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Review Article

Wound healing

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Abstract

Wound healing is an important physiological process to maintain the integrity of skin after trauma, either by accident or by intent procedure. The normal wound healing involves three successive but overlapping phases, including hemostasis/inflammatory phase, proliferative phase, and remodeling phase. Aberration of wound healing, such as excessive wound healing (hypertrophic scar and keloid) or chronic wound (ulcer) impairs the normal physical function. A large number of sophisticated experimental studies have provided insights into wound healing. This article highlights the information after 2010, and the main text includes (i) wound healing; (ii) wound healing in fetus and adult; (iii) prostaglandins and wound healing; (iv) the pathogenesis of excessive wound healing; (v) the epidemiology of excessive wound healing; (vi) *in vitro* and *in vivo* studies for excessive wound healing; (vii) stem cell therapy for excessive wound healing; and (viii) the prevention strategy for excessive wound healing.

Keywords: Pathophysiology; Wound healing

1. Introduction

Wound healing is an important but complicated process in human or animal, containing a multifaceted process governed by sequential yet overlapping phases, including hemostasis/inflammation phase, proliferation phase, and remodeling phase.[1] After an injury to skin, the exposed sub-endothelium, collagen and tissue factor will activate platelet aggregation, which results in degranulation and releasing chemotactic factors (chemokines) and growth factors (GFs) to form the clot, and all above-mentioned procedures will achieve successful hemostasis.[2] Neutrophils, the first cells to appear at the injury site, cleanse debris and bacteria to provide a good environment for wound healing. In the following, macrophages accumulate and facilitate phagocytosis of bacteria and damage tissue.[3] The hemostasis and inflammatory phase often takes 72 h to finish.

The following proliferative phase is characterized with an accumulation of lots of cells and profuse connective tissue. The wound encompasses fibroblasts, keratinocytes, and endothelial cells. Extracellular matrix (ECM), including proteoglycans, hyaluronic acid, collagen, and elastin forms a granulation tissue to replace the original formation of clot.[4] Many kinds of cytokines and GFs participate this phase, such as transforming growth factor-β family (TGF-β, including TGF-β1, TGF-β2, and TGF-β3), interleukin (IL)

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family and angiogenesis factors (i.e., vascular epidermal growth factor). This phase continues days and weeks.[4]

The last step of wound healing is a remodeling phase, which needs a precise balance between apoptosis of existing cells and production of new cells. Gradual degradation of profuse ECM and the immature type III collagen and formation of mature type I collagen are critical in this phase, which continues a few months and years. Any aberration in this phase may lead to excessive wound healing or chronic wound.[5,6]

Since a better understanding of the mechanism of wound healing can be presumed from the increased number of *in vitro* or *in vivo* experiments and a better treatment algorithm to maintain a regulated and orchestrated inflammatory response will be developed,[7,8] the following is an update of wound healing.

2. Wound healing in the fetus and adult

It is evident that the ability to repair wounds without excessive wound healing is age-dependent.[9] The more advanced age is and the higher possibility of excessive wound healing occurs. Fetal wound healing is characterized by regeneration of normal dermal architecture, which includes restoration of neurovasculature and dermal appendages.[9] Wound healing in the fetal skin involves a distinct GF profile, a lower inflammatory response with an anti-inflammatory cytokine profile, lower biomechanical stress, an ECM rich in hyaluronic acid and type III collagen, and a potential role for stem cells.[6,8–11] Compared with fetal skin, adult has a higher risk of scar formation.

There are at least four mechanisms to show the difference of wound healing between fetal skin and adult's skin.[10] The early stage of adult healing is characterized by an inflammatory reaction with migration of neutrophils and macrophages but inflammation is not apparent in fetus. Studies show that fewer of the inflammatory cells are found in the fetal wound than those in the adult wound.[10]

Studies found that several cytokines, including IL-6 and IL-8, are elevated significantly in adult healing process compared with those in fetal healing process.[8–11] By contrast, while IL-10 is higher in fetal healing than that in adult healing. TGF-β1 and TGF-β2 concentrations are higher in the adult wound, while TGF-β3 is lower in the adult wound.

