Harnessing the Electric Spark of Life to Cure Skin Wounds

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Significance: Skin wounds cause great distress and are a huge economic burden, particularly with an increasingly aging population that heals poorly. There is an urgent need for better therapies that improve repair. Intracellular signaling pathways that regulate wound repair are activated by growth factors, hormones, and cytokines released at the wound. In addition, endogenous electric fields (EFs) are generated by epithelia in response to injury and are an important cue that coordinates cell behavior at wounds. Electrical stimulation (ES), therefore, holds the potential to be effective therapeutically in treating wounds.

Recent Advances: ES of wounds is an old idea based on observations of the natural occurrence of EF at wound sites. However, it is now receiving increasing attention, because (1) the underpinning mechanisms are being clarified; (2) devices that measure skin wound currents are in place; and (3) medical devices that apply EF to poorly healing wounds are in clinical use with promising results.

Critical Issues: Several signaling proteins transduce the EF influence to cells. However, a bigger picture of the EF-proteome is needed in order to understand this complex process and target it in a controlled manner.

Future Directions: Dissecting the signaling pathways driving electrical wound healing will allow further identification of key molecular switches that control the cellular response to EFs. These findings herald the development of a new concept, the use of hydrogel electrodes impregnated with small molecules that target signaling pathways to explore the potential of dual electric-pharmacological therapies to repair wounds.

SCOPE AND SIGNIFICANCE

Poor wound healing is an enormous clinical problem and a socio-economic challenge. Skin wounds are frequently painful, cause scarring, and may require hospitalization, special nutrition, and medication. Annually, about 1% of the population incurs skin wounds that need medical attention.1 Surgical wound infection affects 30–40 patients per 1,000 operations, and its effects can be life threatening. Pressure ulcers have a major negative effect on patient function and quality of life and strikingly; around one in five in-patients in European hospitals has a pressure ulcer. Wound care generally, and the treatment of chronic wounds in particular, will become increasingly important in the provision of healthcare as the population ages, as chronic wounds are highly age correlated.

Individual therapies that promote wound healing include the use of biomimetic scaffolds and negative pressure, the topical administration of specific small molecules, gene-therapy approaches, and cell-based strategies such as the administration...
of epithelial stem cells. Nonhealing wounds may benefit additionally from physical approaches to achieve wound healing. Numerous animal studies and clinical trials have provided evidence and mechanistic insights into the effectiveness of Electrical stimulation (ES) for wound healing. Consequently, clinicians and scientists are becoming increasingly aware of the potential for electrical therapies, and new electrical devices have been introduced clinically. Indeed, ES is the most effective treatment for long-term, nonhealing ulcers, and this has been adopted as a policy by the European Pressure Ulcer Advisory Panel (www.epuap.org) and the National Pressure Ulcer Advisory Panel, Washington DC (www.npuap.org/resources.htm). In the United States, ES is now approved for payment by the Centers for Medicare and Medicaid Services for treating pressure ulcers and wounds that have not responded to standard wound treatment.

This clinical awareness coincides with recent advances in our understanding of the molecular mechanisms underlying electrically stimulated wound repair. The hypothesis that wound repair is guided by electric signals is supported by three main lines of evidence: (1) Strong electric currents exist at wounds and are required for effective wound healing; (2) inhibition of endogenous currents specifically impairs wound closure; and (3) applying an exogenous electric current of physiological intensity can induce faster wound closure both in vitro and in vivo.

In this review, we have compiled the present knowledge on the effects that electric fields (EFs) have on the behavior of cells involved in the healing response, and we focus on the mechanistic understanding of how electric signals are sensed and transmitted within these cells to influence their physiological behavior. In addition, we explore the potential of interfering with EF signaling to enhance skin wound repair by highlighting the potential of dual therapies using pharmacological compounds that regulate phosphorylation signaling and ES of wounds. In vitro and Phase I preclinical studies in animal models of wound healing will be useful to assess the potential of these dual therapies to treat nonhealing wounds.

**TRANSLATIONAL RELEVANCE**

Uncovering the mechanisms of ES wound healing has translated into new healthcare guidelines and enhanced clinical use. ES is the most effective treatment for long-term, nonhealing ulcers, and this has been adopted as policy by the European Pressure Ulcer Advisory Panel (www.epuap.org) and the National Pressure Ulcer Advisory Panel, Washington DC (www.npuap.org/resources.htm). One device, WoundEl has seen increasing clinical use. Since 2006, around 800 WoundEl devices have been manufactured to treat in excess of 6,000 patients in Europe. Further translation is likely through the development of a next generation, hydrogel-based electrical dressing that is doped with appropriate small-molecule pharmacology.

