

APPROACH TO WOUND HEALING

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Abstract:

Wound healing is still an unmet challenge among surgical society. As wound healing called the process of the complex and carefully regulated physiologic response to a traumatic injury. Herein, a brief review of the literature concerning the wound healing process is presented. Wound healing process can be divided into at least 3 continuous and overlapping processes: inflammatory reaction, proliferative process which leads to tissue restoration, and finally tissue remodeling. This review summarizes the current information regarding wound healing responses and explains the underlying pathophysiology.

Keywords: Wound Healing, Cell proliferation, Hedgehog proteins, Inflammation,

INTRODUCTION:

Wound healing is one of the most complex processes in multi-cellular organisms, involving multi phases during process which include hemostasis/ inflammation phase, proliferation phase, and remodeling phase [1]. Unbalancing one or more of these phases could lead to two distinct damaging outcomes: either chronic wound development or the formation of a hypertrophic scar/keloid [2]. The healing process depends on local wound factors, systemic mediators, the underlying disease, and the type of injury [3]. Primary intention of wound healing involves the close approximation of the wound edges of a laceration or surgical wound by sutures, clips or skin adhesive. Secondary intention occurs when the wound edges cannot be approximated, the wound is left open and the defect will slowly fill with connective tissue. Such wounds healed slowly and can be easily infected. Commonly, this type of wound healing arises in patients who have underlying co-morbidities (e.g. vascular or diabetic ulcers, pressure ulcers) or in patients with post-surgical wound susceptibility (itself often due to infection, haematoma or mechanical tension). Wound healing by tertiary intention, which is often called 'delayed primary intention', involves the wound to be left open until any infection or contamination with non-viable tissue is removed, the wound edges are then approximated and healing continues as by primary intention [4].

Haemostasis

'Haemostasis' is the normal response of the vessel to injury by forming a clot that limit haemorrhage. Due to increased cytoplasmic calcium levels, damaged arterial vessels quickly constrict through the contraction of vessel wall localized smooth muscle. The decreased blood flow mediated by arteriolar narrowing, in a few minutes leads to tissue hypoxia and acidosis. This fact supports the production of adenosine, nitric oxide, and other vasoactive metabolites in order to cause a reflex vasodilatation of the arterial vessels. At the same time, histamine release from mast cells may also increase vasodilatation and increase vascular permeability, helping the inflammatory cells to enter the extracellular space around the wound. For this reason, early wounds appeared as characteristicly warm, red, swollen [5].

The coagulation involves thrombocytes aggregation and platelets in a fibrin network, confiding on the action of specific factors through the activation and aggregation of

these cells. In addition to reestablishing homeostasis and establishing a barrier against the invasion of microorganisms, the fibrin network organizes the transient matrix necessary for cell migration, restoring skin function as a protective barrier, protecting the integrity of the skin [6].

Inflammation

The inflammatory response to wounding begins immediately with the passive leakage of circulating leukocytes (largely neutrophils) from damaged blood vessels into the wound. There is also rapid activation of immune cells that are already found within the tissue such as mast cells, $\gamma\delta$ T cells and Langerhans cells, which in turn release a rapid pulse of chemokines and cytokines. The inflammatory response continues with active recruitment of neutrophils and then macrophages from nearby vessels, which is orchestrated by growth factor signals from the resident cells and serum, and by foreign epitopes such as the lipopolysaccharides (LPS) of invading microorganisms [6,7]. Altogether, these signals trigger local endothelial cell 'activation' and thus expression of selectins. Selectins control the rolling and then tethering of leukocytes to the vessel wall and subsequent crossing of the endothelial barrier [6]. This fact is enhanced by vessel dilation and an increase in vascular permeability that is triggered by inflammation associated nitric oxide (NO), mast cell-derived histamine, tissue plasminogen activator and other factors [7].

It has known that pro-inflammatory cytokines and active antimicrobial substances, such as reactive oxygen species (ROS), cationic peptides, and proteases at the location of the lesion are expressed by neutrophils. Recruitment of the activated neutrophils in answer to the activation of the complement system, platelet degranulation, and bacterial degradation products provides continuance of the inflammatory response [8]. These are attracted by many inflammatory cytokines produced by degradation products of pathogenic agents, endothelial cells, and activated platelets. In this way, the neutrophils are primary activated and collected cells that play a role in clearing the tissue and at the same time contribute to the death of the invading agents [9]. Only a few hours after the formation of the lesion, a large quantity of neutrophils transmigrate through the endothelial cells present in the blood capillary walls, which are activated by pro-inflammatory cytokines, such as TNF- α (tumor necrosis factor alpha), IL-1 β , and IFN- γ (interferon gamma) at the location of the lesion [6].

When the neutrophils have expired, either are phagocytosed by macrophages or undergo apoptosis, are sloughed from the wound surface. Macrophages are much larger phagocytic cells that reach peak concentration in a wound at 2-3 days after injury. They are attracted to the wound by the chemical messengers released from platelets and damaged cells and are able to survive in the more acidic wound environment present at this stage [10]. Macrophages harbour a large reservoir of growth factors, such as PDGF, TGF- β , TGF- α , FGF and VEGF. These growth factors are important in regulating the inflammatory response, stimulating angiogenesis and enhancing the formation of granulation tissue. Lymphocytes appear in the wound after 3 days and are thought to be important in regulating wound healing, through the production of an extracellular matrix scaffold and collagen remodelling [5].

