Calcium in Wound Healing

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Calcium is a critical coagulation factor during hemostasis and a key signaling molecule for a variety of signaling pathways that regulate angiogenesis. In addition, the calcium ion has also been shown to act as a fundamental cue, directing the cellular functions of different types of cells during wound healing. Calcium plays a vital role as the extracellular signaling molecule and intracellular second messenger for keratinocytes and fibroblasts.

calcium skin wound healing fibroblast keratinocyte

1. Introduction

Wound healing is a complex process aimed at restoring the damaged skin to preserve tissue homeostasis. It involves the interaction between different cell types, growth hormones, cytokines, and a stable supply of metal ions, such as calcium, zinc, and magnesium [1]. Hemostasis, inflammation, proliferation, and remodeling are the four overlapping phases of normal wound healing [2][3].

Apart from being a critical coagulation factor during hemostasis, the calcium ion has also been shown to act as a fundamental cue, directing the cellular functions of different types of cells during wound healing. Calcium plays a vital role as the extracellular signaling molecule and intracellular second messenger for keratinocytes and fibroblasts. However, the effects of calcium on dermal fibroblasts have yet to be fully elucidated. A modest number of studies have shown that calcium influences the morphology, proliferation, and collagen deposition of fibroblasts [4][5].

2. Skin Injury

As the first protective barrier of the human body, skin is subjected to various environmental insults from time to time [6][7]. In addition, pathological changes such as diabetes mellitus and reduced blood circulation can also lead to disruptions in skin integrity [8]. A wound is defined as a break in the skin's epithelial integrity, which may affect the structure and function of the underlying tissue. The severity of skin injuries such as burns can be classified based on the depth of the injuries.

Wound management is a major public health issue worldwide. It is anticipated that the prevalence of chronic wounds in developed countries is approximately 1–2% of the total population [9]. In a study, the authors reported that around 15% of the 8.2 million Medicare beneficiaries in the year 2014 had a skin wound or infection and a total of USD 28.1 billion to USD 96.8 billion was spent on wound management [10].

In developing countries like Malaysia, diabetic wounds seem to have higher prevalence [11]. It is more alarming that this number is predicted to increase dramatically in the coming years [12]. Diabetic foot ulcer (DFU) affects 15–25% of diabetic patients during their lifetime and it is also the leading cause of amputation. Sultanah et al. found that various care modalities, i.e., antibiotics, surgical debridement, and dressing, should be used concurrently to treat DFU [13].

The medical cost for wound treatment is high and continues to grow rapidly. Hence, there is a need for researchers, scientists, doctors, and the government to work closely in providing an effective wound care scheme to ease the financial burden of patients and the country.

3. Calcium and Wound Healing

Calcium ions are known to regulate the intracellular signals that modulate many cellular activities. As early as 1983, Chapman demonstrated changes in the calcium gradient after chemical or physical stimuli, which coincided with the activation of calcium channels around the cell membrane [14]. Local calcium has been shown to modulate the proliferation, differentiation, and maturation of keratinocytes and fibroblasts, as well as the formation of epidermal lipid barrier function via signal transduction and gene expression [15].

Xu and Chisholm examined the early stages of wound healing in a living organism, i.e., the worm Caenorhabditis elegans, expressing the fluorescent calcium sensor. They discovered that both laser and mechanical wounding were effective in stimulating the formation of a rapid calcium wave that spread from the site of injury and contributed to a sustained rise in epidermal calcium. The results from this study indicated that calcium was involved in the earliest wound signaling activities and may play a significant role in modulating would healing [16]. Furthermore calcium flux has been shown to promote wound healing in early Xenopus embryos and a rapid, transient increase in intracellular calcium has been observed in the in vitro ‘scratch’ wound assay, as well as the single-cell wound healing assay [17][18].

The results of these experiments demonstrated the importance of determining the function of calcium in cutaneous wound healing and its mechanism of action. This information will contribute to better wound management to achieve rapid wound closure and to restore the original functions and mechanical strength of the regenerated tissue.

Calcium is the main regulator of keratinocyte differentiation [19]. A calcium gradient within the epidermis facilitates the differentiation of keratinocytes as they cross various strata, eventually forming the semipermeable stratum corneum [20]. The stratum basale and spinosum have lower calcium concentrations, and the calcium concentration gradually increases towards the stratum granulosum and decreases again in the stratum corneum. Calcium is essential for keratinocyte differentiation, whereby it stimulates the differentiation of basal keratinocytes in the stratum basale and spinosum, as well as triggering terminal differentiation of cells in the stratum granulosum. In an in vitro study, researchers studied the influence of calcium concentrations, i.e., 1.4 mM, 0.4 mM, and 0.03 mM, on the proliferation and differentiation of primary keratinocytes [21]. In another study, the authors found that

keratinocytes cultured in lower calcium concentrations (0.05–0.1 mM) proliferated steadily but were unable to differentiate and form stratified layers [20]. The keratinocytes begin to differentiate and establish intracellular mechanisms that are essential for differentiation once the calcium concentration was increased. Calcium is known to regulate the formation of desmosomes, adherens junctions, and tight junctions, as well as activating the calcium-sensing receptor (CaSR), which is required to initiate the intracellular mechanisms that regulate keratinocyte differentiation and survival [22][23][24].

