Reparation of the Ion Gradients: The Role of Ion Channels and their Potential to Guide the Clinical Management of Externally Induced Skin Wounds

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ABSTRACT

Unique ion gradients have been discovered in the skin and have been shown to play an important role in wound healing. While their mechanism of involvement remains unclear, recent research into respective cutaneous ion channels may provide further insight into this process.

Cutaneous calcium, potassium, water, sodium and chloride gradients were investigated with their potentially contributing ion channels identified. These channels include Kcnj8, Kcnh2, TRVP1, TRVP2, TRVP3, TRVP4, Orai1, Na+/K+ ATPase, and AQP3.

INTRODUCTION

The skin holds unique ion gradients that play a vital role in wound healing[1]. The physiology behind this process remains unclear, however, recent innovations regarding cutaneous ion channels may provide a better understanding of this biophysiological process. A deeper understanding of these ion channels is pertinent in not only understanding ion gradient associated wound healing but would also provide a clinical significance in its potential to differentiate wound stage and wound types.

METHODS AND MATERIALS

- A comprehensive literature search was utilized to identify studies evaluating ion channels in the context of skin wounds
- Inclusion criteria included ion channels studied in the context of ion gradients, wound stage determination and types of skin wounds

Wound healing phase	Homeostatic	Inflammatory	Proliferative	Remodeling/ maturation
Potential measurement/ marker	Kcnh2, Kcnj8	Calcium (undetermined channel), Low Na/K (TEP), Low Kcnh2, Kcnj8	AQP3	TRPV2

Table 1: Potential ion channel markers for the determination of wound age

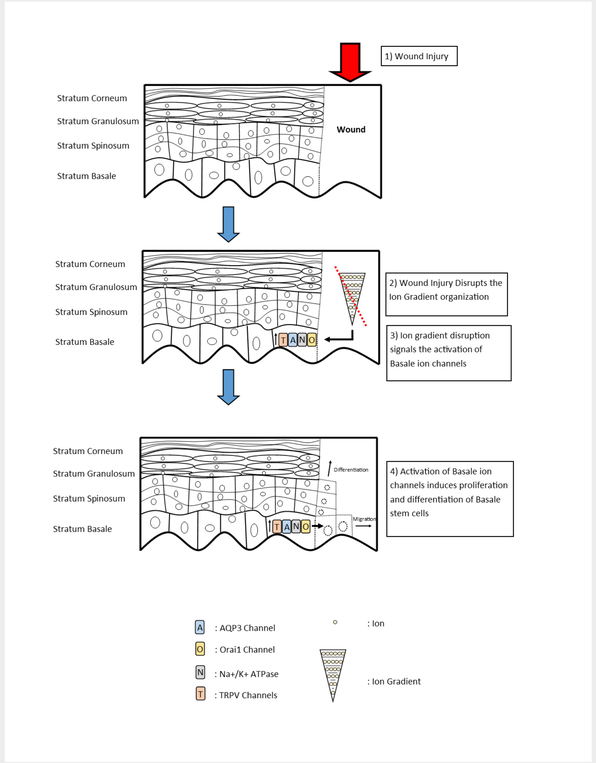

Figure 1. Proposed Theory of Ion Gradient's Role in Wound Healing

RESULTS

- Cutaneous Potassium, aqueous, sodium and chloride gradients were evaluated
- Respective ion channels identified with possible roles in these gradients were Kcnj8, Kcnh2, TRVP1, TRVP2, TRVP3, TRVP4, Orai1, Na+/K+ ATPase and AQP3 channels

Ion Channels as a Wound Age Determinant

- Kcnh2 and Kcnj8 were found in association with the homeostatic phase of wound healing[1]
- AQP3 channels were found in association with the proliferative phase[2]
- TRVP2 channels were found in association with the remodeling/maturation phase[3]
- Although no exact channel was found in association with the inflammatory phase, a combination of low Na+/K+ ATPase, Kcnh2 and Kcnj8 activity may be indicative of this phase[1,4]

Ion Channels in Differentiating Skin Wounds

- Cutaneous Ion Channels have the potential for differentiating different types of wounds
  - TRVP3 and AQP3 channels were associated with burn wounds[5-6]
  - Orai1 channels were associated with UVB-induced wounds[7]

Epidermal Distribution of Ion Gradients and Channels

- Contrary to the ion gradients, respective ion channels believed to contribute to their establishment have been shown to hold a different spatial arrangement
- Na+/K+ ATPase, AQP3, TRPV and Orai1 have been found highly expressed in the Stratum Basale layer[8-9]
- The calcium gradient stretches from the stratum basal layer to the stratum granulosa layer[10]
- The potassium gradient stretches from the stratum granulosum to the stratum spinosum layer[11]
- The sodium and chloride gradient stretches from the stratum corneum upwards[12]
- The aqueous gradient stretches from the stratum corneum to the stratum granulosum[13]

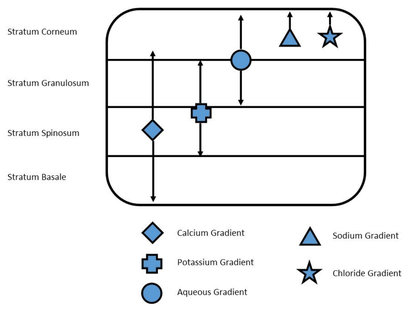

Figure 2: Epidermal Distribution of the Ion Gradients

DISCUSSION

The connections we built between ion channels and ion gradients in skin wounds provides a look into their potential clinical significance

- The ability to use ion channels to determine the phase of wound healing provides possible therapeutic targets. The precision gained by a phase targeted approach will allow for a greater degree of individualism and personalization of therapeutic regimes
- Determining skin wound age would also be beneficial in differentiating diseases with lesions at different phases of healing such as chicken pox from pox virus or confirming a care taker's history in the context of abuse
- The ability to differentiate wounds such as UVB damage would be applicable in photosensitive disorders such as porphyria cutanea tarda
- Tracing burn wounds and differentiating affected regions from uninjured skin through the identification of TRPV expression may be significant in situations where donor grafts are limited.

CONCLUSIONS

Here, we focus on the clinical significance that may follow a strong understanding of ion channels and ion gradients in skin wounds. With the recent research surrounding ion gradients, we draw several connections with epidermal ion channels. We also propose possible mechanisms of interactions between ion channels and gradients in the process of wound healing. An understanding of these elements has provided an idea of their clinical importance such as possible roles in determining wound age and differentiating skin wounds.
Hence, solid foundational understanding of these basic components of skin wounds may expedite the development of higher precision therapeutic targeting and diagnostic mediums.

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