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Review article

High-glucose environment disturbs the physiologic functions of keratinocytes: Focusing on diabetic wound healing

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ABSTRACT

Impaired wound healing is a common and potentially serious complication in patients with diabetes. In recent years, disturbed physiologic functions of epidermal keratinocytes have been found to play a central role in the poor healing ability of diabetic wounds. Factors involving keratinocytes that may contribute to the dysfunctional wound healing process in diabetes include impaired keratinocyte migration and proliferation, gap junction abnormalities, chronic inflammation, chronic infections associated with defective innate immunity, impaired angiogenesis, increased oxidative stress, and abnormal expression of matrix metalloproteinases (MMPs). In this review article, we provide evidence from the scientific literature for the molecular mechanisms of delayed wound healing in diabetes, with particular emphasis on keratinocytes. Elucidating the spectrum of molecular and functional abnormalities in keratinocytes induced by high-glucose environment may lead to more effective and individualized therapeutic strategies for the prevention and management of chronic diabetic wounds.

Contents

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1. Introduction

Diabetes mellitus is a common disease associated with poor glucose control, and its incidence is increasing worldwide [1]. Type I diabetes is characterized by an absolute lack of insulin, while type II diabetes is characterized by relative lack of insulin associated with insulin resistance. Both these conditions may result in a hyperglycemic state and lead to the development of various complications in different organ systems.

Impaired wound healing is a common and potentially serious complication in patients with diabetes. It may have adverse impacts on a patient's functional ability and life quality, and is associated with increased morbidity and mortality. Poor wound healing may result in the development of chronic diabetic foot ulcers, which is clinically challenging to manage and may lead to severe infections that require amputations [2]. Many factors have been shown to be involved in the poor wound healing ability of diabetic patients, including hyperglycemic environment, chronic inflammation, wound infection, vascular insufficiency, hypoxia, sensory neuropathy, and abnormal neuropeptide signaling [3]. In recent years, disturbed physiologic functions of epidermal keratinocytes have been shown to be an important underlying factor in the poor healing ability of chronic diabetic wounds.

2. Normal wound healing

2.1. Hemostasis

Normal wound healing occurs through four stages—hemostatic, inflammatory, proliferative, and remodeling phases [4]. Hemostasis is the first stage in the wound healing process. It is initiated by contact of platelets with the collagen of injured tissue, leading to platelet activation, adhesion to injured endothelium, and aggregation. In addition, the coagulation process is activated, which involves the conversion of fibrinogen to fibrin and the formation of the thrombus.

2.2. Inflammation

The second phase of wound healing is characterized by migration of inflammatory cells to the wound site. Neutrophils are usually the first inflammatory cells to arrive. The expression and activation of adhesion molecules on vascular endothelial cells promote the adhesion of neutrophils to the endothelium, which then migrate into the extravascular space. Neutrophils possess antimicrobial ability and are involved in tissue debridement [5]. This is followed by differentiation of circulating monocytes into macrophages and their migration into the extravascular space. Pro-inflammatory M1 macrophages play an important role in removing bacteria and tissue debris by phagocytosis. Later, lymphocytes enter into the wound site. A recent study has shown that the vasoactive peptides kinins and their receptors play important roles in mediating the inflammatory phase of wound healing [6].

2.3. Proliferative phase

During the proliferative phase, M2 macrophages (possessing anti-inflammatory function) secrete anti-inflammatory cytokines and various growth factors, including vascular endothelial growth factor (VEGF) and transforming growth factor beta (TFG-β), which induce cell proliferation. The wound provisional matrix is replaced by granulation tissue, which is composed of fibroblasts, inflammatory cells, endothelial cells and extracellular matrix (glycosaminoglycans and proteoglycans). Fibroblasts become activated and migrate into the wound site, where they proliferate and synthesize collagen and extracellular matrix [3]. In addition, the endothelial cells proliferate, migrate and form new vessels during this phase. Angiogenesis is induced by various angiogenic factors produced by keratinocytes, fibroblasts and inflammatory cells, including VEGF and fibroblast growth factor-2 (FGF-2).

Furthermore, keratinocytes proliferate and migrate from the wound edges or skin adnexal structures during this phase and play a crucial role in wound re-epithelialization [7]. Keratinocyte proliferation and migration is induced by various growth factors, such as endothelial growth factor (EGF), keratinocyte growth factor (KGF) and FGF-2 produced by keratinocytes and other cells [3].

2.4. Remodeling phase

In normal circumstances, the remodeling phase occurs around 2–3 weeks following the initial injury, and may last several months. During this phase, the granulation tissue is transformed into mature scar tissue [8]. The vessel density is reduced, and collagen is remodeled along tension lines, which increases the tensile strength of healed skin. For this to occur, new collagen is synthesized while collagen degradation also takes place, a process which is mediated by matrix metalloproteinases (MMPs). Collagen type III is gradually replaced by collagen type I which has greater tensile strength. The presence of myofibroblasts also allows wound contraction to occur, leading to potential scar formation [9].

3. Impaired physiologic functions of keratinocytes in chronic diabetic wounds

The skin of patients with diabetes is characterized by poor wound healing, resulting in chronic wounds which are defined as wounds that fail to heal after 12 weeks. Factors involving keratinocytes that may contribute to the dysfunctional wound healing process in diabetes include impaired keratinocyte migration and proliferation, gap junction abnormalities, chronic inflammation, chronic infections, reduced angiogenesis, oxidative stress, and abnormal expression of matrix metalloproteinases (MMPs) [2–4,10] (Table 1, Fig. 1). In the sections that follow, we provide evidence from the scientific literature for the molecular mechanisms of delayed wound healing in diabetes, with particular focus on the impaired physiologic functions of keratinocytes.

3.1. Abnormal keratinocyte migration

Wound re-epithelialization requires the proliferation and migration of keratinocytes from the wound edges or adnexal structures. Various abnormalities in keratinocyte functions have been demonstrated in diabetes, including migration, proliferation and differentiation.

Keratinocyte migration is known to be crucial for re-epithelialization of wounds. Previously, we have shown that high glucose environment decreased the migratory ability of cultured keratinocytes [11]. An important factor which determines keratinocyte motility is the expression of focal adhesion kinase ($p125^{FAK}$) by keratinocytes. Upregulated expression and phosphorylation of $p125^{FAK}$ is known to be involved in regulating cytoskeletal protein organization, cell spreading, and cell migration. In our previous study, we demonstrated that high glucose environment downregulated the expression of phosphorylated $p125^{FAK}$ ($pp125^{FAK}$) [11]. This may provide a possible explanation for the decreased mobility of keratinocytes in diabetic wounds.

Other studies have confirmed the impaired mobility of keratinocytes in diabetes. Advanced glycation end-products (AGEs)

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