Fibroblasts also respond to extracellular calcium but are 100 times less sensitive to it than keratinocytes. Fibroblasts mainly use calcium intracellularly for contraction and this contraction is important in reducing the wound size during wound healing [25]. In another study, the authors found that intracellular calcium is needed for cell–cell adhesion in fibroblasts by mediate remodeling of actin and the recruitment of cadherins into the intracellular junctions [26]. Navarro-Requena et al. conducted a study to examine the effects of extracellular calcium on skin fibroblasts cultured in vitro [4]. Supplementation of extracellular calcium was found to increase the cell metabolic activity, migration, MMP production, collagen synthesis, and cytokine release, as well as decreasing the cell contraction ability. Kawai et al. also investigated the use of calcium to facilitate cutaneous wound healing [5]. The study discovered that intravenous injection of calcium-based nanoparticles (NPs) and calcium chloride accelerated wound healing but only calcium chloride was able to hasten wound healing when they were applied topically. The topical application of calcium-based NPs failed to promote wound healing probably due to the failure of calcium release from the NPs. NPs delivered intravenously accumulated at the wound site and improved the calcium absorption of fibroblasts, subsequently hastening wound healing by enhancing fibroblast proliferation and contraction.

Calcium is a key signaling molecule for a variety of signaling pathways that regulate angiogenesis [27]. The majority of the mitogens, including the angiogenic factors, are known to activate calcium influx through the opening of plasma membrane calcium channels or releases from intracellular organelles such as endoplasmic reticulum [28]. Calcium influx into endothelial cells has been reported to play a crucial role in endothelial cell migration, adhesion, proliferation, and vessel formation in vitro and in vivo [29][30]. Blockage of non-voltage gated calcium channels by carboxyamidotriazole was found to inhibit the above cellular processes [30].

4. Role of Calcium in Different Phases of Wound healing

The importance of calcium in wound healing is evident in the delayed wound healing and higher prevalence of chronic wound formation in animals with dietary calcium deficiency and the presence of calcium chelating agents in their diet [31][32]. The calcium concentration in the wound area varies in accordance with the biochemical activities of the healing process. The extracellular calcium concentration has been shown to increase upon injury, persisting through the inflammatory and proliferative phases, and declining during the remodeling phase [33].

During the hemostasis phase, calcium aids in blood clotting by facilitating the formation of the platelet plug [34].

In the inflammatory phase, high extracellular calcium is thought to enter neutrophils and cause the intracellular calcium to increase, subsequently modulating the neutrophil function [35]. Extracellular calcium is a key regulator of epidermal homeostasis and its receptor (CaSR) sends calcium signals to promote keratinocyte adhesion, differentiation, and survival by inducing intracellular calcium and E-cadherin-mediated signaling [24]. The rapid induction of calcium ion propagation at the wound site signifies a transcription-independent damage signal to initiate epithelial healing [36].

Calcium ions, also known as clotting factor IV, can trigger the intrinsic coagulation cascade along with other clotting factors, thus accelerating the synthesis of enough thrombin to facilitate early fibrin formation [37][38]. Calcium ions mediate the binding of the tenase and prothrombinase complexes to the phospholipid surfaces expressed by platelets to the procoagulant microparticles or microvesicles secreted by them and are required for stable platelet incorporation into the developing thrombus [39].

Keratinocyte proliferation was found to be inversely proportional to the extracellular calcium concentration, whereby the cell proliferation was faster at a low calcium concentration and cells became differentiated at higher calcium concentrations [40]. reported that wound-induced calcium ion propagation is essential for successful keratinocyte migration [41][42]. The strongest response was found in the stratum basale, where CaSR was strongly expressed, and injury induced the cells to proliferate and migrate. Endogenous CaSR stimulation improved wound re-epithelization by increasing calcium ion signals and E-cadherin membrane expression.

Excessive calcium concentrations in the wound area inhibited keratinocyte proliferation and migration and is thought to slow down wound healing [43][44]. Therefore, it is extremely important to determine the appropriate calcium concentration that would facilitate epidermal cell proliferation and migration in vivo, which could be a key factor in facilitating the process of re-epithelization and ultimately wound healing [45]. Less is known about the effects of changes in the calcium concentration during wound healing on fibroblasts and endothelial cells. However, it has been postulated that a higher calcium concentration in the wounds could increase collagen synthesis and blood vessel formation [46].