**CLINICAL RELEVANCE**

Skin wounds cause great distress and place a huge economic burden on health care, particularly with an increasingly aging population that heals poorly. Better therapies to improve wound repair are needed. Intracellular signaling pathways regulating wound repair are activated by growth factors, hormones, and cytokines released at the wound site. EFs are also generated by epithelial layers in response to injury and are an important cue orchestrating multiple cell behaviors at wounds. Identification of the signaling proteins regulating EF-mediated cell migration and
wound closure is revealing the clinical potential of dual electric-pharmacological therapies to repair wounds.

**DISCUSSION**

**The epidermis: a powerful healing battery**

The structure of the skin. The skin is a multifunctional system that covers and protects the organism. Mammalian skin consists of two main tissue layers: a stratified squamous epithelium (epidermis), which overlies a dense connective tissue (dermis), depicted in Fig. 1.

The stages of skin wound healing. Cutaneous wound healing is a complex and evolutionarily conserved process that serves to restore the skin barrier and prevent infection after injury. It involves three temporally overlapping phases: inflammation, new tissue formation, and remodeling. Inflammation takes place immediately after tissue damage to prevent fluid loss and infection, and to remove dead cells. This first step is orchestrated by components of the coagulation cascade, inflammatory pathways, and the immune system. After inflammation, new tissue formation occurs, involving cellular proliferation and migration of keratinocytes over the injured dermis. New blood vessels then form during the angiogenic process, and this is regulated by vascular endothelial growth factor-A and fibroblast growth factor-2. The resulting capillaries associated with fibroblasts and macrophages replace the fibrin matrix with granulation tissue, which forms a new substrate for keratinocyte migration at later stages of the repair process. The barrier function of the epithelium is restored when the opposing wound edges rejoin, and the keratinocytes behind the leading edge proliferate and mature. In the later part of this stage, fibroblasts from the edge of the wound or from the bone marrow are stimulated by macrophages, and some differentiate into myofibroblasts that close the wound edges. Fibroblasts and myofibroblasts interact and produce collagen that ultimately forms the bulk of the mature scar. Finally, remodeling takes place. This involves apoptosis or wound exit of endothelial cells, macrophages, and myofibroblasts, leaving a mass that contains a few cells and consists mostly of collagen and other proteins of the extracellular matrix (ECM). This stage completes the wound repair process when the matrix is further remodeled by metalloproteinases that are secreted by fibroblasts, macrophages, and endothelial cells.

The three stages of the repair process are activated and co-ordinated via various intercellular and intracellular signaling cascades. These trigger specific changes in gene expression and promote the proliferation, differentiation, and migration of endothelial cells, keratinocytes, and fibroblasts, which is in concert with different types of immune cells. As recovery progresses, these signaling cascades are gradually down-regulated in an orchestrated manner. Deregulation of the repair process can cause defects ranging from

![Figure 1. Structure of the mammalian skin. The dermis contains fibroblasts, endothelial cells, and inflammatory cells that are surrounded by an organized extracellular matrix (ECM) of collagen type I, fibronectin, and elastin. The epidermis is a continuously renewing tissue composed of keratinocytes at different stages of differentiation represented by three layers: granular (composed of three cell sheets SG1–SG3), spinous, and basal. The granular layer is overlain by a stratum corneum that represents the endpoint of epidermal differentiation and cell death. The stratum corneum confers the barrier function to the skin and protects internal organs from the environment. As the differentiation process progresses, keratinocytes express proteins involved in both the scaffold function and the eventual formation of the insoluble cornified envelope (CE). The CE replaces the plasma membrane of differentiating keratinocytes and consists of keratins that are enclosed within an insoluble amalgam of proteins, which are crosslinked by transglutaminases and surrounded by a lipid envelope forming a "mortar-brick" structure. Intercellular lipids are primarily generated from exocytosis of lipid-containing granules called lamellar bodies, during the terminal differentiation of keratinocytes. Tight junctions (TJs) are intercellular junctions that are formed by various TJ transmembrane proteins; for example, claudins, occludin, tricellulin, and junctional adhesion molecule, as well as intracellular scaffold proteins, for example, ZO-1, ZO-2, ZO-3, and cingulin. These proteins regulate the passage of ions and molecules through the paracellular pathway in epithelial and endothelial cells. TJs in the skin are located in the granulous SG2 layer. TJ formation is a prerequisite for the formation of the epidermal permeability barrier and the maintenance of barrier function, in addition to the sealing of proteins into CE. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound.](webversion.png)
chronic, nonhealing wounds to excessive matrix deposition leading to hypertrophic scars and keloids. Venous insufficiency and diabetes mellitus also contribute to the formation of chronic, nonhealing wounds and ulcers.

