

## Wound healing angiogenesis: A perspective of nurse

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### INTRODUCTION

Wounds healing can be a clinical challenge, and a cause of morbidity and mortality. One aspect of wound repair that plays an important role for adequate healing is the creation of new blood vessels from pre-existing vessels; this process is called angiogenesis. Clinically, new capillaries first become visible in the wound bed 3 – 5 days after injury, and their appearance is synonymous with granulation tissue, which acts as a matrix for proliferating blood vessels, migrating fibroblasts and new collagen. Impaired granulation is a hallmark of chronic wounds, as encountered in patients with type 2 diabetes and venous or arterial insufficiency [1]. A number of researchers have reported, chronic non-healing wounds are impacted by insufficient angiogenesis; decreased vascularity and capillary density delay wound closure. This perspective describes the principles of wound healing angiogenesis, especially to the wound nurse specialist, in order to identify the impact and interventions that may promote wound repair. Through this perspective, nurse specialists are expected to understand the concept of angiogenesis comprehensively. Clinical nurses with good insight of angiogenesis must be able to select the appropriate dress which suitable for wound healing. Utilizing modern bandage in acute and chronic wound management will accelerate the formation of growth factors that induce angiogenesis, and production of blood vessels.

### THE ROLE OF ANGIOGENESIS IN WOUND HEALING

The process of angiogenesis provides oxygen required for wound repair. It plays a central role in wound healing by

forming new blood vessels from pre-existing ones, as it promotes the growth of new capillaries to form granulation tissue. About three to five days after tissue injury, new capillaries become visible in the wound bed as granulation tissue, which acts as a matrix for proliferating blood vessels, migrating fibroblasts and new collagen. Proliferating capillaries bring oxygen, cells, and micronutrients to growing tissue and eliminate catabolic waste products. During angiogenesis and proliferation excess cells either leave the wound or undergo apoptosis, and neovessels undergo regression, leaving mostly collagen and extracellular matrix (ECM) proteins in the wound. During this process, the ECM is broken down by matrix metalloproteinase (MMPs) and metalloproteinase tissue inhibitors (TIMPs) The type III collagen was deposited during the proliferation phase is degraded and was replaced with stronger, thicker, and more permanent type I collagen forming the final scar [2, 3].

### PHYSIOLOGICAL CONTROL OF ANGIOGENESIS

The basic physiological processes involved in angiogenesis during wound healing are also seen in several female reproductive organs, including the ovary, endometrial lining of the uterus, and placenta. The vessels produced during this form of non-pathologic angiogenesis are characterized by their refinement, integrity, and ability to deliver nutrients to tissues in a controlled manner [4]. The production of angiogenic growth factors is regulated by genes expressed in response to hypoxia and inflammation, such as hypoxia inducible factor (HIF) and cyclooxygenase-2 (COX-2). These factors are stored in platelets and inflammatory cells that circulate in the bloodstream, and are sequestered within the ECM.

Conversely, angiogenesis inhibitor factors suppress blood vessel growth. Vascular growth is suppressed when there is a physiological balance between angiogenesis stimulators and inhibitors. During tumor growth, an “angiogenic switch” is always activated and remained on.

## ANGIOGENESIS REGULATING FACTORS IN WOUND HEALING

Wound Healing is a natural physiological reaction to tissue injury; successful wound healing depends upon angiogenesis. The cascade of healing is divided into four overlapping phases: hemostatic, inflammatory, proliferative, and a remodeling stage. Although, granulation is assigned to the proliferative stage, the growth of new blood vessels is initiated immediately after wounding occurs and is mediated throughout the entire wound healing process. A number of factors regulate wound angiogenesis including inflammation, growth factors, and hypoxia.

### *Inflammation*

The inflammatory phase is characterized by an influx of inflammatory cells and increased pro-angiogenic factor molecules in the wound. The level of angiogenesis in wounds often correlates with the inflammatory response, largely because inflammatory cells produce an abundance of proangiogenic factors. Tissue injury leads to a rapid acute inflammatory response designed to clear microbes, dying cells, and debris. A high level of proangiogenic factors produced by stimulated macrophages and keratinocytes, and at least a part of the wound angiogenic response lies downstream of inflammation. Thus, inflammation and the angiogenic response seem to be linked in the healing wound [5].