The content of ECM is significantly different between the fetal and adult wounds. Fibroblasts produce ECM at a higher rate in the fetal wound, and the ratio of type III to type I collagen is higher in the fetal wound. The amount of hyaluronic acid in the ECM is also high in the fetal wound but low in the adult wound.

Myofibroblasts are only found in the adult wound. When mechanical tension of the adult wound increases, myofibroblasts become more apparent in the adult wound. By contrast, no or very few myofibroblasts can be found in the fetal wound.[8] Therefore, further studies of the fundamental mechanisms of fetal wound healing will identify the potential remedies to minimize scar formation.

3. Prostaglandins and their inhibitors on wound healing

Prostaglandins (PGs) are lipid compounds that participate in a variety of physiologic and pathologic processes. Prostaglandin synthesis is dependent on three enzymatic conversions beginning with the conversion of membrane-derived phospholipids to arachidonic acid by phospholipase.[4] Among them, PGE2 is a major mediator for inflammation,[12] and also involves various kinds of diseases, such as rheumatoid arthritis and osteoarthritis. The cyclooxygenase (COX) pathway is essential for the conversion of arachidonic acid into PGH2, a precursor of various biologically active mediators including thromboxane A2, PGE2 and prostacyclin. Two types of COXs have been identified, including (i) COX-1 (house keeping gene) has been expressed constitutively in various tissues, including stomach, and (ii) COX-2 (induction gene) has been induced by cytokines, growth factors, tumor promoters, and other agents.[4,13] COX-2-derived PGE2 and nitric oxide synthase (NOS)-derived NO is upregulated by pro-inflammatory mediators such as tumor necrosis factor (TNF)-α, lipopolysaccharide, and IL-1β. This induced inflammatory response triggers further damage to adjacent cells and tissues around the wound site, thus delaying the wound healing process. Prostaglandin E2 regulates fibroblasts in an autocrine pattern, including inhibition of fibroblast proliferation, migration, myofibroblast differentiation and collagen synthesis.[4] As the aforementioned role of pro-fibrotic effect, overexpressed TGF-β1 is found in fibrotic tissues and widely involved in fibroblast functions. Nitric oxide is a highly reactive radical that is generated by the activation of iNOS and contributes to various biological processes including inflammation.[14] Nitric oxide is thought to be a main disruptive factor in the wound healing process. Excessive generation of COX-2-derived PGE2 is a crucial physiological factor accelerating inflammation. Prostaglandin E2 is related to keratinocyte proliferation, angiogenesis and mediation of the inflammatory response. There are four receptors for PGE2, including EP1, EP2, EP3 and EP4. PGE2 through EP2 and EP4, known as coupling to G-proteins, increases intracellular cAMP formation.[15,16]

Newly synthesized PGE2 simply diffused and actively extruded by the multidrug resistance 4 from the cells. Subsequently, EP receptor is activated followed by pericellular PGE2 is cleared via re-uptake of PGE2 by PG transporter and then rapidly metabolized by cytosolic enzyme named nicotinamide adenine dinucleotide (NAD)+-dependent 15-hydroxyprostaglandin dehydrogenase.[17] This enzyme is expressed ubiquitously in mammalian tissues and responsible for biologic inactivation of PGE2 to 15-keto PGs.[4]

Prostaglandin E2 has been also known as an important mediator for bone formation, gastric ulcer healing, and dermal wound healing. The level of PGE2 is positively correlated with wound healing rate. The release of PGE2 from skin tissue after toxic stimuli produces local edema and hyperalgesia. Prostaglandin E2 elevation using 15-hydroxy PGDH inhibitor would be valuable for the management disease that required elevated PGE2, like wound healing, contributing to the clinical use of