Electric properties of the healthy and wounded skin. Voltages measured across rodent skin free of epithelial appendages (e.g., glands, hair) range from 30 to 100 mV (surface of the skin negative), and 0 to 10 mV across hairy regions. In human skin, the voltages range from 10 to ~60 mV depending on the region measured (Fig. 2). The ionic current in healthy epidermis moves between superficial and deep layers of the epidermis, and it does not have a significant net component in a lateral direction (i.e., parallel to the skin surface). Thus, the voltage gradient of the healthy skin battery is aligned approximately perpendicularly to the skin surface. This changes when the epidermis is injured.

Following a wound, naturally occurring electric currents flow parallel to the epithelial layers (Fig. 3). This current arises the instant an epithelial barrier is breached due to the flow of ions down concentration gradients and out through the damaged epidermis. These wound currents generate lateral, intraepidermal voltage gradients (EFs) ranging from 100 to 200 mV/mm that decline with distance from the wound. Currents escaping through healing wounds and their accompanying lateral voltage gradients fall off gradually over time and ultimately become nonexistent due to the increasing resistance created by the newly regenerating epithelium. More recent work has confirmed the existence and intensity of these endogenously generated electric currents in mouse and human skin wounds. These epidermal electrical currents activate several major signaling cascades and promote the directional migration of many cell types involved in wound healing.

Skin-electric currents control the behavior of cells involved in the wound healing response. Electrotaxis studies carried out in the last 40 years have shown that individual cells respond to EFs in a number of different ways. Several cell types that are implicated in wound repair increase their speed and direction of migration (electrotaxis) in response to an EF, as summarized in Table 1. Along with the antibacterial effect that EFs have shown in several studies, cells involved in the immune response such as neutrophils, lymphocytes, and monocytes show cathodal migration (toward the wound center) in an EF. Granulocytes migrate toward the anode at 2.5 mM Ca²⁺ and toward the cathode at 0.1 mM Ca²⁺. Macrophages also migrate in an EF, although the significance of their anodal response during wound closure is unclear. EFs cause macrophage migration on laminin and fibronectin by integrin-dependent cell crawling and possibly rolling. Intriguingly, EF stimulation of a marrow culture system increases the release of the cytokine macrophage colony stimulating factor, which is implicated in angiogenesis and acceler-
Vascular endothelial cell migration also determines the rate and pattern of new vessel out-growth, and this drives angiogenesis during wound repair. Endothelial cells respond to EFs by projecting broad, actin-filled lamellipodia. Keratinocytes that are involved in the later stages of the wound repair process migrate cathodally on several matrices. Fibroblasts, which are also implicated in later stages of wound repair, show voltage- and time-dependent electro tactic responses. Several studies have shown that fibroblasts can show both cathodal and anodal electrotactic responses. Additional studies on animal models and in cell cultures of dermal fibroblasts stimulated with a direct current (DC) EF demonstrated a significant increase in the ability of fibroblasts to synthesize collagen, produce DNA, and synthesize protein. In addition, the speed of epithelialization in the wound was noticeably increased. Fibroblasts that were exposed to EF had receptor levels of transforming growth factor-β which were six times greater than those of control fibroblasts, and this may explain the increase in collagen synthesis. Despite the variation in the directional response of fibroblasts reported by different studies, it seems highly probable that in the

Table 1. Directional responses of different cell types under a physiological electric field during the wound repair process

