**ANA 404: INTRODUCTION TO HISTOPATHOLOGY (WOUND HEALING)**

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16/MHS01/046

**1.1: Cytokine Signaling and Wound healing**

The term “cytokine” has been used to refer to the immune-modulating agents, such as interleukins (ILs) and interferons (IFNs), cytokines are small, cell-signalling protein molecules that were first characterized as components of the immune response, but have since been found to play a much broader part in diverse aspects of physiology (Mousa & Bakhiet, 2013). The cytokines are a diverse group of proteins of proteins that may be regarded as the hormones of the immune system, they may be considered to be hormones because their properties are similar to those of the classic hormones of the endocrine system (Kronfol & Remick 2000). Cytokine signaling 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 signaling, they are local regulators that alert and activate lymphocytes. Some cytokine-signaling pathways involve hormones such as growth hormones and leptin (O'Shea & Murray, 2008). The immune system depends on cytokine signaling to keep the human body healthy, macrophages and dendritic cells engulf foreign particles and send a cytokine signal to nearby dormant lymphocytes, and their receptors recognize the signal and activate and are specialized to recognize certain antigens (O'Shea & Murray, 2008). The combination of the macrophages and activation of lymphocytes through cytokine signaling 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 (O'Shea *et al.,* 2011). 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, their most common of these pathways is through 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 (O'Shea *et al.,* 2011).

**1.2: Role of Cytokines in Wound healing**

The cytokines which are produced and released following an immune event can initially dictate whether an immune response is necessary and, if so, whether that response is cytotoxic, humoral, cellular mediated or allergic in nature (Feng *et al.,* 2016). Wound healing is tightly regulated by a large number of cytokines and growth factors through various sophisticated signaling pathways. Throughout the wound healing process cytokines and growth factors act as important mediators of differentiation, proliferation, maturation and various other functions of the cells which contribute to wound closure (Feng *et al.,* 2016). A variety of extracellular matrix components, cytokines and growth factors are derived from activated keratinocytes during the proliferation and re-epithelialization phase of wound healing, and act as chemo-attractants which can then activate fibroblasts, endothelial cells and lymphocytes, as well as neighboring keratinocytes (Barrientos *et al.,* 2008). Some of these cytokines and growth factors, such as IL-1 and TNF-α, regulate activation of keratinocytes, whereas TGF-α also mediates keratinocyte proliferation. Once the wound has healed, dermal–fibroblast-derived TGF-β acts as a regulator to suppress the proliferation of keratinocytes and to induce synthesis of ECM. IFN-γ was found to strongly and specifically induce the expression of keratin-17, a protein expressed in various healthy epithelia that are characterized as contractile tissue (Feng *et al.,* 2016). Thus, IFN-γ was suggested to contribute to the contractile nature of keratinocytes in the later stage of wound healing. IL-6 derived from fibroblasts, macrophages, endothelial cells and keratinocytes is another essential cytokine which affects granulation tissue formation, re-epithelialization, angiogenesis, cell infiltration and remodeling. Additionally, IL-6 showed enhanced expression in chronic wounds exhibiting aberrant inflammation, suggesting the importance of the precise control of IL-6 expression patterns in normal wound healing (Feng *et al.,* 2016).

**2.1: Impaired Wound Healing**

Chronic wounds are, by definition, wounds that have failed to progress through the normal stages of healing and therefore enter a state of pathologic inflammation. As a result, the healing process is delayed, incomplete, and does not proceed in a coordinated manner, subsequently resulting in poor anatomical and functional outcome (Menke *et al.,* 2007). These wounds cause a major disability and are characterized by chronicity and frequent relapse. The differential diagnosis of the underlying etiology of a non-healing wound is large, but most (70%) ulcers are caused by ischemia, secondary to diabetes mellitus, venous stasis, and pressure (Demidova *et al.,* 2012). Wound healing is said to be impaired when the balance between tissue degradation and synthesis is shifted toward degradation (Menke *et al.,* 2007). 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 (Menke *et al.,* 2007).

**2.2: Factors that Impair Wound Healing**

These factors can be classified into the following categories: comorbidities, medications, oncology interventions, and life style habits (Anderson & Hamm, 2012).

**2.2.1: Co-Morbidities**

Diabetes is an increasingly prevalent issue in modern-day health care. One complication of diabetes is ulceration of the foot secondary to neuropathic involvement. Peripheral neuropathy leads to decreased protective sensation and foot deformities. The deformities then lead to a redistribution of pressure during gait and can result in ulceration at high pressure areas. 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 (Anderson & Hamm, 2012).

Obesity is prevalent amongst adult population. 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. If tissue near a wound is not adequately oxygenated, fibroblasts cannot form collagen and oxygen-dependent cellular repair processes cannot occur (Anderson & Hamm, 2012).

**2.2.2: Medications**

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 Prostaglandin-E2, an inflammatory mediating prostaglandin, and can thereby reduce pain (Anderson & Hamm, 2012). 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. 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 (Anderson & Hamm, 2012).

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 (Anderson & Hamm, 2012).

**3.1: Role of Oxidative stress in Development of impaired wound healing**

Daily, humans use about 250 g of oxygen out of which 2–5% is converted to reactive oxygen species (ROS) (Soneja *et al.,* 2005). ROS means all oxygen associated species that have higher oxidative potential (higher reactivity) than molecular oxygen: singlet oxygen, superoxide anion, hydrogen peroxide and hydroxyl radical (OH). In the ground state, molecular oxygen is in a relatively inert triplet state, 3O2 (Soneja *et al.,* 2005). The initial event that activates oxygen in biological systems is a change of electron spin pairing. This change results from one of at least three different chemical mechanisms. Redox signaling and increased oxidative stress play a significant role in regulating normal wound healing by facilitating hemostasis, inflammation, angiogenesis, granulation tissue formation, wound closure, and development and maturation of the extracellular matrix (Schäfer & Werner, 2008). ROS are centrally involved in all wound healing processes as low concentrations of ROS generation are required to fight against invading microorganisms and cell surviving signaling (Schäfer & Werner, 2008). Excessive and uncontrolled oxidative stress contribute to sustaining and deregulating inflammation processes, which play a central role in the pathogenesis of chronic non-healing wounds. In line, antioxidant and anti-inflammatory properties of several antioxidant strategies have proven beneficial to improve non-healing state (Barku, 2019). A delicate balance exists between the positive role of ROS and their deleterious effects is important for proper wound healing (Barku, 2019). Whereas production of ROS is essential to initiate wound repair, excessive amount of ROS generation is deleterious in wound healing. Ongoing oxidative stress, associated with lipid peroxidation, protein modification and DNA damage has been shown to impair wound healing processes via increased cell apoptosis and senescence (Cano Sanchez *et al.,* 2018). In physiological conditions, low levels of ROS production by NOX (Nitro-Oxide) activation in neutrophils and macrophages are responsible for respiratory bursts during phagocytosis of the inflammatory phase (Cano Sanchez *et al.,* 2018). In contrast, as chronic inflammation develops in pathological conditions, NOX activation is exacerbated, which may lead to excessive production of ROS production, further accelerating inflammation and oxidative stress cellular damage. Clinical studies suggest that non-healing wounds are maintained in highly oxidizing environment, which lead to impaired wound repair (Cano Sanchez *et al.,* 2018). Clinical conditions such as tissue hypoxia and hyperglycemia are typically associated with highly oxidizing environments (Cano Sanchez *et al.,* 2018).

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