenation is not restored, healing is impaired. Temporary hypoxia after injury triggers wound healing, but prolonged or chronic hypoxia delays wound healing ([Bishop, 2008](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2903966/#bibr5-0022034509359125); [Rodriguez et al., 2008](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2903966/#bibr81-0022034509359125)). In acute wounds, hypoxia serves as a signal that stimulates many aspects of the wound-healing process. Hypoxia can induce cytokine and growth factor production from macrophages, keratinocytes, and fibroblasts. Cytokines that are produced in response to hypoxia include PDGF, TGF-β, VEGF, tumor necrosis factor-α (TNF-α), and endothelin-1, and are crucial promoters of cell proliferation, migration and chemotaxis, and angiogenesis in wound healing ([Rodriguez et al., 2008](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2903966/#bibr81-0022034509359125)).

In normally healing wounds, ROS such as hydrogen peroxide (H2O2) and superoxide (O2) are thought to act as cellular messengers to stimulate key processes associated with wound healing, including cell motility, cytokine action (including PDGF signal transduction), and angiogenesis. Both hypoxia and hyperoxia increase ROS production, but an increased level of ROS transcends the beneficial effect and causes additional tissue damage ([Rodriguez et al., 2008](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2903966/#bibr81-0022034509359125)).

In summary, the proper oxygen level is crucial for optimum wound healing. Hypoxia stimulates wound healing such as the release of growth factors and angiogenesis, while oxygen is needed to sustain the healing process ([Bishop, 2008](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2903966/#bibr5-0022034509359125)). One therapeutic option that can sometimes overcome the influence of tissue hypoxia is hyperbaric oxygen therapy (HBOT; [Rodriguez et al., 2008](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2903966/#bibr81-0022034509359125)). While HBOT can be an effective treatment for hypoxic wounds, its availability is limited.

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