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The Role of the Epidermis and the Mechanism of Action of Occlusive Dressings in Scarring

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Abstract

The problem of cutaneous scarring has conventionally been approached as a pathology of the dermis. Multiple lines of evidence from the clinic, in vitro experiments, and in vivo animal and human studies, however, increasingly suggest that the epidermis plays a major role in the control of underlying dermal scar. Building on the demonstrated efficacy of silicone gel occlusion, in this paper we review the evidence for epidermal regulation of scar, and propose the novel hypothesis that dermal fibrosis is exquisitely linked to the inflammatory state of the epidermis, which in turn is linked to hydration state as a function of epidermal barrier function. In the spectrum of factors contributing to dermal scar, the epidermis and its downstream effectors offer promising new targets for the development of anti-scar therapies.

Keywords

epidermis; dermis; scar; hypertrophic scar; occlusion; inflammation

INTRODUCTION

Cutaneous scarring is the most visible aspect of any surgical procedure or traumatic injury. Optimally incisions heal as fine, flat lines, but the problem of suboptimal or even hypertrophic scars has remained a major challenge. Although a great deal of progress has been made in understanding the evolution of scarring, lack of animal models has hampered research, and most knowledge has been based on clinical observations. The role of genetics (both individual inheritable predisposition to scarring, and general racial characteristics) has long been recognized, but as of yet is not open to therapeutic intervention.¹ Mechanical tension is thought to play a role in hypertrophic scar formation, and in recent years the field of mechanobiology has increased our understanding of the pivotal role tension plays in enhancing scarring, with relief of tension by pressure, sutures, or tape now commonly practiced.² Prolonged inflammation is a tenet of increased scar, whether from infection, nonviable tissue within the wound, foreign body, or delayed healing.³ As scar is defined as an accumulation of disorganized collagen within the dermis, and hypertrophic scar as an excess of collagen within the dermis, it is natural that research has centered on the dermis as the primary site of interest.

In the past several years, however, our laboratory has been focused on the role of the epidermis as a potential cofactor in the control of scarring, indirectly through its effects on inflammation. This work has been grounded on clinical observations buttressed by work in

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our rabbit ear model of hypertrophic scarring, as well as supporting work in other wound healing models in the rat and mouse. Previously, the epidermis has largely been ignored as playing a role in scarring, because it is not a site for collagen synthesis, and at least in incisions that are closed, epithelialization occurs quickly within 24–48 hours.

Our *hypothesis* is briefly that the epidermis plays a significant role in the development of cutaneous scarring along with the other major contributing factors of individual genetic predisposition, and other sources of prolonged or excessive inflammation. To elaborate further on the hypothesis, the outer layer of the epidermis, the stratum corneum, functions as a water barrier, and until that water barrier becomes fully competent, there is a driving proliferative signal to restore homeostasis, and those stimulatory signals have secondary effects on the dermis with a net increase in scar. As a direct corollary, therapeutic maneuvers that mimic a competent stratum corneum (occlusive coverings) should decrease scarring by early restoration of homeostasis, and a reduction in proliferative or inflammatory signals. As a secondary corollary, mucosa which lacks a stratum corneum and needs to function as a water barrier, should have a different healing profile which in part is an explanation for the well-recognized decreased scarring in mucosal versus cutaneous injury.

The Epidermis as a Regulator of Dermal Scar Formation

There are several different pieces of evidence that point to the role of the epidermis in impacting collagen synthesis and inflammation in the underlying dermis.

In animal experiments, placing a skin graft or flap over an open wound results in an immediate, profound reduction in inflammatory cells by apoptosis.⁴ Clinically, partial thickness injuries such as burns or those created deliberately (*e.g.*, by dermabrasion or laser) that re-epithelialize in 10 days or less virtually never result in hypertrophic scarring. However, burns or other open wounds that fail to epithelialize by 14 days often result in hypertrophic scarring, and in burns that fail to epithelialize by 21 days virtually always result in hypertrophic scar in children and young adults.⁵ In a recent study by Koskela *et al.*, in an organotypic keratinocyte-fibroblast co-culture model, keratinocytes were shown to downregulate multiple fibroblast genes modulating the extracellular matrix, including connective tissue growth factor (CTGF), collagen I and III, and fibronectin, even in the presence of pro-fibrotic transforming growth factor beta (TGFβ).⁶