### *Growth factors*

The angiogenic process involves growth factor activation of endothelial cells, leading to proliferation, migration, tubular morphogenesis, vascular loop formation, and stabilization of vessels to form a mature vascular network. The term growth factor refers to a broad family of proteins that promote cell proliferation and migration. At least 20 growth factors that stimulate angiogenesis have been identified, sequenced, and been cloned. Among these are Vascular Endothelial Growth Factor, Platelet Derived Growth Factor, Fibroblast Growth Factors, and Transforming Growth Factors. One day after wounding, PDGF expression is detected on the vascular endothelium of injured skin. At day 5, basic FGF is expressed at its peak levels, which, by day 7 returns to baseline levels [6]. TGF- $\beta$  stimulates the formation of granulation tissue by acting as a chemoattractant for neutrophils, macrophages and fibroblasts. Hence, TGF- $\beta$  is an important modulator of angiogenesis during wound healing by regulating cell proliferation, migration, capillary tube formation and

deposition of ECM. Vascular Endothelial Growth Factor (VEGF) is a potent vascular endothelial cell-specific mitogen that activates endothelial cell proliferation, microvascular permeability and regulates of several endothelial integrin receptors during sprouting of new blood [5]. VEGF stimulates angiogenesis by inducing cell proliferation and vascular hyper permeability, and by promoting vascular survival.

### *Hypoxia*

Hypoxia is an important driving force for angiogenesis process; in response, the damaged capillaries experiencing hypoxia show increased, abnormal expression of hypoxia-inducible factor-1 (HIF-1) transcription factor. HIF-1 is a transcriptional activator that promotes angiogenesis by upregulating target genes such as VEGF-A, the main isoform in the wound, binds to its receptors on endothelial cells, directing vessel growth. VEGF and other pro-angiogenic factors guide vascular growth to areas of low oxygen starting from the wound periphery into the wound bed [7]. This hypoxic gradient can also affect stromal cell function, as the proliferation of human dermal fibroblasts is greatly enhanced under acute hypoxia. Fibroblasts were found to secrete up to nine times more transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) when exposed to hypoxic conditions, which demonstrates this increased activity. Acute hypoxia thus induces a temporary increase in cellular replication and contributes to initiation of the healing process [8]. However, healing is defective where oxygenation is not sufficient. Wound healing is triggered by temporary hypoxia after injury, however, prolonged or chronic hypoxia will impair the wound healing [9].

## IMPAIRED ANGIOGENESIS IN DELAYED WOUND HEALING

Imperfect angiogenesis is evident in all chronic wounds, such as diabetic ulcers, venous insufficiency ulcers and ischemic ulcers, and contributes to further tissue damage from chronic hypoxia and impaired micronutrient delivery. Diabetic wounds, impacted by insufficient angiogenesis, show decreased vascularity and capillary density. Wound closure is greatly delayed in diabetes, and chronic non-healing wounds are common [7]. Venous insufficiency ulcers or venous stasis ulcers result from incompetent valves in lower extremity veins, leading to venous stasis and hypertension that makes the skin susceptible to ulceration. Peripheral arterial disease (PAD) may result in severe ischemia. Konya, et al (2014) reported tissue hypoxia should initiate angiogenesis via inducing an HIF-1 $\alpha$  and angiogenic growth factors [10]. In patients with PAD, serum levels of hepatocyte growth factor are elevated, as compared to normal subjects [10]. In contrast, a high level of angiogenesis has been

described in the formation of keloids, a particularly vigorous type of skin scarring. This idea is supported by clinical studies that have demonstrated that hypertrophic scar formation is linked to increased microvascular content. However, the mechanism by which excessive angiogenesis influences abnormal scarring, fibrosis and fibroblasts is currently unknown.

## CONCLUSION

Angiogenesis is one of fundamental process during wound healing and hysto-integration of biomaterials. Hypoxia, inflammation and growth factors have been known as angiogenic regulating factors. Prolonged healing may occur in diseases such as diabetes, which characterized by a prolonged inflammatory phase and exhibit inadequate angiogenesis leading to the development of a chronic wounds, which is presented a significant health and economic burden to millions of individuals worldwide

## CONFLICT OF INTERESTS

Authors declared there is no conflict of interests.

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