**WRITE ON CYTOKINES SIGNALLING AND ITS ROLE IN WOUND HEALING.**

Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system. Cytokines are a category of signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis. Cytokines are produced throughout the body by cells of diverse embryological origin. Cytokine is a general name; other names are defined based on their presumed function, cell of secretion, or target of action. For example, cytokines made by lymphocytes can also be referred to as lymphokines. Many of the lymphokines are also known as interleukins (ILs), since they are not only secreted by leukocytes but also able to affect the cellular responses of leukocytes. Those cytokines secreted by monocytes or macrophages are termed monokines. And chemokines are cytokines with chemotactic activities. Cytokines and their receptors exhibit very high affinity for each other. Because of this high affinity, picomolar concentrations of cytokines can mediate a biological effect.

**A particular cytokine may exhibit:**

Autocrine action by binding to receptor on the membrane of the same cell that secreted it.

Paracrine action binding to receptors on a target cell in close proximity to the producer cell.

Endocrine activity by traveling through circulation and acting on target cells in distant parts of the bod.

Wound healing is a multistep process with four overlapping but distinct stages: hemostasis, inflammation, proliferation, and remodeling. An alteration at any stage may lead to the development of chronic non-healing wounds or excessive scar formation. Impaired wound healing presents a significant health and economic burden to millions of individuals worldwide, with diabetes mellitus and aging being major risk factors. Ongoing understanding of the mechanisms that underly wound healing is required for the development of new and improved therapies that increase repair. Chemokines are key regulators of the wound healing process. They are involved in the promotion and inhibition of angiogenesis and the recruitment of inflammatory cells, which release growth factors and cytokines to facilitate the wound healing process. Preclinical research studies in mice show that the administration of CCL2, CCL21, CXCL12, and a CXCR4 antagonist as well as broad-spectrum inhibition of the CC-chemokine class improve the wound healing process. The focus of this review is to highlight the contributions of chemokines during each stage of wound healing and to discuss the related molecular pathologies in complex and chronic non-healing wounds. We explore the therapeutic potential of targeting chemokines as a novel approach to overcome the debilitating effects of impaired wound healing. In wound healing, chemokines are primarily involved in orchestrating the prevention or promotion of angiogenesis at each different healing stage. Angiogenesis is prevented at the hemostasis stage to allow for clot formation, while angiogenesis is promoted in the inflammatory phase to promote the migration of inflammatory cells in and out of the wound. During the proliferation phase, neovessels are needed to meet the metabolic requirements of the proliferating cells during re-epithelialization and granulation. However, in the remodeling phase, neovessel regression is more important to allow for the reorganization of the collagen matrix to form scar tissue. This changing state of angiogenesis requires precise coordination of cytokines, chemokines, and growth factors, making chemokines extremely important in wound healing.

An imbalance in the chemokine environment may alter the wound healing process to cause either prolonged healing or excessive scar formation. Prolonged healing may occur in diseases such as diabetes, where there is an excess of inflammation preventing the wound from progressing to the proliferation stage, leading to the development of a chronic wound that either does not heal or heals with a remaining scar. Excessive scarring, such as with hypertrophic scars, occurs when there is an overproduction of collagen in the wound. In this case, the scar often becomes thick, raised, and may be red in color.

Given the importance of chemokines to the wound healing process, there is therapeutic potential to target chemokines as a treatment for faster healing with reduced scar formation. Several studies have explored the treatment of wounds by either inhibiting or promoting individual chemokines.

**WHEN IS WOUND HEALING REFERRED TO AS “IMPAIRED”? AND WHY?**

The factors discussed include oxygenation, infection, age and sex hormones, stress, diabetes, obesity, medications, alcoholism, smoking, and nutrition. A better understanding of the influence of these factors on repair may lead to therapeutics that improve wound healing and resolve impaired wounds.