Proliferation

The proliferative phase occurs between 4 to 21 days, and represents angiogenesis, extracellular matrix (ECM) formation, and epithelialization. Although, there is considerable overlap between the phases of wound healing, the ability to transition into the next phase can determine whether a wound heals appropriately. ECM formation likely starts with platelet degranulation, because PDGF is a known promoter of proteoglycan and collagen formation [11]. During the proliferative phase the wound defect is filled with highly vascular connective tissue, commonly referred to as 'granulation tissue' [4].

Angiogenesis is triggered from the moment the haemostatic plug has formed as platelets release TGF- β , PDGF and FGF. In response to hypoxia, VEGF is released which, in combination with the other cytokines, induce endothelial cells to trigger neovascularization and the repair of damaged blood vessels [5]. The process of angiogenesis is interdependent on the production of a new extracellular matrix (ECM) which acts as a scaffold to support the newly formed blood vessels [4]. Transforming growth factor-beta (TGF- β) has been described as a potent growth factor involved in wound healing. It has been shown to influence the inflammatory response, angiogenesis, reepithelialization, extracellular matrix deposition, and remodeling [12]. Following the wound insult, fibroblasts are stimulated to proliferate by growth factors released from the haemostatic clot and then migrate to the wound [4]. Migration of epithelial cells starts from the wound edges within a few hours of wounding. A single

layer of cells initially forms over the defect, accompanied by a marked increase in epithelial cell mitotic activity around the wound edges. Cells migrating across them attach to the provisional matrix below. When the advancing epithelial cells meet, migration stops and the basement membrane starts to form [10].

Remodelling

Remodeling, the third phase of healing, begins two to three weeks after the onset of the lesion and can continue for one year or more. This step is associated with the apoptosis of myofibroblasts, endothelial cells and macrophages. The remaining tissue is therefore composed mostly of extracellular matrix proteins, essentially collagen type III that will be remodelled by the metalloproteinase produced by the epidermal cells, endothelial cells, fibroblasts and the macrophages remaining in the scar and be replaced by collagen type [9,13]. Remodelling occurs throughout the entire wound repair process as fibrin clot formed in the early inflammatory phase is replaced by the granulation tissue that is rich in type III collagen and blood vessels during the proliferative phase and subsequently replaced by a collagenous scar predominantly of type I collagen predominant with much less mature blood vessels [13] [14]. Growth factors are the focal regulatory points of the repair process. They are polypeptides that are released by a variety of activated cells at the wound site. In general, they stimulate cellular proliferation and chemoattract new cells to the wound [15].

Important factors in wound healing

Nutrition

Malnutrition adversely affects healing by prolonging inflammation, inhibiting fibroblast function and reducing angiogenesis and collagen deposition. Many essential nutrients are prescribed which are important for wound healing, including vitamin C and vitamin A, proteins, carbohydrates, zinc and omega-3 fatty acids [16].

Hypoxia

All wounds are hypoxic to some extent as their local vascular supply is disrupted. While a degree of hypoxia is required to facilitate re-epithelialization, sufficient oxygen is an

essential requirement for wounds to heal. Oxygen is essential for collagen deposition as it acts as a substrate in the hydroxylation of proline and lysine residues [5].

Smoking

Smoking impairs wound healing by its effects on chemotaxis, migratory function and oxidative bactericidal mechanisms in the inflammatory phase [16]. Nicotine, tar, nitric oxide, hydrogen cyanide, carbon monoxide and aromatic amines which are smoking compounds, inhibit healing through the effects of anoxia, hypoxia, impaired epithelialisation, vasoconstriction and enzymatic system toxicity. Nicotine is a vasoconstrictor that reduces nutritional blood flow to the skin, leading to tissue ischemia and impaired healing of injured tissue [17].

Immunosuppression

Many drugs which impair the inflammatory response can impede the healing cascade. Oral steroids, such as prednisolone, found to decrease cytokine concentrations during wound repair, leading to reduced collagen deposition [5].

Chronic disease

Diabetes is one of the metabolic diseases which were associated with problematic wounds. It is hypothesized that impaired wound healing in diabetic patients is a result of decreased angiogenesis that could be secondary to a diminished production of vascular endothelial growth factor (VEGF) [18].

Age

Elderly patients have a thinner epidermal layer and have slower inflammatory, migratory and proliferation responses. They are also more likely to have chronic disease, which also affects the process and a slower wound healing is seen to them and so be at higher risk of wound complications such as dehiscence [5].

Conclusions

The skin is the biggest human organ which possesses many functions. Therefore, skin wound healing displays an extraordinary mechanism of cascading cellular functions

which is unique in nature. Nonhealing wounds increase morbidity and mortality among population. Healing is a complex and evolving process, and because of their plasticity, WAM progress with the wound, adapting their cytokine expression profile. Although, wound healing mechanisms and specific cell functions in wound repair have been delineated in part, many underlying pathophysiological processes are still unknown.

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