


Regulation of K⁺ channels may enhance wound healing in the skin

Abstract

In the process of promoting wound healing, epidermal growth factor (EGF) activates protein kinase C, protein tyrosine kinase and ERK MAPK (mitogen-activated protein kinase). The activation of these mediators in signal pathways can regulate the operation of K⁺ channels. In addition, the K⁺ channel is involved with cell migration and proliferation, both of which are requisite for wound healing. Recent studies, although not conducted on skin wounds, have found that the K⁺ channel is associated with wound healing and that wound healing can be promoted by regulating the K⁺ channels. Therefore, the authors hypothesize that healing of skin wounds could be promoted by regulating K⁺ channel distribution in skin keratinocytes or fibroblasts. We plan to conduct a study of the promotion of skin wound healing using K⁺ channel regulators.

Epidermal growth factor (EGF) is frequently used to promote the healing of various types of wounds. EGF was discovered in mouse salivary glands in 1962 and was the first growth factor to be described [1]. EGF promotes wound healing by increasing epidermal proliferation and

accelerating wound contraction, which is related to myofibroblast proliferation and collagen deposition [2]. In granulation tissue, EGF increases cellularity and the accumulation of collagen and glycosaminoglycans [3]. In addition, EGF  influences keratinocyte shape and induces the contraction and migration of keratinocytes [4].

Many functions of EGF in wound healing operate through various signaling pathways. EGF exerts its actions by binding to its receptor (EGF-R), which is a transmembrane protein tyrosine kinase. The binding of EGF to its receptor triggers receptor dimerization and autophosphorylation, and recruitment of kinase substrates, which are signaling enzyme adapter proteins possessing an SH2 domain, Grb2 adapter protein, and Grb2-SOS complex. These events lead to phosphorylation of Ras (GTP-binding protein) and activation of the Ras/Raf/MAP kinase pathway, which in turn leads to phosphorylation of regulatory proteins and transcription factors and culminates in cell proliferation. Other pathways potentially activated by EGF include the phosphatidylinositol pathway, which leads to activation of protein kinase C (PKC) and an increase in cytosolic calcium, and the JAK/STAT signaling pathway [5].

Two-pore domain potassium channels (K2P channels) are highly regulated by phosphorylation and by G protein-mediated pathways. PKC inhibits recombinant TASK3 channels [6]. The agonist-induced inhibition of TREK-2 via the M3 receptor occurs primarily via PKC-mediated phosphorylation [7]. In addition, activation of protein tyrosine kinase (PTK) and ERK MAPK, a

mitogen-activated protein kinase, contribute to impairment of K_{ATP} and K_{Ca} channels pial artery dilation [8].

Therefore, EGF activates PKC, and activated PKC may regulate (i.e. inhibit) K^+ channels (TASK3, TREK-2) during the process of promoting wound healing. Similarly, EGF activates PTK, and the activated PTK and ERK MAPK may also regulate K^+ channels (K_{ATP} and K_{Ca} channels, in this case) during wound healing.

Localized changes in cell volume, controlled by ion channels and transporters, also contribute to single cell migration. Actin polymerization and cell volume are likely to be tightly co-regulated during cell migration. Plasma membrane K conductance is central to both actin polymerization and volume regulation [9]. Cell migration was inhibited by the application of a K^+ channel blocker in transformed Madin-Darby canine kidney focus cells [10]. Blockade of K^+ channel activity has also been demonstrated to inhibit cell proliferation in human melanoma cells, normal human lymphocytes, and breast cancer cells [10]. In addition, EGF has been found to stimulate cell proliferation via the activation of K^+ channel activity in fibroblasts and breast cancer cells [10]. According to the results of the above-mentioned studies, the K^+ channel is known to be related to cell migration or proliferation, both of which are required for wound healing.

In summary, research has shown, first, that in the process of promoting wound healing by EGF, activated secondary mediators in one or more activated signal pathways can regulate K^+ channels. Second, the K^+ channel is related to cell migration or proliferation, which are both required for wound healing.

This has been confirmed by recent studies, although not conducted on skin wounds, that have shown that the K^+ channel is associated with wound healing, and that wound healing could be promoted by regulating the K^+ channel. For example, nicotine suppresses gastric wound repair via the inhibition of K^+ channel expression [10]. Inhibition of K^+ channels also accelerates intestinal epithelial cell wound healing [9]. Wound healing is stimulated by pinacidil, an ATP-dependent K^+ channel (K_{ATP}) activator, which also increases alveolar epithelial cell migration [11]. The K_{ATP} channel plays a role in gastric mucosal restitution through a polyamine-independent pathway in rats [12].

Other recent studies have shown that the two-pore domain K^+ channel is expressed in keratinocytes, the principal cells of the epidermis of the skin [13], and that Ca^{2+} -activated K^+ channels are expressed in fibroblasts, the principal cells of the dermis [14].

Therefore, the authors hypothesize that wound healing in skin could be promoted by regulating the K^+ channels distributed in the keratinocytes or fibroblasts of the skin. This could be

performed using well-known K^+ channel activators or inhibitors, or a potassium chloride solution with a lower or higher concentration than the intracellular K^+ concentration.

A trial to heal donor sites of split thickness skin grafts using potassium chloride has been published; the procedure was performed using 1 molar potassium/calcium chloride solution in hydrogel [15]. We plan to conduct a study of the promotion of skin wound healing using K^+ channel regulators.

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