There is a significant body of literature which describes the epidermal layer as playing a key function as the inflammatory “first responder” of the body’s largest protective organ.^{7–10} The epidermis is exquisitely sensitive to injury, with immediate activation of well-characterized pathways intended to rapidly restore barrier function and mount a protective immune response. Recent evidence indicates that independent of infection, injury to the epidermis stimulates a profound expression of interleukin-8 which is chemotactic to neutrophils.¹¹ Many years of study of inflammatory dermatitis in its many manifestations also point to elaboration of interleukin-1 as the primary response of the epidermal layer to various forms of injury, in a feed forward stimulatory loop which leads to keratinocyte activation and proliferation which persists until barrier function is restored.¹² Inflammatory dermatitides due autoimmune states result in reduced barrier function, with transepidermal water loss (TEWL) increasing inflammation and release of IL-1 and other inflammatory mediators;⁸ support of barrier function with creams and lotions is an integral part of the therapy for these conditions. Modulation of the inflammatory state of the epidermis—especially through restoration of barrier function—is therefore be a key target in the control of dermal scar formation.

The Importance of Epidermal Barrier Function in Maintenance of Hydration State

Epithelialization initially occurs by migration of a single layer of basal epithelium which then stratifies over many days and eventually forms a stratum corneum consisting of a lamellar structure of cell membranes from many cell layers. The maturity or functionality of the stratum corneum as a water barrier can be quantified by measuring water loss from the skin or indirectly by the hydration level of the epidermis. Evidence indicates that full competence of the water barrier function of skin is still not restored at one month;¹³ the exact time it takes for full restoration of the epidermal water barrier is unknown. The ability of silicone gel sheeting to improve scarring at least for two months in immature scars suggests the stratum corneum may take substantially longer to reach homeostasis.¹⁴ In fact when human hypertrophic scars have been analyzed, there is evidence of epidermal abnormalities,^{15,16} including increased water loss,¹⁷ indicating that the stratum corneum is abnormal for much longer periods of time. The lack of normal epidermal barrier function in hypertrophic scars is a key piece of clinical evidence linking compromised epidermis to increased underlying dermal scar.

What is the clinical evidence that supports the impact of epidermal hydration on actual scar formation? Silicone gel sheeting was first reported to reduce scarring in a report from 1983 as an empirical observation,¹⁸ and then Quinn furthered those studies with additional observations, but without controlled studies.¹⁹ The first controlled studies were done in 1989 by Ahn, Monafo, and Mustoe, in which immature hypertrophic scars in which a paired control scar was left untreated responded by both visual improvement, and a quantitative increase in scar elasticity which had previously been demonstrated to correlate to scar maturity.¹⁴ In a subsequent study in 1991, the same group demonstrated an ability to prevent hypertrophic scar formation as measured by a quantitative reduction in scar volume, again with patients serving as their own control.²⁰ Since that time there have been a number of prospective, randomized studies as well as multiple other studies, which have confirmed those results and expanded the observations to demonstrate an equivalency to steroid injections for a reduction in symptoms and appearance for painful or itchy sternal hypertrophic scars, as well as a variety of burn and incisional scars. An international panel reviewed the evidence for various scar therapies, and came to the conclusion in a meta-analysis that silicone gel sheeting is effective for the treatment of hypertrophic scars, and also the prevention of hypertrophic scars in high risk patients after burns and surgical incisions.²¹

The mechanism of action of silicone gel was not defined for many years, although a chemical effect of absorbed silicone was excluded as well as pressure and temperature by Quinn.¹⁹ Silicone gel is permeable to oxygen, and the hypothesis that that property contributed to the mechanism was finally excluded experimentally in the rabbit hypertrophic scar model in a group of experiments in which silicone gel covered with multiple layers of polyurethane film which made the occlusive dressing oxygen impermeable actually had reduced scar when compared to silicone gel alone, presumably due to the increased occlusion.²²

Experimental Evidence for Mechanism of Occlusive Effects from *in vitro* and Animal Studies

Our laboratory has employed the rabbit ear hypertrophic scar model to investigate the mechanism of hypertrophic scar formation for a number of years.²³ The model has been demonstrated to replicate the clinical behavior of human hypertrophic scar in appearance, histological appearance, reduced scar formation in age rabbits,²⁴ increased scar when epithelialization is delayed, and response to therapeutic maneuvers including steroid injections and silicone gel sheeting. Multiple studies in the model have confirmed the

benefits of silicone gel in reducing scar. In one study, nonadherent silicone gel sheeting had reduced effectiveness, which was hypothesized to be due to reduced occlusive properties.

