CLINICAL IMPLICATIONS OF BASIC RESEARCH

Wound Healing with Electric Potential

Anna Huttenlocher, M.D., and Alan Rick Horwitz, Ph.D.

The efficient and effective repair of damaged tissue is fundamental to human survival. Wound repair has therefore challenged generations of health care providers, and various strategies have been used to accelerate and perfect the healing process. One such strategy has involved the application of an exogenous electrical stimulus to chronic wounds with the aim of instigating electrotaxis (also called galvanotaxis). Electrotaxis — the movement of diverse cell types in response to electric gradients — has been implicated in the migration of cells to endogenous electric gradients generated in wounded tissue. Even though endogenous electric fields were first identified more than 150 years ago,[1] the mechanisms that underlie electrotaxis have remained poorly understood. A recent study by Zhao et al.[2] shows that common signaling pathways are able to steer cell movement in both electrical and chemical gradients.

Substantial progress has been made in defining the key signaling components that mediate chemotaxis, the directed migration of cells in gradients of a chemoattractant. A series of studies by investigators using both the slime mold *Dictyostelium discoideum* and leukocytes have shown that the sensing of chemical gradients involves the asymmetric recruitment of signaling and cytoskeletal components that mediate cell polarization and directed movement.[3,4] A critical event in gradient sensing during chemotaxis is the recruitment of phosphatidylinositol 3,4,5-triphosphate (PIP3) to the part of the cell that faces the gradient of chemoattractant. The pathway that is mediated by phosphatidylinositol 3-kinase (PI3K) has been implicated in the polarization and chemotaxis of diverse cell types exposed to chemical gradients (Fig. 1). A key role of PIP3 signaling is also supported by the importance of the tumor-suppressor phosphatase and tensin homologue (PTEN) during chemotaxis. PTEN is a lipid phosphatase that negatively regulates the generation of PIP3; it is recruited to the trailing portion of *D. discoideum* during chemotaxis and serves to enhance the concentration of PIP3 at the front. Abrogation of PTEN in slime mold cells reduces the efficiency of chemotaxis, again supporting a critical role of the asymmetric regulation of phosphoinositide signaling during chemotaxis.

The work of Zhao et al. suggests that the tension between PTEN and PI3K is also relevant to electrotaxis in wound healing. The researchers tested the effect of removing phosphoinositide-signaling components on both directional sensing and migration of keratinocytes. They used gradients of electric potential of the same magnitude as those observed in endogenous settings

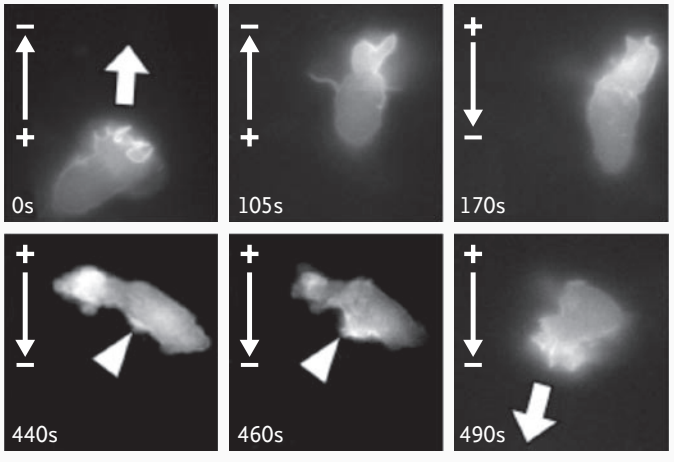

Figure 1. Wound Healing, Electric Current, and Cell Migration.

A recent study by Zhao et al.[2] showed that polarized phosphatidylinositol 3-kinase (PI3K) signaling steers the migration of human cells across a gradient of electric potential, a process called electrotaxis. The lipid phosphatidylinositol 3,4,5-triphosphate (PIP3) appears to be a pivotal molecule. It is concentrated at the leading edge of the cell, where signaling components bind to it. These signaling components, in turn, lead to the localized polymerization of actin and the formation of a protrusion in the direction of migration. Depicted in the figure is a promyelocytic cell; its leading edge is labeled with a probe that detects PIP3 production. The narrow arrows at the top left show the gradient of electric potential in which the cells are migrating. The wide arrows show the direction of cellular movement. Reversal of the polarity of the electric field is followed by a change in locale of PIP3 to a region that becomes the new leading edge (arrowheads).

and showed that gradients govern the movement of keratinocytes during wound repair, an observation that is consistent with previous findings. They also showed that electrotaxis requires PI3K, by engineering keratinocytes deficient in one of its subunits. These cells display reduced directed movement in gradients of electric fields with the use of both in vitro and in vivo wound assays. Zhao et al. showed that PTEN is a negative regulator of electrotaxis and that genetic depletion of PTEN enhances electrostatic-mediated migration of keratinocytes. The authors went on to show that gradients of electric potential can mediate the asymmetric recruitment of PIP3 to the leading edge of a promyelocytic cell line (Fig. 1), analogous to the effects observed in chemical gradients. These findings point to an essential role of PI3K and PTEN signaling in directed cell migration induced in electric fields, suggesting that electrotaxis and chemotaxis share common signaling pathways.

Therapeutic modulation of endogenous electric fields represents an attractive means of optimizing wound healing. Physical therapists frequently apply exogenous electric gradients to treat chronic wounds, with evidence of some therapeutic benefit. Perhaps a more attractive strategy would be the topical application of agents that increase ionic transport and thereby enhance endogenous electric fields and wound closure. Zhao et al. showed that silver nitrate, an agent commonly used to treat wounds and prevent infection, also increased electric potential and migration of keratinocytes. Future studies that further elucidate the mechanisms regulating electrotaxis will pave the way for the development of new therapeutic agents for wound healing. It may be equally important to identify agents that weaken endogenous electric fields, such as furosemide (a diuretic) and inhibitors of the ion channel NHE1, in light of the recent observation[5] that the enhanced electrotaxis characteristic of invasive breast and prostate cancer cells may contribute to their metastatic potential.

No potential conflict of interest relevant to this article was reported.

From the Departments of Pediatrics and Pharmacology, University of Wisconsin Medical School, Madison (A.H.); and the Department of Cell Biology, University of Virginia School of Medicine, Charlottesville (A.R.H.).

1. McCaig CD, Rajnicek AM, Song B, Zhao M. Controlling cell behavior electrically: current views and future potential. Physiol Rev 2005;85:943-78.
2. Zhao M, Song B, Pu J, et al. Electrical signals control wound healing through phosphatidylinositol-3-OH kinase-gamma and PTEN. Nature 2006;442:457-60.
3. Van Haastert PJ, Devreotes PN. Chemotaxis: signalling the way forward. Nat Rev Mol Cell Biol 2004;5:626-34.
4. Chung CY, Funamoto S, Firtel RA. Signaling pathways controlling cell polarity and chemotaxis. Trends Biochem Sci 2001;26:557-66.
5. Mycielska ME, Djamgoz MB. Cellular mechanisms of direct-current electric field effects: galvanotaxis and metastatic disease. J Cell Sci 2004;117:1631-9.