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The Role of Inflammatory Markers in Wound Healing: A Review

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Abstract

In the study of wound healing, comprehending the intricate interactions between pro- and anti-inflammatory cytokines is essential since it provides the framework for creating potent treatments. Pro-inflammatory cytokines, including as IL-1β, IL-6, TNF-α, and other chemokines, are essential for drawing cells for debris removal and growth factor recruitment during the early phases of wound healing. For the best possible wound healing, this early inflammation must be carefully controlled and promptly resolved. Anti-inflammatory proteins like IL-10 and IL-4 play a crucial role in easing the healing process's progression to later phases, when pro-inflammatory cytokines encourage angiogenesis and wound remodeling. The intricacy of inflammatory cytokines in wound healing research is highlighted by this perspective, which also highlights the necessity of thorough and objective approaches in their assessment.

Keywords: Inflammation, wound healing, pro-inflammatory cytokines, angiogenesis

Background on wound healing

Any damage to the integrity of living tissue could be considered a wound. The largest organ in the human body, the skin's primary job is to shield the body's water-rich interior organs from the dry outside air. [1] The ability to repair wounds and preserve skin integrity are essential requirements for a healthy life. Moreover, the process of wound healing can pose a considerable obstacle and strain on healthcare systems. In 2014, Medicare's estimated costs for treating both acute and chronic wounds ranged from $28.1 billion to $96.8 billion. [2] Surgical wounds were shown to incur the largest costs associated with wounds, whereas diabetic foot ulcers came in second. [3] Optimizing the healing of surgical wounds and incisions can be greatly aided by a strong understanding of this basic subject.

The goal of the wound healing process is to restore the integrity of the skin through a series of coordinated actions. While later articles in this series will cover chronic wounds, experimental skin substitutes, and improper wound healing (keloids and hypertrophic scars), this page seeks to provide an overview of the acute cutaneous wound healing process. Wound care can be approached in three general ways. [4] These consist of healing by secondary intention, which permits the wound to heal without the need for surgery, primary closure using suture material, and 6 healing by tertiary intention, which involves surgical closure of the wound following a time of secondary healing. [5]

Role of cytokines in wound healing

A diverse class of low molecular weight proteins known as cytokines function as signaling molecules that promote intercellular communication relevant to wound healing processes. Their diverse roles include initiating inflammatory responses and promoting tissue regeneration, making them essential components in the series of events that make up the wound healing cascade. The first stage of inflammation, which is crucial for coordinating the restorative processes that follow, is marked by the arrival of immune cells at the site of damage along with the release of pro-inflammatory cytokines. [6] Tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) are important players in this phase (Figure 1). They mediate a number of functions, including activating fibroblasts to trigger an acute phase response and inducing endothelial cell adhesion molecules to promote leukocyte recruitment. [7]