In a recent study, O'Shaughnessey compared the effects of multiple occlusive dressings including cyanoacrylate based tissue adhesive, a synthetic barrier film, and silicone gel, all significantly and similarly reducing both TEWL in skin, and scar formation (see Figure 1).²⁵ Several studies have confirmed that occlusive dressings resulted in decreased epidermal thickness, and the thickness of the epidermis correlated with the degree of scar reduction, supporting the hypothesis that the occlusive treatment resulted in a decreased signal for epidermal proliferation, and a corresponding decrease in epidermal-dermal signaling.²⁶ Conversely, perturbation of the stratum corneum water barrier by tape stripping in murine skin resulted in increased TEWL, increased epidermal thickness, and increased scarring. Electron microscopy studies confirmed an earlier study in which the appearance of the basal cell layer of the epidermis was normalized by occlusion.²⁷ In untreated scars, the basal cell layer contained many vacuoles in comparison to unwounded skin. Although the contents of the vacuoles were not determined, it is plausible that they contain soluble factors which could cross the basement membrane and impact the underlying dermis. In each barrier occlusive dressing, in addition to the epidermal changes, the cellularity of the underlying dermis was reduced, while cellularity was increased when barrier function was disturbed.

In order to investigate the mechanism of occlusion further we have utilized a rat model of incisional wound healing and examined the effects of occlusion by paper tape on wound healing over the first 10 days.²⁸ Although this is not a model of hypertrophic scarring, it is an effective reproducible model to examine healing over time with early epithelialization which occurs within 48 hours. A substantial effect was seen on epithelial thickness and proliferation as measured by bromodeoxyuridine staining, and a corresponding marked decrease in inflammation and cellularity was seen in the underlying dermis {see Figure 2).

Although there is a correlation between reduced epidermal thickness and decreased proliferation in the underlying dermis in response to occlusion in both the rat and rabbit models, the molecular signaling remains to be clarified. In an *in vitro* system, Tandara *et al.* described decreased IL-1 beta released into the media as measured by ELISA when keratinocytes differentiated into a stratified epidermis were hydrated versus an air interface as well as decreased collagen synthesis. Moreover, in a co-culture system with a fibroblast layer underneath separated by a porous surface allowing diffusion, hydration of keratinocytes resulted in decreased collagen synthesis by the fibroblast layer.²⁹ In the rat linear incisional model, IL-1 alpha and TNF alpha mRNA were decreased with occlusion at early time points versus non-occluded controls, when whole tissue samples were examined.²⁸ In follow up experiments in mice utilizing shallow incisional wounds, once more IL-1 beta and TNF alpha mRNA were decreased by occlusion at early time points in the epidermis which was analyzed separately.³⁰ In the rabbit ear hypertrophic scar model, treated with occlusion, again IL-1 beta mRNA was downregulated in the epidermis (Gallant-Behm, Mustoe, unpublished data). IL-1 alpha and IL-1 beta are therefore important cytokines expressed in the epidermis and are strong candidates for the epidermal-dermal communication influencing regulation of scar.

Another line of evidence points to the important role that hydration of the epidermis plays in controlling scarring. It has been a long standing clinical observation that mucosal wounds heal with minimal scar. Although the vascularity is greater, and the liquid environment also contributes to faster healing, the lack of a need for a stratum corneum and the potential for a faster return to a homeostatic fully healed epidermis has also been hypothesized to play a role in the reduced scar formation which is observed. Comparing a novel vaginal mucosal model,³¹ with similar shallow incisions in the rabbit ear, the mucosa shows reduced

epithelial thickness and an early return to homeostasis in terms of gene expression, while the cutaneous wounds showed sustained expression of IL-beta and a sustained response in terms of epithelial thickness.³² A feasible interpretation is that in injury to an epithelium with a stratum corneum, the reparative process requires not only epithelial coverage, but also reestablishing a competent stratum corneum water barrier, the delay of which leads to increased scar versus mucosa.