<table>
<thead>
<tr>
<th>Phase of Wound Repair</th>
<th>Cell Type</th>
<th>Directional Response to EF</th>
<th>References</th>
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<tbody>
<tr>
<td>Inflammatory</td>
<td>Macrophages</td>
<td>Anodal</td>
<td>21,22</td>
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<td></td>
<td>Lymphocytes</td>
<td>Cathodal</td>
<td>19</td>
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<td></td>
<td>Monocytes</td>
<td>Cathodal</td>
<td>14</td>
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<tr>
<td></td>
<td>Neutrophils</td>
<td>Cathodal</td>
<td>14</td>
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<tr>
<td></td>
<td>Granulocytes</td>
<td>Cathodal/anodal</td>
<td>20</td>
</tr>
<tr>
<td>Proliferative</td>
<td>Fibroblast</td>
<td>Cathodal/anodal</td>
<td>14, 23, 27–30</td>
</tr>
<tr>
<td>Remodeling (wound</td>
<td>Keratinocytes</td>
<td>Cathodal</td>
<td>14, 25, 26</td>
</tr>
<tr>
<td>contraction and</td>
<td>Myofibroblasts</td>
<td>?</td>
<td>24</td>
</tr>
<tr>
<td>re-epithelialization)</td>
<td>Vascular endothelial cells</td>
<td>Cathodal</td>
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EF, electric field.
proliferative phase of wound healing, endogenous EFs activate the production of ECM by fibroblasts and induce fibroblast migration to the cathode (wound centre).7 Further studies are necessary to uncover whether differentiation of fibroblasts into myofibroblasts results in changes in the electrotactic response. Such effects could explain polarity changes in different phases of wound healing.

How is the electric signal transduced to canonical signaling pathways in the skin? Mammalian skin contains an array of voltage-sensor proteins (e.g., sodium, potassium and calcium channels, and the sodium/potassium pump).32,33 In addition, G protein-coupled receptor of keratinocytes function as voltage sensors.34 Changes in the membrane potential or in extracellular currents, therefore, may affect the activity of these voltage sensors and, in turn, activate signaling cascades. Another potential way in which cells could respond to a wound-induced EF is the redistribution of charged or glycosylated (i.e., negatively charged residues) membrane proteins protruding from the cell surface. For example, epidermal growth factor receptors (EGFR) are glycosylated proteins that translocate within the plane of the lipid bilayer to accumulate at the cathodal, apical side of cells. For keratinocytes and corneal epithelial cells, this occurs within 5–10 min of EF exposure.35,36 As a consequence, EGF signaling becomes polarized, causing greater cathodal activation of extracellular signal-regulated kinases 1/2 (ERK1/2) and downstream cathodal polymerization of Filamentous actin.35,36 EF exposure also up-regulates the expression of EGF receptors in epithelial cells.35 Pharmacological inhibition of multiple tyrosine kinases, including EGFR, reduces the cell migration rate; whereas specific pharmacological inhibition of EGFR kinase activity reduces directed motility in EFs.36 EGF receptor signaling is, therefore, considered an important signaling component of the EF-mediated contribution to wound closure.

Integrins are large membrane spanning proteins that are N-glycosylated, and, hence, negatively charged in their extracellular region. Their ability to form functional heterodimers (α and β subunits) and contribute to cell migration depends on the presence of N-linked oligosaccharides. Therefore, as for EGFR, integrins may redistribute asymmetrically in EFs due to their external negative charge. Indeed, integrins α5 and α5β1 redistribute and aggregate cathodally on fibroblasts migrating cathodally, as does β1 in epithelial cells.29 Moreover, depletion of β4 integrin or an anti-integrin β1 antibody suppresses EF-directed migration.37,38 Interestingly, addition of EGF receptor recovers the electrotactic response of β4 integrin null cells, suggesting that cooperativity between EF-activated EGF and β4 integrin signaling through the small GTPase Rac might occur, possibly at focal adhesions.37 In support of the pivotal role that membrane receptors such as integrins and growth factor receptor signaling play in the directional response of cells to EF, a recent study in cancer epithelial cells demonstrates that changes in the expression of several types of these receptors and/or modulation of the activity of their downstream effectors causes robust changes in cell polarization and directional migration in DC EF.39

Other mechanisms that may contribute to the early steps of the transduction of the EF signal are electro-osmosis40 or electrophoresis of morphogens through gap junctions.41

Phosphorylation of proteins underlies the effects of EF on cell behavior Phosphorylation can lead to conformational changes in proteins, which affect their affinity for ligands and results in functional changes. Protein (de)phosphorylation on serine/threonine/tyrosine (Ser/Thr/Tyr) is the most widespread mechanism of post-translational modification and is involved in an enormous range of cellular processes. Protein phosphorylation reactions are catalyzed by protein kinases, while the hydrolysis of phosphate esters involves protein phosphatases (PPs). Ser/Thr/Tyr dephosphorylation is involved in crucial cellular processes that are implicated in the establishment of cell polarity, cell division, and cell migration; therefore, it is not surprising that an increasing number of reports demonstrates that phosphorylation of proteins is a key signaling event underlying the effect of EFs on cells (Fig. 4).

