Fibrotic skin conditions, such as hypertrophic and keloid scars, frequently result from injury to the skin and as sequelae to surgical procedures. The development of skin fibrosis may lead to patient discomfort, limitation in range of motion, and cosmetic disfigurement. Despite the frequency of skin fibrosis, treatments that seek to address the root causes of fibrosis are lacking. Much research into fibrotic pathophysiology has focused on dermal pathology, but less research has been performed to understand aberrations in fibrotic epidermis, leading to an incomplete understanding of dermal fibrosis. Herein, literature on occlusion, a treatment modality known to reduce dermal fibrosis, in part through accelerating wound healing and regulating aberrant epidermal inflammation that otherwise drives fibrosis in the dermis, is reviewed. The review focuses on epidermal–dermal crosstalk, which contributes to the development and maintenance of dermal fibrosis, an underemphasized interplay that may yield novel strategies for treatment if understood in more detail. (Am J Pathol 2023, 193: 510–519; https://doi.org/10.1016/j.ajpath.2023.01.008)
formation of a scab over the course of healing. In a follow-up report, Winter and Scales\textsuperscript{10} showed that, in pigs, superficial dorsal wounds that were dried out by blowing air showed slowed epithelialization and exacerbation of scar formation, further supporting the idea that the degree of dehydration influenced the rate of wound re-epithelialization. It has long been recognized that fast-healing wounds show lessened fibrosis, and that delays in wound healing are associated with increased scar formation.\textsuperscript{11–16} Thus, because occlusion of open wounds accelerates wound healing and re-epithelialization, early wound closure is likely a key mechanism by which occlusion lessens resultant scar hypertrophy. Consistent with this idea, Dyson et al\textsuperscript{17} showed that full-thickness porcine dorsal excisional wounds kept moist by application of Opsite (Smith & Nephew, London, UK) underwent accelerated angiogenesis early after wounding, followed by a more rapid reduction in vessel density to more closely resemble that of uninjured skin, consistent with accelerated healing. Occlusion of skin graft donor sites in human patients using Opsite or Tegaderm (3M, St. Paul, MN) dressings resulted in significantly accelerated re-epithelialization and reduced pain compared to coverage with mesh gauze, suggesting that occlusion regulated epithelialization and pain in human wounds as well.\textsuperscript{18}

**Understanding the Therapeutic Mechanism of Occlusion after Epithelialization**

In addition to their ability to accelerate healing of open wounds, occlusive dressings also have been shown to limit the degree of scarring when applied to wounds after epithelialization, or when applied to scars that already have formed. Early reports of promising clinical benefit describe successful application of silicone gel, an occluding agent, as a therapeutic modality for management of burn scars.\textsuperscript{19} Subsequent studies showed further successful use of silicone gel to manage burn scars, as well as other hypertrophic scars and keloids,\textsuperscript{20–24} leading to controlled comparative studies\textsuperscript{25,26} and randomized controlled clinical trials.\textsuperscript{27–30} As a result of notable clinical success, research into mechanisms underlying the therapeutic effects of silicone gel application and of other occlusive modalities was warranted.

Several groups sought to better understand occlusion through experimentation. Chang et al\textsuperscript{31} showed that exposure to silicone of the apical surface of a stratified epithelial culture failed to influence proliferation, collagen production, or glycosaminoglycan production in co-cultured fibroblasts derived from healthy skin or from keloids. This suggests that the antagonistic effects of epidermal silicone application toward dermal fibroblast activation were not the result of silicone acting as a bioactive chemical agent. Tandara and Mustoe\textsuperscript{32} showed that occlusion of excisional wounds in rabbit ears, after they had fully re-epithelialized, by applying silicone gel sheets resulted in a decreased scar elevation index and decreased epidermal hyperproliferation. This suggests that occlusion of closed wounds led to suppression of aberrant epidermal phenotypes associated with the development of hypertrophic scars. Gallant-Behm and Mustoe\textsuperscript{33} confirmed that application of occlusive dressings to rabbit ear wounds after closure maintained skin hydration and regulated expression of keratins and inflammatory genes in the epidermis, potentially implicating epidermal signaling downstream of dehydration as an aggravating factor in dermal fibrosis. Oral mucosal wounds, which are exposed to hydrated environments throughout the healing process and after epithelialization, heal more effectively and with reduced scarring relative to comparable skin wounds.\textsuperscript{34} This has spurred further investigation into whether there is a relationship between the superior healing of hydrated skin wounds and of mucosal wounds. Chen et al\textsuperscript{35} found in mice that wounds of tongue mucosa, which heal more quickly than skin wounds, showed dampened wound-induced gene expression profiles, particularly for inflammatory and cytokine-related genes, compared with skin wounds. The investigators attributed differences in healing of these wounds to differential gene expression profiles induced by wounding. The same group very recently described a similar paradigm at play in human palatal mucosa healing in comparison with skin.\textsuperscript{36} Similar to oral mucosa, Gallant-Behm et al\textsuperscript{37} showed that incisional wounds generated on rabbit vaginal mucosa healed in a manner superior to paired skin wounds. The investigators also used microarray transcriptomic analyses to compare basal and wound-induced gene expression profiles in the epithelia of skin and of mucosal wounds. Compared with wounded mucosal epithelium, wounded epidermis showed sustained, dramatic increases in the expression of genes encoding a number of key proinflammatory mediators including IL-1α, IL-1β, and tumor necrosis factor-α, among others. Although the dermis underlying the injured epidermis showed a notable fibrotic response, as determined by analysis of gene expression, the lamina propria beneath the injured mucosal epithelium showed a comparably dampened or absent fibrotic response. The investigators subsequently showed that local administration of an IL-1 receptor antagonist was sufficient to reduce hypertrophic scarring in the rabbit ear wound model, implicating aberrant IL-1 signaling in the development of scar hypertrophy in the skin. Taken together, these reports suggest that the reduced hydration response of epithelia to injury can regulate signaling in underlying mesenchymal tissue, leading to adverse effects on the wound healing process, and that occlusion can regulate some of these responses to improve healing.