* Oxygenation 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; Rodriguez et al., 2008). In addition, the level of superoxide production (a key factor for oxidative killing pathogens) by polymorphonuclear leukocytes is critically dependent on oxygen levels.
* Infections Once skin is injured, micro-organisms that are normally sequestered at the skin surface obtain access to the underlying tissues. The state of infection and replication status of the micro-organisms determine whether the wound is classified as having contamination, colonization, local infection/critical colonization, and/or spreading invasive infection. Contamination is the presence of non-replicating organisms on a wound, while colonization is defined as the presence of replicating micro-organisms on the wound without tissue damage. Local infection/critical colonization is an intermediate stage, with micro-organism replication and the beginning of local tissue responses. Invasive infection is defined as the presence of replicating organisms within a wound with subsequent host injury (Edwards and Harding, 2004).
* Age The elderly population (people over 60 years of age) is growing faster than any other age group (World Health Organization [WHO, www.who.int/topics/ageing]), and increased age is a major risk factor for impaired wound healing. Many clinical and animal studies at the cellular and molecular level have examined age-related changes and delays in wound healing. It is commonly recognized that, in healthy older adults, the effect of aging causes a temporal delay in wound healing, but not an actual impairment in terms of the quality of healing (Gosain and DiPietro, 2004; Keylock et al., 2008). Delayed wound healing in the aged is associated with an altered inflammatory response, such as delayed T-cell infiltration into the wound area with alterations in chemokine production and reduced macrophage phagocytic capacity (Swift et al., 2001). Delayed re-epithelialization, collagen synthesis, and angiogenesis have also been observed in aged mice as compared with young mice (Swift et al., 1999). Overall, there are global differences in wound healing between young and aged individuals. A review of the age-related changes in healing capacity demonstrates that every phase of healing undergoes characteristic age-related changes, including enhanced platelet aggregation, increased secretion of inflammatory mediators, delayed infiltration of macrophages and lymphocytes, impaired macrophage function, decreased secretion of growth factors, delayed re-epithelialization, delayed angiogenesis and collagen deposition, reduced collagen turnover and remodeling, and decreased wound strength (Gosain and DiPietro, 2004). Several treatments to reduce the age-related impairment of healing have been studied. Interestingly, exercise has been reported to improve cutaneous wound healing in older adults as well as aged mice, and the improvement is associated with decreased levels of pro-inflammatory cytokines in the wound tissue. The improved healing response may be due to an exercise-induced anti-inflammatory response in the wound (Emery et al., 2005; Keylock et al., 2008).
* Stress Stress has a great impact on human health and social behavior. Many diseases—such as cardiovascular disease, cancer, compromised wound healing, and diabetes—are associated with stress. Numerous studies have confirmed that stress-induced disruption of neuroendocrine immune equilibrium is consequential to health (Glaser and Kiecolt-Glaser, 2005; Vileikyte, 2007). The pathophysiology of stress results in the deregulation of the immune system, mediated primarily through the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal medullary axes or sympathetic nervous system (SNS; Godbout and Glaser, 2006; Boyapati and Wang, 2007).
* Diabetes Diabetes affects hundreds of millions of people worldwide. Diabetic individuals exhibit a documented impairment in the healing of acute wounds. Moreover, this population is prone to develop chronic non-healing diabetic foot ulcers (DFUs), which are estimated to occur in 15% of all persons with diabetes. DFUs are a serious complication of diabetes, and precede 84% of all diabetes-related lower leg amputations (Brem and Tomic-Canic, 2007). The impaired healing of both DFUs and acute cutaneous wounds in persons with diabetes involves multiple complex pathophysiological mechanisms. DFUs, like venous stasis disease and pressure-related chronic non-healing wounds, are always accompanied by hypoxia (Tandara and Mustoe, 2004). A situation of prolonged hypoxia, which may be derived from both insufficient perfusion and insufficient angiogenesis, is detrimental for wound healing. Hypoxia can amplify the early inflammatory response, thereby prolonging injury by increasing the levels of oxygen radicals (Mathieu et al., 2006; Woo et al., 2007).

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

Reactive oxygen species (ROS) play a pivotal role in the orchestration of the normal wound‐healing response. They act as secondary messengers to many immunocytes and non‐lymphoid cells, which are involved in the repair process, and appear to be important in coordinating the recruitment of lymphoid cells to the wound site and effective tissue repair. ROS also possess the ability to regulate the formation of blood vessels (angiogenesis) at the wound site and the optimal perfusion of blood into the wound‐healing area. ROS act in the host's defence through phagocytes that induce an ROS burst onto the pathogens present in wounds, leading to their destruction, and during this period, excess ROS leakage into the surrounding environment has further bacteriostatic effects. In light of these important roles of ROS in wound healing and the continued quest for therapeutic strategies to treat wounds in general and chronic wounds, such as diabetic foot ulcers, venous and arterial leg ulcers and pressure ulcers in particular, the manipulation of ROS represents a promising avenue for improving wound‐healing responses when they are stalled. This article presents a review of the evidence supporting the critical role of ROS in wound healing and infection control at the wound site, and some of the new emerging concepts associated with ROS modulation and its potential in improving wound healing are discussed.

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