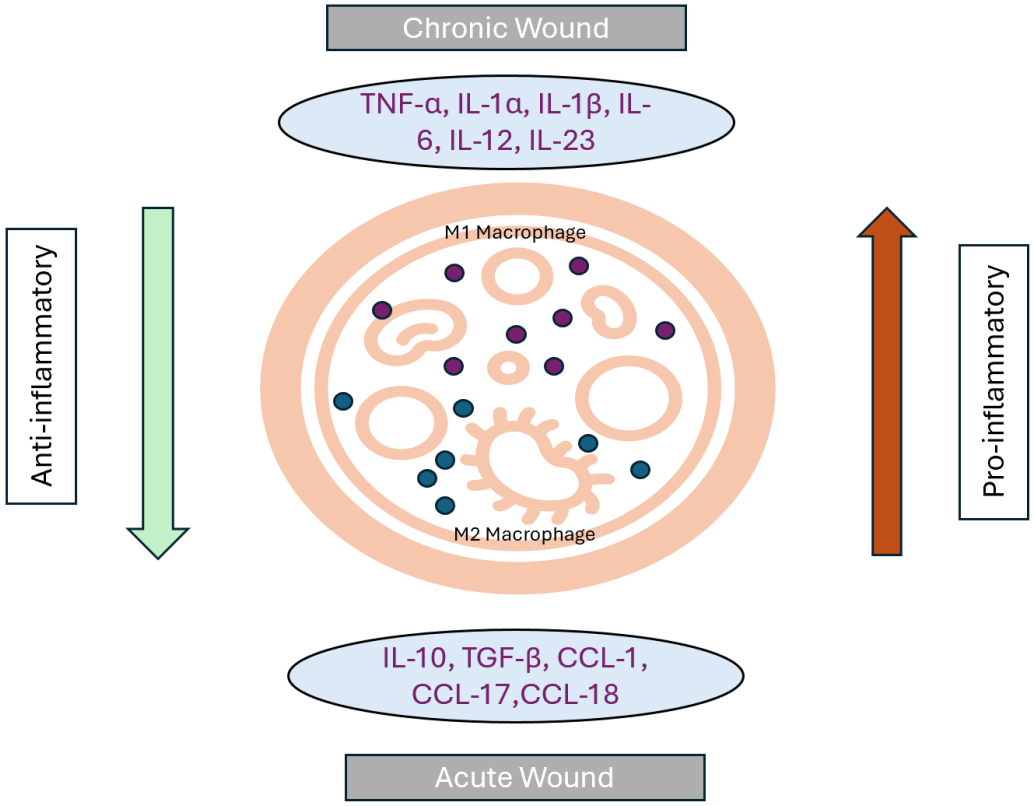

Figure 1: Role of inflammatory mediators in wound healing

Subsequent to the inflammatory phase, during the proliferative phase, cytokines play crucial roles in stimulating cell proliferation, angiogenesis, and deposition of extracellular matrix (ECM). In this stage, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF-β) become important mediators, coordinating mechanisms like fibroblast migration and proliferation, extracellular matrix (ECM) control, and angiogenic induction to promote tissue regeneration. [8] The remodeling stage that follows involves the tissue's refining and restructuring in order to restore its structural integrity and functionality. Notable cytokines at this stage include matrix metalloproteinases (MMPs), which are essential in mediating ECM protein breakdown and tissue remodeling, and TGF-β, which controls ECM turnover and scar formation. [9] In conclusion, cytokines perform a variety of dynamic roles.

Role of macrophages in wound healing

Significant research conducted in the early 1970s and 1980s confirmed the importance of macrophages in the healing of wounds, as well as their proven capacity to produce angiogenesis- and fibroplasia-stimulating substances. The involvement of this cell in the healing wound was studied in the early experiments using guinea pigs that had been depleted of macrophages by treatment with both glucocorticoids and anti-macrophage antiserum (Ref. 9). These early observations were limited in their interpretation since glucocorticoids have a wide

range of other actions that could affect healing. This restriction has been removed by recent developments in the usage of genetically engineered mice. These methods enable the depletion of macrophages in wounds in a very selective and targeted manner, confirming the pivotal role that macrophages play in the process of wound healing. [10-12]

Toxin-mediated selective depletion of macrophages prior to wound insertion has been achieved by two different groups using mouse strains expressing the human receptor for diphtheria toxin with restriction on macrophage expression. Mice whose wounds were macrophage-depleted showed delayed wound closure, reduced angiogenesis and granulation tissue formation, decreased synthesis of collagen, and reduced levels of growth factors such as TGF-beta and VEGF. Furthermore, the reduction in macrophages was accompanied by a decrease in myofibroblasts, a contractile cell crucial for wound healing. [13, 14]

Discussion

There are concerns regarding the interactions between cells, more especially the interactions between the various resident cell types and subtypes and the circulating cells in the wound environment.Moreover, the existence of circulating progenitor cells has been disputed and they are elusive. It's critical to comprehend these cells' function in wound healing as well as what happens to them when wound healing is complete. The effects of external variables on cellular activity in wound healing, such as variations in mechanical stresses, oxygen availability, and infection, are also taken into account. Additionally, it's possible that the skin contains unidentified stem and progenitor cells.

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Conclusion

Our understanding of inflammation biology will ultimately be determined by a detailed investigation of 1) cellular variety and function in wound healing and 2) cellular changes in poor wound healing stages. Effective treatments for any skin injury will be aided by the identification of cell surface markers, which may be used to identify the cells that are best for healing wounds.

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