ES triggers the phosphorylation of focal adhesion kinase (FAK) in human epithelial cells, which is attenuated by an anti-integrin β1 subunit antibody.38 There is also evidence linking the proto-oncogenic protein tyrosine kinase Src to electrotaxis.14,42 Mouse keratinocyte EF-migration and the migration of several types of immune cells are dependent on the activity of protein kinases Akt/Protein kinase B, ERK1/2, Src, and p38.14,19 Most importantly, although EFs share signaling cascades with other growth factor receptors that also provide migrational cues, studies in neutrophils and keratinocytes have uncovered that the electric signal can induce rapid, sustained, and specific phosphorylation of protein kinases, including mitogen-activated protein kinases, ERK,
Src, and Akt in serum-free medium. These findings uncover the importance of the electrical signal as a cue that is able to activate major signaling routes, independently of growth-factor signaling activation.

Recent studies revealed that protein kinase C (PKC) and glycogen synthase kinase-3b (GSK-3b) activities are required for optimal electrotaxis. Pharmacological inhibition of PKC significantly reduced EF-induced directedness of cell migration for 1–2 h in an EF. Further, pharmacological inhibition of GSK-3b completely abolished EF-induced Golgi polarization and significantly inhibited the directional cell migration, but only at 2–3 h in an EF.

Interestingly, pharmacological inhibition of protein kinase A (PKA) does not affect cell motility in general; however, PKA activity regulates the directional migratory response to an applied EF.

The sodium/hydrogen exchanger 1 (NHE1) is an upstream transducer of electrotaxis, as two different types of NHE1 inhibitors, cariporide and ethylisopropyl amiloride, inhibited electric-field-induced Akt activation and directed migration of fibroblasts. NHE1 functions as a scaffold for several signaling complexes, including MAP kinases that are activated by EFs; it is possible, therefore, that NHE1 acts as an integrator of kinase signaling which promotes the response to EFs.

**Known and potential “molecular switches” controlling the directional response of cells**

Identification of molecules that control the direction of cell migration by turning it on/off or by acting as switches controlling attraction/repulsion of migration holds the potential to find new targets for combined electrical and pharmacological therapies to treat wounds. Here, we have compiled information on known and potential molecular switches, the modulation of which may have a beneficial effect in ES wounds by “sensitizing” cells to the effect of exogenously applied EFs.

**The PI3K/PTEN axis.** The molecular signaling cascades controlling the process of skin wound healing have gained new significant insights in recent years. The emerging picture of the field is that a diversity of molecular signaling cascades involved in the process of wound healing ultimately converges on the activation of the phosphoinositide 3 kinase (PI3K) pathway. Consistent with this new notion, phosphatidylinositol-3,4,5-triphosphate (PIP3), the
Phosphatase and tensin homolog (PTEN) is a lipid phosphatase that functions by hydrolyzing phosphates in position 3' from phosphoinositides, and, therefore, the major function of PTEN is the buffering of PI3K signaling. PTEN has been proposed as a pharmacological target to enhance wound healing in epithelia. Unsurprisingly, PTEN deletion enhances the rate and directionality of cellular migration of keratinocytes in single-cell assays and wounded monolayers. These findings highlight that PI3K/PTEN act as a cellular compass during both chemotaxis and electrotaxis and, therefore, are critical signaling molecules at wound sites where both electric and chemical signals arise. Interestingly, there are a number of useful side-effects for inhibiting PTEN in the context of wound healing. Ulcers that fail to heal are a common vascular complication of diabetes, and it is well documented that tissue vascularization enhances wound healing. Therapies that increase tissue vascularization in such patients may, therefore, prove effective in the reduction of ulcers. Although the mechanisms of vascular remodeling are as yet incompletely understood, initial evidence indicates that physiological EFs induce angiogenic responses in endothelial cells which are mediated by both the VEGF receptor and PI3K. PTEN has been identified as a negative regulator of angiogenesis. Therefore, PTEN inhibition would potentially be advantageous to enhance EF-mediated angiogenesis and wound repair responses in diabetic patients. Interestingly, PTEN has also emerged as an attractive target to treat diabetes, because it counteracts insulin-stimulated glucose uptake. Hence, all evidence thus far indicates that PTEN inhibition may be a good strategy to aid wound healing and, in particular, in the context of defective healing in diabetic patients.