CONCLUSION

Based on multiple lines of evidence, we have been able to put forth a formal theory for the mechanism of action of occlusion in scar management (see Figure 3).³³ There is a growing body of evidence that the epidermis plays an important role in initiating inflammation in response to injury and continuing to mediate inflammation long after reepithelization has occurred, until full competence of the stratum corneum as a water barrier is achieved. Persistent epidermal activation by IL-1 may exert effects on the underlying dermis through activation of well-known downstream effectors of scar such as TGFb and CTGF.³⁴ Occlusive dressings such as silicone gel in its various forms, or other alternatives reduce reactive epidermal hyperplasia, and IL-1 signaling, presumably due to their ability to restore barrier function, reducing TEWL and therefore increasing skin hydration.

Further work is necessary in establishing the key links in our hypothesis, including mechanisms for transduction of decreased hydration state to the epidermal inflammatory cascade. It is reasonable to hypothesize that changes in osmolarity play an important role in this signal transduction.^{35,36} Delineation of the exact epidermal to dermal communication pathways and their convergence on effectors of scar formation will also be essential. In answering both these questions we anticipate that further *in vitro* co-culture studies manipulating osmolarity, microarray studies for identifying signal transduction mediators, and *in vivo* studies using highly compartmentalized laser capture microdissection of the epidermis and dermis will be key. Although these mechanisms have yet to be elucidated, it is our opinion that an overwhelming amount of evidence exists to suggest that epidermal regulation of dermal scar is a promising new target for continued therapeutic efforts at scar reduction.

Acknowledgments

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ABBREVIATIONS

TGFb	transforming growth factor beta
CTGF	connective tissue growth factor
IL-1	interleukin 1

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Figure 1. The effects of various methods of occlusion on TEWL and scar formation

(A) Transepidermal water loss (TEWL). Barrier function of eight forearms in four healthy volunteers was measured for the four different cohorts of the study (Kelocote, Cavilon, Indermil, and Tape Stripping [TS]). Each person served as his or her own internal control. Tape-stripped skin had the highest amount of TEWL. All occluded test sites had similar low TEWL rates, regardless of the agent used. (B) Scar elevation index (SEI) from the rabbit hypertrophic model. Hypertrophic scars occluded with Kelocote (n= 10), Cavilon (n= 11) or Indermil (n= 11) displayed significantly (*p<0.05) decreased SEI values when compared with nonoccluded control scars. Tape-stripped scars (n= 9) exhibited significantly (*p<0.05) increased SEI values when compared with untreated control scars. (Reprinted from O'Shaughnessy KD, De La Garza M, Roy NK, Mustoe TA. Homeostasis of the epidermal barrier layer: a theory of how occlusion reduces hypertrophic scarring. *Wound Repair Regen.* Sep-Oct 2009;17(5):700–708.)

Figure 2. Effects of occlusion on epidermal thickness and dermal cellularity in the rat incisional model

H&E-stained histological sections on Post Operative Day (POD) 3, 7, and 10 (magnification: 100 ×). From POD 3 (A+B), via POD7 (C+D) to POD 10 (E+F), semiocluded wounds showed a more matured and flattened epithelium with less epithelial and especially dermal cellularity count as opposed to nonoccluded wounds. This indicates accelerating properties of semioclusive dressings on the wound healing process and specifically on reepithelialization along with scar ameliorating effects via reduced dermal proliferation. (Reprinted from Kloeters O, Schierle C, Tandara A, Mustoe TA. The use of a semioclusive dressing reduces epidermal inflammatory cytokine expression and mitigates dermal proliferation and inflammation in a rat incisional model. *Wound Repair Regen.* Jul-Aug 2008;16(4):568–575.)

Figure 3. Proposed mechanism for epidermal-dermal interaction in scar formation

Injury to the epidermis disrupts barrier function, leading to increased TEWL and decreased hydration. The IL-1 inflammatory axis is activated in order to stimulate keratinocyte activation and proliferation to restore barrier function, which in turn may have dermal effects by stimulation of pro-fibrotic pathways leading to scar formation.