Principles of wound healing

A wound is any break in the skin or an organ or part as the result of trauma or surgical incision. The process of wound healing can be defined as the physiological responses by which the body replaces and restores function to damaged tissues. In normal skin, the epidermis and dermis exists in a steady-state equilibrium, forming a protective barrier against the external environment. Once the protective barrier is broken, the normal physiological process of wound healing is immediately set in motion. This is a complex and dynamic process dependent on local and systemic factors affecting the patient's health status. Understanding of the mechanism of wound healing has increased dramatically during last decade. Today wound-healing abnormalities are among the greatest causes of disability and deformity. This chapter reviews the principles and factors that affect wound healing. There are four main non-discrete phases involved in acute wound healing.

Haemostasis

Haemostasis begins immediately following the tissue injury occurs. Damaged endothelium within the wound releases von-Willebrand factor (vWF) and tissue thromboplastin. vWF facilitates platelet adhesion to sub-endothelial collagen and discharges adenosine diphosphate (ADP) and thromboxane A2 leading to platelet aggregation. Alpha granules within the platelets release platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF-β). PDGF is chemotactic for fibroblasts, neutrophils and monocytes and, along with TGF-β, lead to prolific collagen construction. Tissue thromboplastin activates the coagulation pathways producing fibrin. Fibrin provides the structural support for the inflammation phase.

Inflammation

Early phase (days 1–2): activation of the complement cascade – polymorphonuclear leukocytes (PMNs) infiltration which adhere to endothelial cells in adjacent blood vessels (margination) and begin to move through vessel walls (diapedesis). They are attracted to the site by fibronectin, growth factors, and kinins. Neutrophils phagocytize debris and bacteria and also kill bacteria by releasing free radicals. They cleanse the wound by secreting proteases that break down damaged tissue. The cut edges of dermis begin to exhibit increased mitotic activity and epithelial cells from the edges begin to migrate and proliferate, depositing a basement membrane.

Late phase (days 2–3): monocytes replace PMNs as the predominant cells in the wound by 2 days after injury. Monocytes are attracted to the wound by the release of complement, clotting components, immunoglobulin G and cytokines. The monocytes then undergo phenotypic change to macrophages, which are the key regulator cells in this phase. Macrophages have two key roles in the late phase:

1. Phagocytosis and proteolytic enzyme release which aid in the debridement of the wound.
2. Primary producers of growth factors (platelet-derived growth factor, TGF-β) stimulated by the low oxygen content of their surroundings. These factors are responsible for inducing and accelerating angiogenesis and stimulating cells to re-epithelialize and deposit of new ECM.

Regeneration and proliferation (day 3–week 2)

This phase starts at day 3 and can continue for further 2–4 weeks. During this phase there is deposition of ECM, fibroblast migration and formation of granulation tissue.

Formation of granulation tissue/fibroplasia/matrix deposition: this occurs simultaneously with angiogenesis. Fibroblasts begin accumulating in the wound site and release PDGF and TGF-β which are mitogenic for epithelium and fibroblasts. Proliferation of epithelial cells and fibroblasts lead to ECM production. ECM is composed of collagen, adhesive glycoproteins and proteoglycans. Examples of glycoproteins are fibronectin and laminin which help link the components of the matrix. Proteoglycans help regulate the structure and permeability of the matrix. Hypoxia also contributes to fibroblast proliferation and excretion of growth factors, though too little oxygen will inhibit their growth and deposition of ECM components, and can lead to excessive, fibrotic scarring.

Angiogenesis: it occurs at 3–5 days concurrently with fibroblast proliferation. Angiogenesis is imperative because the activity of fibroblasts and epithelial cells is oxygen- and nutrient-dependent. Stem cells of endothelial cells, originating from parts of uninjured blood vessels, develop pseudopodia and push through the ECM into the wound site to establish new blood vessels. Hypoxia stimulates monocytes to release vascular endothelial growth factor which is mitogenic for endothelial cells leading to further angiogenesis.

Re-epithelialization: the formation of granulation tissue in an open wound allows the re-epithelialization phase to take place, as epithelial cells migrate across the new tissue to form a barrier between the wound and the environment. Basal keratinocytes from the wound edges and dermal appendages such as hair follicles, sweat glands and sebaceous glands are the main cells responsible for the epithelialization phase of wound healing. Increase in mitotic activity of the basal epithelial cells modulated by several growth factors encourages migration over the matrix leading to re-establishment of stratified epithelium.

Remodelling, maturation and contracture (>1 week)

Constant synthesis and remodelling of ECM with concurrent granulation tissue formation can occur for years after initial injury. The maturation phase begins when equilibrium between collagen deposition and degradation occurs, usually around 3 weeks. Type III collagen, which is prevalent during proliferation, is gradually degraded and the stronger type I collagen is laid down in its place. Metalloproteinases, whose activity is reliant on zinc ions, has the potential to impair or improve wound healing in this stage.

Contraction is a key phase of wound healing. If contraction continues for too long, it can lead to disfigurement and loss of function. Contraction commences approximately a week after wounding, when fibroblasts have differentiated into myofibroblasts. Contraction can last for several weeks and continues even after the wound is completely re-epithelialized. The scar usually achieves its maximum tensile strength by 12 weeks, with approximately 70–80% of its original strength.

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