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ANATOMY

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INTRODUCTION TO HISTOPATHOLOGY

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 ASSIGNMENT

1. WRITE ON CYTOKINE SIGNALING AND ITS ROLE IN WOUND HEALING.

2. WHEN IS WOUND HEALING REFERRED TO AS ‘IMPAIRED’ AND WHY?

3. EXAMINE THE ROLE OF OXIDATIVE STRESS IN THE DEVELOPMENT AND PROGRESSION OF IMPAIRED WOUND HEALING.

**1. CYTOKINE SIGNALING**

Wound healing is a dynamic process, involving phases of inflammation, characterized by vasoconstriction and platelet aggregation to induce blood clotting, proliferation and remodeling that overlap in space and time.

Cytokines are a broad and loose category of small proteins (~5–20 kDa) important in cell signaling and serve as molecular messengers between cells. They are peptides and cannot cross the lipid bilayer of cells to enter the cytoplasm and have been shown to be involved in autocrine, paracrine and endocrine signaling as immunomodulating agents and are peptides which have a fundamental role in communication within the immune system and in allowing the immune system and host tissue cells to exchange information.

**ROLE OF CYTOKINE SIGNALING IN WOUND HEALING**

Cytokine signaling plays an important role in wound healing . Most cytokines are local regulators that alert and activate lymphocytes. 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. 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 signaling help keep the body in homeostasis.

The process of wound healing is highly complex and requires substantial interaction and coordination between different cell types to succeed in an orderly and timely manner. Cytokines are a class of small proteins involved in both paracrine and autocrine cell signaling. Cytokines include, among others, chemokines (which promote chemotaxis), interferons and interleukins (which are vital for the function of a healthy immune system) and members of the TNF family (which can induce apoptosis). 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 . 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. A variety of ECM components, cytokines and growth factors are derived from activated keratinocytes during the proliferation and re-epithelialization phase of wound healing, and act as chemoattractants which can then activate fibroblasts, endothelial cells and lymphocytes, as well as neighboring keratinocytes . They play important roles in regulating cell function such as proliferation, migration, and matrix synthesis. It is the balance or the net effect of the complex interplay between these mediators, which appears to play a major role in regulating the initiation, progression and resolution of wounds.

These cytokines and growth factors, such as interleukin-1(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. In addition, it was found that the expression of EGFR was reduced in chronic wounds, and that keratinocytes at the nonhealing edge of chronic wounds are incapable of responding to EGF stimulation due to the cytoplasmic localization of Epidermal Growth Factor Receptor(EGFR), indicating the essential role of EGFR on pathological wound healing. As a result of extensive studies on angiogenesis, many cytokines and growth factors have since been identified as either proangiogenic or antiangiogenic molecules . Fibroblast Growth Factor(FGF) is a potent mitogen for vascular and capillary endothelial cells and has been shown to stimulate their proliferation, differentiation, migration, invasion and tubule formation ability.

2**. WHEN IS WOUND HEALING REFERRED TO AS ‘IMPAIRED’ AND WHY?**

The wound-healing process consists of four highly integrated and overlapping phases: hemostasis, inflammation, proliferation, and tissue remodeling or resolution (Gosain and DiPietro, 2004). There are many factors that can affect wound healing which interfere with one or more phases in this process, thus causing improper or impaired tissue repair. wound healing is impaired when there is a disruption of the normal structure and function of the skin and underlying soft tissue  and where oxygenation is not restored.

The proper oxygen level is crucial for optimum wound healing and plays a 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 (Rodriguez, *et.,al* 2008).

There are many risk factors both modifiable (such as stress, smoking, inappropriate alcohol consumption, malnutrition, obesity, diabetes, cardio-vascular disease, etc.) and non-modifiable (such as genetic diseases and ageing) strongly contributing to the impaired WH.

Inborn genetic disorders causing a connective tissue disease such as the Ehlers-Danlos syndrome lead to impairments in the remodelling phase of wound healing .Furthermore, Progeroid syndromes such as Werner syndrome tend to generate skin ulcerations. Smoking attenuates the inflammation phase by impairing white blood cell migration, reducing neutrophil bactericidal activity, and depressing IL-1 production.

**3. ROLE OF OXIDATIVE STRESS IN THE DEVELOPMENT AND PROGRESSION OF IMPAIRED WOUND HEALING**

The wound healing process is regulated by a large variety of different growth factors, cytokines and hormones. In addition, a series of recent studies revealed that nitric oxide as well ROS (reactive oxygen species) are crucial regulators of this process (Wlaschek and Scharffetter-Kochanek 2005). ROS are required for the defense against invading pathogens, and low levels of ROS are also essential mediators of intracellular signaling (D’Autreaux and Toledano 2007). For example, a recent study revealed that low levels of hydrogen peroxide are important for efficient wound angiogenesis (Roy *et al*., 2006). However, excessive amounts of ROS are deleterious due to their high reactivity. In this review, we will first summarize the evidence for the presence of oxidative stress in skin wounds, in particular in chronic non-healing wounds. Subsequently, we will report on the presence of low molecular weight antioxidants in the wound tissue and their function in the repair process. Finally, we will summarize recent results on the expression and function of ROS-detoxifying enzymes in the wound healing process.

Due to the short half-life of ROS, their concentrations in vivo are difficult to determine. Nevertheless, H2O2 levels could recently be determined in wound fluid from acute murine excisional wounds using a real-time electrochemical H2O2 measurement (Roy et al., 2006). These studies revealed that low concentrations (100–250M) of H2O2 are present at the wound site. Higher levels were found during the early inflammatory phase (day 2 after injury) compared to the later phase, when new tissue formation occurs (day 5 after injury). In addition to H2O2, the presence of superoxide at the wound edge was detected by staining of frozen sections with the redox-sensitive dye dihydroethidium (Roy et al., 2006). The same group recently confirmed these results using an electron paramagnetic resonance spectroscopy-based approach, where the metabolism of topically applied nitroxide 15N-perdeuterated tempone was measured noninvasively. These studies revealed that superoxide levels peak at around day 2 after injury in full-thickness excisional mouse wounds (Ojha et al., 2008). Superoxide production was impaired in mice lacking Rac2, one of the essential subunits of NADPH oxidase, and this correlated with impaired wound healing in these mice (Ojha *et al*., 2008). These results suggest that the low levels of ROS that are produced in normal wounds are important for the repair process. It will be interesting in the future to use these technologies for the analysis of ROS levels in chronic, non-healing wounds.

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