

How Electricity Relates to the Process of Wound Healing

A Summary Review

Compiled by Dr David Chapman-Jones & Lucy Thirkell

Introduction

Wound healing is one of the most important regenerative processes that most organisms exhibit and, as the complexity of healing becomes increasingly apparent, the importance of accurate evaluation and assessment cannot be overstated, alongside the need to fully understand the entire wound repair process and factors that may impair it.

Communication occurring at a cellular level prompted and regulated by the huge number of chemical and molecular interactions is fundamental to the principal actions and interactions of cells during wound healing (Bryant. 2000). Cells can act both singularly or as part of a group however, it is the processes of chemotactic migration, galvanotaxis, mitosis, angiogenesis and the synthesis and remodelling of scar tissue, regulated by an array of growth factors, cytokines, proteases etc, that are crucial in effective and successful tissue repair (Chapman-Jones 1998)

A significant amount of research has been carried out in the last twenty year to establish precisely how wounds heal from both a cellular and molecular perspective. However, many papers have now been published that report on the importance of an endogenous supply of electricity and the significant role it plays. The new concept of a bioelectric current appears to mediate many diverse physiological phenomena and wound healing is one of those arenas.

There remains debate as to precisely how a biologically mediated electric current affects a cell's structure and function and its contribution to the wound healing and other physiological processes.

The first stage of this scientific journey is to review the literature available to date, particularly within the last ten years, and establish the probable from the conjecture.

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Literature based evidence

There is growing evidence to suggest that electrical fields exist 'naturally' in embryos and adults generated by chemical and electrochemical events. All cells generate a voltage across their plasma membranes called the membrane potential and this plays important roles in the transportation of molecules across the membrane, signalling to the cell that an event has occurred somewhere on its surface, and for sending signals to other cells singularly and as functional groups.

The epithelium surrounding an organ works in a similar manner as the plasma membrane in that it determines what enters and leaves the organ that it encapsulates and its electrical properties play a vital role in establishing this (Nuccitelli R. 2003). The presence of a 'skin battery' was found to reside in the epidermis, and was originally demonstrated by Barker et al (1982) and later by Foulds and Barker (1983) [see footnote].

The cells that make up the epithelial layer are coupled with gap junctions so they can be considered as one continuous layer that electrically generates a transepithelial potential (TEP). Typical values for TEP range from 15 to 60mV, and it is this potential that is believed to be the driving force for generating endogenous electric fields and the electric current that arise when the integrity of an electrically polarised layer of cells is compromised, for example in wounding to the skin (Robinson. 1985).

Wound fields of 100-200mV/mm are generated immediately when skin is wounded and the current present is driven out of these regions of low resistance by the TEP. This in turn generates a lateral electrical field that focuses towards the wound from all directions. Nishimura's (1996) proposed that this lateral electric field beneath the epidermis, generated by the skin battery, provides the earliest signal to keratinocytes in that region to migrate towards the wound.

Footnote: It is interesting to note that it was the same Barker, in association with Illingworth (1983) that first identified the presence of a measurable biological current in the range of 30 – 50 μ A that exuded from the stumps of newly amputated limbs. This finding formed the basis for some of the important in-vitro studies using micro-current and significantly influenced the manner in which wounds were managed moving away from traditional dry dressing to a moist one.

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The lateral electric field (LEF) produced is proportional to the resistance in that area and it is generated with the cathode pole of the field residing in the centre of the wound. This electric field persists until the resistance increases, which occurs as the wound heals, and is believed to be an important mechanism for not only the migration of keratinocytes but also of other cells into the wound to effect healing, for example collagen producing dermoblasts. These signalling properties are paramount in initiating tissue repair and cell migration and are seen as one of the earliest signs of epithelial repair of epidermal wounds.

All epithelial cells will be exposed to an electric field generated from leakage currents driven by the TEP and they both detect and respond to them (Nuccitelli. 2003) by a process known as galvanotaxis. The polarity of the LEF is opposite to that above the epidermis and consequently keratinocytes are directed to migrate towards the wound.

There is an increasing amount of literature now available on the role of endogenous electric fields in guiding a variety of different types of cells to move and migrate directionally including epidermal, corneal and lens epithelial cells (Zhao et al. 2002, Wang et al. 2003). As the field strength increases the degree of directed migration appears to increase reaching a maximum orientation towards the negative pole at 100mV/mm.

By manipulating the field strengths and reversing the polarity, Venable's group demonstrated that corneal epithelialisation could be enhanced (Ingles and Venable.1998). Cells closest to the wound edge where the field is highest were orientated most strongly by the field and in addition to influencing the orientation of cell division (Zhao et al. 1999); the wound field also affect the rate at which a wound closes (Song et al. 2002).

Certain factors have to be present for cells to detect and respond to the electric field and these include calcium influx (Fang et al. 1998, Trollinger et al. 2002b), specific growth factors, for example, epidermal growth factor and fibroblast growth factor (Fang et al. 1998); and epidermal growth factor receptor phosphorylation (Fang et al. 1999) which requires the activity of cAMP-dependent protein kinase (PKA) for successful galvanotaxis of human keratinocytes (Pullar et al. 2001). According to Fang's team (1998), if these growth factors are absent the cell migration rate can decrease, although directionality appears to be unaffected, and that keratinocytes migrate well in both high or low calcium concentrations.

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Farboud et al. 2000, proposed that “the endogenous electric fields generated in a wounded cornea may function as an early cue to guide the directional migratory response of corneal epithelial cells”.

Significant research has been carried out investigating the cells response to an externally applied electric field and the role that the potential wound current plays in initiating cellular response and behaviour (Nishimura et al. 1996, Li and Kolega. 2001). It is suggested that this external application can manipulate cell behaviour in the following ways; directing cell migration, affecting cell motility, growth and polarity (Nuccitelli.1988) manipulating rates of cell division and protein production (Song et al. 2002, Chapman-Jones 1998) ^{see footnote} and initiating pre-angiogenic responses (Zhao et al. 2004)

A number of clinical trials are being undertaken using electric field and current in wound management, Borgens team have been studying its use in the treatment of spinal cord lesions (Borgens RB. 1999), McCaig’s team has been investigating its use in corneal epithelium and there is considerable evidence of the effect that a DC electric field has on a variety of cell types (McCaig et al. 2002).

Footnote:

Chapman-Jones in association with the Department of Human Morphology, Queens Medical Centre, University of Nottingham. Unpublished MSc Thesis: Sport and Exercise Medicine (1997)

The purpose of the study was to examine tenocyte activity in the Achilles tendon. Micro-current electrical stimulation was applied to whole Achilles tendon sections at two different intensities, 40uA and 1uA. Cell activity was evaluated using electron microscopy and the results of the experimental groups were compared with a non-stimulated control group.

The appearance of the tendon sections that received electrical simulation at intensity of 40uA were remarkably different from the non-stimulated tendon in the control group. There was disruption of the mature formed compact collagen with increased numbers of active tenocytes that appeared to have acquired the cytoplasmic organelles to synthesise new protein. The tendons in the group that received 1 uA of electrical stimulation showed inactive and degenerating fibroblasts suggesting a down regulation of regenerative activity.

The tendon sections were taken from cadaver specimens and remained viable for the duration of the experiment. However, infection contamination with two of the tendon sections reduced the sample size.

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