Cyclic AMP/GMP ratio. Cyclic AMP (cAMP) levels influence whether scratch wounds in epithelial monolayers close or open in response to a DC EF, probably through modulation of PKA activity. Indeed, cAMP-dependent-PKA has a role in the regulation of the directional migratory response to applied EFs. In parallel with these observations, studies in Dictyostelium revealed that the catalytic domains of soluble guanylate cyclase and cyclic guanosine monophosphate (cGMP)-binding protein C also mediate the cathodal response via cGMP. By contrast, the N-terminal domain of soluble guanylate cyclase is responsible for the anode-directed signaling in conjunction with both the inhibition of PI3Ks and cGMP production.

Protein kinase/phosphatase switches. Ser/Thr/Tyr kinases and PPs regulate human physiology, and dysregulation of their signaling is linked to an array of human diseases. Therefore, kinases and phosphatase enzymes are used as drug targets to treat several human pathologies underlying protein phosphorylation dysregulation such as cancer, diabetes, Alzheimer’s, liver fibrosis, or viral infections.

PPs have essential roles during cell migration, orchestrating the formation and maintenance of the actin cytoskeleton, regulating small GTPase molecular switches, and modulating the dynamics of matrix–adhesion interaction, actin contraction, and cell detachment at the trailing edge, all of which are required during wound repair. Despite all reports highlighting the involvement of protein kinases in electrotaxis, the potential role of PPs in regulating the directional migration of cells in response to an EF has been largely ignored. The activity of most transmitters of the electric signal recruited and activated by EFs, such as membrane receptors, integrins, and ion exchangers, is modulated by phosphorylation; therefore, it seems likely that a balance between kinases and their counteracting phosphatases is required for electrotaxis and ES wound healing. For example, FAK activity, integrins, and growth factor receptors are modulated by several phosphatases. Moreover, NHE1 is phosphorylated by several kinases which are activated by EFs, and a number of reports demonstrate that NHE1 is also a target of several phosphatases. Interestingly, phosphorylation of NHE1 by these kinases is correlated with an increase in NHE1 activity, whereas dephosphorylation of NHE1 by protein phosphatase 1 (PP1) down-regulates NHE1 activity. It is, therefore, interesting to suggest that by modulating the bal-
ance between kinase and phosphatase activity, one could, in turn, modify the transmission of the electric signal and, therefore, cell behavior during ES-wound closure. Hence, studies to decipher the individual roles of phosphatases in electrotaxis are much required to gain a full mechanistic understanding of this complex process.

The PP1/NIPP1 phosphatase complex. PP1 is a ubiquitous enzyme that regulates diverse essential cellular processes by catalyzing most dephosphorylation reactions of ser/thr residues on proteins. Substrate specificity by PP1 requires its binding to a myriad of regulatory proteins. Nuclear inhibitor of PP1 (NIPP1) was first identified as an inhibitory protein of PP1, although more recent work indicates that NIPP1 directs PP1 activity to the nucleus to dephosphorylate a number of substrates. A recent report has identified PP1 and NIPP1 as essential for directional cell migration and activation of the PP1/NIPP1 complex as a cellular mechanism that controls the cathodal/anodal -polarisation and directed migration of epithelial cells in a physiological DC EF. Interestingly, the PP1/NIPP1 complex mediates this effect via up-regulation of growth factor and integrin expression and Cdc42 activity. These findings provide the identification of two genes that are required for directional switching in electrotaxis and suggest that activation of PP1/NIPP1 before ES or during ES (anode at wound side in this last case) could induce changes in gene expression which would make cells more prone to the healing effects of exogenously applied EFs.

FUTURE DIRECTIONS
Trends for wound repair therapies
Clinicians and scientists are increasingly aware of the potential for electrical therapies, and new electrical devices are now available that measure wound-induced electric currents (Dermacorder™). Moreover, the WoundEL™-therapy (GerroMed now owned by Molnlycke), which produces pulsed DC ES, has been used with some success to treat more than 6,000 patients in Germany since 2006. Most of these were patients with nonhealing wounds that had shown no response to any alternative treatment over many months. Both the WoundEL-therapy and a former similar device called Dermapulse® were CE marked and are currently being used in both European and U.S. hospitals.