Finally, in the remodeling phase, the epidermal hyperplasia is diminished, and the dermal collagen is reorganized. However, the role of calcium in these tissue events remains unclear.

5. Calcium-Releasing Scaffolds

The functionalization of scaffolds that have been traditionally designed to provide a physical barrier, mechanical strength, and excellent biocompatibility to support cell bioactivities, and to maintain a moist wound environment, is a new trend in the field of wound healing [47]. Many biomolecules can be incorporated into these scaffolds to functionalize them and calcium is one of the relatively new biomolecules that has been added to facilitate wound healing. Calcium has been chosen because it plays an important role in normal skin physiology and wound healing.

Dressings are used to protect wounds and help to maintain a moist wound environment, which favors wound healing. Particulate leaching, freeze-drying, supercritical fluid technology, thermally mediated phase separation, quick prototyping, powder compaction, sol-gel, melt molding, and electrospinning are some the techniques used to fabricate wound dressings [48]. Many forms of wound dressing have been developed and used in the clinic. However, preventing wound infection and hastening the regeneration of chronic wounds remain challenges when using existing dressings. **Table 1** summarizes the findings of papers using calcium-based dressings to promote wound healing.

Table 1. Studies using calcium-based dressings to promote wound healing.

Study	Key Finding	Reference
Calcium alginate enhances wound healing by upregulating the ratio of collagen types I/III in diabetic rats	Calcium alginate dressing showed excellent cytocompatibility and histocompatibility, and promoted diabetic wound healing by expediting wound re-epithelialization, attenuating inflammatory reactions, and increasing collagen synthesis and wound tensile strength.	[49]
Chitosan-calcium alginate dressing promotes wound healing: A preliminary study	Chitosan-calcium alginate dressing was able to promote wound healing by suppressing the inflammation, promoting angiogenesis, and preserving wound moisture. In addition, the scaffold also possesses antibacterial property and excellent biocompatibility, with no cytotoxicity.	[50]
Preparation and characterization of chitosan/gelatin/nanocrystalline cellulose/calcium peroxide films for potential wound dressing applications	The addition of calcium peroxide particles increased the antibacterial activity of the films against *E. coli*.	[51]
Effective wound healing by antibacterial and bioactive calcium-fluoride-containing composite hydrogel dressings prepared using in-situ preparation	The calcium and fluoride ions released from the hydrogel dressings enhanced the migration of fibroblasts and endothelial cells, as well as inhibiting bacterial growth. In vivo, the ions were found to accelerate wound healing, as indicated by the faster wound re-epithelialization, higher migration of surrounding skin cells, and higher recruitment of inflammatory cells.	[52]

NPs are nanometer-scale small structures which can bind and deliver ions, proteins, and other organic molecules. These tiny NPs can regulate the concentration of extracellular calcium by controlling the ion release, thus modulating wound healing. **Table 2** summarizes the findings of papers using calcium-releasing NPs to promote wound healing.

Table 2. Studies using calcium-releasing nanoparticles.

Study	Key Finding	Reference
Degradable, antibacterial silver exchanged mesoporous silica spheres for hemorrhage control	Mesoporous silica spheres (MSSs) with calcium are more effective compared to MSSs without calcium in supporting thrombosis and platelet adhesion in vitro, as well as stopping the bleeding in vivo.	[53]
Metal doped calcium silicate biomaterial for skin tissue regeneration in vitro	The zinc-doped calcium silicate particles were non-toxic to the fibroblasts at low concentrations (≤0.1 mg/mL), promoted fibroblast wound closure, and were antibacterial in vitro.	[54]
Wound healing-promoting effects stimulated by extracellular calcium and calcium releasing nanoparticles on dermal fibroblasts	The calcium-phosphate-based ormoglass nanoparticles, coded SG5, and extracellular calcium at similar concentrations were found to increase skin fibroblast migration, collagen synthesis, and cytokine release, as well as decreasing the cell contraction ability. However, lower expression of inflammatory factors and MMP activity were recorded in the SG5 group compared to the extracellular calcium group. These results indicate that SG5 is more suitable to promote the healing of chronic wounds.	[8]
Polymeric composite dressings containing calcium-releasing nanoparticles accelerate wound healing in diabetic mice	The poly(lactic acid) (PLA) nanofiber mats with SG5 nanoparticles promote angiogenesis, collagen synthesis, wound re-epithelialization, and fibroblast migration in diabetic mice with ischemic wounds compared to PLA nanofiber mats and Mepilex®.	[55]

6. Summary

Although studies have been performed to elucidate the role of calcium in wound healing, the effect of extracellular calcium in acute and chronic wound healing remains unclear. Several studies have showed the potential of incorporating and controlling calcium release from scaffolds to accelerate wound healing. However, the number of studies reported thus far is extremely limited. More preclinical and clinical studies are required to validate the findings of these studies.

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