The dissection of the various signaling pathways that regulate electrotaxis and EF-mediated wound closure is underway and paves the way for the identification of protein targets for electrically driven tissue repair therapies. Since phosphorylation of lipids and proteins seems to be a hallmark of the effect of EFs on cells, we propose that the use of molecules which modulate the activity of kinases and phosphatases in in vitro and Phase I preclinical studies in combination with exogenously applied EFs may be a promising tool useful for treating nonhealing wounds. Although the individual roles of PPs in electrotaxis and ES-wound healing remain elusive, recent evidence indicates that studies to identify the therapeutic potential of individual phosphatases in electrotaxis and ES-wound healing.

To our knowledge, there have been no clinical attempts as yet to use electrical and chemical therapies together to target skin wound repair. A full mechanistic understanding of the signaling events underpinning electrically mediated wound closure aided by the use of pharmacological

TAKE-HOME MESSAGES

- Intracellular signaling pathways that regulate wound repair are activated by growth factors, hormones, and cytokines that are released at the wound. In addition, endogenous EFs of 100–200 mV/mm intensity arise when the epidermis is injured. These EFs play a pivotal role in wound healing.
- Oriented and increased cell division of epithelial cells and migration of several cell types toward the cathode (wound centre) underline the “healing” effects of these EFs.
- EFs polarize important membrane receptors such as integrins and growth factor receptors and activate canonical phosphorylation signaling pathways.
- The role of PPs in reversing the effects of protein kinases in electrotaxis remains largely unexplored. A bigger picture of the EF proteome is needed in order to understand this complex process and to target it in a controlled manner.
- EF-based therapies may represent a powerful approach and a direction of future wound management. Demonstration of the effect of EFs in directing cell migration has energized the development of devices for ES of wound healing by medical bioengineering companies.
- These findings will pave the way for the development of new concepts, that is, dual electric-pharmacological therapies to repair wounds.
molecules will allow the manipulation of these signals to achieve rational control over skin repair.

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Professor Colin D. McCaig, FRSE, Regius Professor of Physiology and Head of School of Medical Sciences, University of Aberdeen. After completing his PhD with Professor Otto Hutter at Glasgow University, he undertook NIH-funded postdoctoral training in the United States. This introduced him to electrical control of cell behavior and his first scientific paper, J Physiol 314, 121–135 (1981) remains seminal in reopening an entire area of biology: the issue of electrical guidance of nerve growth and of wound healing. He won a prestigious Beit Memorial Research Fellowship in 1983 and established his own lab. He has concentrated on issues of cell polarity and cell migration and leads one of only a few groups in the world that studies the electrical controls of cell behaviors. His group established that electrical signals control wound healing, nerve guidance, and epithelial cell guidance in vivo and also regulate proliferation and guidance of neurons, vascular endothelial cells, tumor cells, and lens epithelial cells. Collectively, these wide-ranging events have major clinical relevance in a tissue engineering and regenerative medicine context. Clinical collaborators are using ES to treat human spinal cord injuries with protocols designed from our experiments, and electrical devices are also marketed to treat skin wounds that are also based on his seminal wound healing studies. Dr. Cristina Martin-Granados, Research Fellow, Division of Applied Medicine, University of Aberdeen. After completing her PhD at the Technischen Universität Berlin, Germany, Cristina Martin-Granados undertook an MRC Career Development Fellowship post in Prof. Patricia Cohen’s lab at the Protein Phosphorylation Unit in Dundee, where she studied the potential for pharmacological inhibition of two different PPs, Ppp4 and PP2C, to treat cancer and metabolic disease, respectively (Martin-Granados et al. 2008J Biochem Cell Biol 40:2315–2332; Voss et al. 2011 Cell Signal 23:114–124). In her current position working with Colin McCaig and John V. Forrester, she has united the field of phosphatase signaling with that of the electrical control of cell behavior, providing the first evidence of the involvement of PPs in electrotaxis. She has uncovered the PP-based mechanism that drives a cathodal/anodal directional switch in human epithelial cells. She is also investigating how dysregulation of phosphatase signalling contributes to altered migration of epithelial and immune cells and how this impinges on inflammation and wound healing.

REFERENCES