**Dehydration-Induced Epidermal Signaling as a Target for Hypertrophic Scarring**

Because dehydrated skin wounds showed slowed wound healing, increased inflammation, and aggravated scar formation, further research sought to better understand the
effects of epidermal dehydration that result in pathologic wound healing outcomes. In one report, incisional wounds were performed on each ear of a rabbit and allowed to epithelialize before application of occlusive dressing to a single ear for the duration of the experiment. Subsequently, wounds were harvested and microarray transcriptomic analysis was performed to determine the effects of occlusion and dehydration on gene expression changes in the healed epidermis. Compared with the epidermis of occluded wounds, nonoccluded wounds showed substantial up-regulation of genes encoding proinflammatory cytokines. These findings were supported by experiments using human ex vivo skin or stratified in vitro cultures of immortalized human keratinocyte cells. Exposing these cultures to reduced hydration conditions up-regulated the expression of inflammatory genes including TNF, CXCL8, PTGS2, and IL1B, suggesting that reduction in hydration is directly responsible for promoting epidermal inflammatory signaling. Further investigation of this phenomenon showed that decreased hydration led to potentiation of proinflammatory signaling via increased Na\(^+\) concentration ([Na\(^+\)]) as a result of transepidermal water loss (TEWL). TEWL leads to local concentration of Na\(^+\) cations, driving activation of the epithelial sodium channel through upstream signaling mediated by the serine protease prostatin and the apical sodium channel Na\(_{c}\). Co-culture experiments between fibroblasts and stratified keratinocyte cultures showed that the stimulatory effects of keratinocyte-released soluble factors on fibroblast activation were attenuated by knockdown of the genes encoding the epithelial sodium channel or Na\(_{c}\). Co-culture experiments between fibroblasts and stratified keratinocyte cultures showed that the stimulatory effects of keratinocyte-released soluble factors on fibroblast activation were attenuated by knockdown of the genes encoding the epithelial sodium channel or Na\(_{c}\). Furthermore, inhibition of these pathways via genetic knockdown or application of small molecules was sufficient to attenuate hypertrophic scarring in a rabbit ear excisional wound model in vivo.\(^{20–21}\) Taken together, these data suggest that the epidermis acts as a hydration sensor that can signal to the dermis to activate profibrotic signaling paradigms.

Other epidermal targets found to be induced by reduced hydration have also been investigated using similar means. Previous work has shown increased expression of the calgranulin proteins S100A8/A9 and S100A12 in hypertrophic scar (HTS) epidermis and keloid epidermis compared with normal skin epidermis. Experimental dehydration also induced expression of these proteins in cultured epidermal constructs in vitro.\(^{42–44}\) Overexpressed calgranulin proteins induced activation of co-cultured fibroblasts in a manner dependent on their receptors Toll-like receptor (TLR)4 and receptor for advanced glycation endproducts (RAGE). Accordingly, intradermal injection of recombinant S100A8 or S100A12 was sufficient to exacerbate hypertrophy in rabbit ear excisional wound—induced HTSs, suggesting that keratinocyte-derived S100 proteins secreted into the dermis exacerbate HTS formation at least in part by activating dermal fibroblasts directly. Similarly, Zhao et al\(^{45}\) showed that dehydration of stratified epidermal cultures induced secretion of high mobility group box (HMGB)1, which activated co-cultured dermal fibroblasts via induction of profibrotic myocardin related transcription factor-A/serum response factor (MRTF-A/SRF) signaling downstream of TLR2/4 and RAGE. Consistent with this, injection of recombinant HMGB1 protein into developing rabbit ear HTS resulted in increased dermal fibrosis characterized by greater scar hypertrophy. Yang et al\(^{46}\) simulated reduced hydration conditions by exposing cultured keratinocytes to increased concentrations of [Na\(^+\)] in vitro. The investigators showed that culture under high [Na\(^+\)] induced epithelial-to-mesenchymal (EMT)—like changes in keratinocytes and induction of proinflammatory gene expression as well. Recently, Shinohara and Hara-Chikuma\(^{47}\) maintained three-dimensional epidermal models consisting of human keratinocytes in high-humidity or low-humidity environments. The investigators noted activation of p38 mitogen-activated protein kinase after only 30 minutes of maintenance under low humidity, as well as significant dysregulation of many genes, including a host of genes encoding proinflammatory cytokines, after 3 and 6 hours. Taken together, these data show that reduced hydration leads to potentiated epidermal inflammatory signaling, which may drive profibrotic processes in the dermis.

**Differential Baseline Gene Expression and Wound Healing Potential in Mucosa and Skin**

As discussed in *Understanding the Therapeutic Mechanism of Occlusion after Epithelialization*, Chen et al,\(^{35}\) Leonardo et al,\(^{46}\) and Gallant-Behm et al\(^{37}\) focused their analyses predominantly on differential responses to wounds in skin and mucosa, enabling them to better understand and contrast the dynamics in gene expression that are associated with different healing outcomes. However, these investigators also showed that the baseline transcriptional profiles of mucosal tissue in general,\(^{35,36}\) and of mucosal epithelium more specifically,\(^{37}\) differed substantially. Consistent with this, Iglesias-Bartolome et al\(^{48}\) recently performed a similar set of experiments in humans. They examined identical paired excisional wounds performed on the skin, which healed more slowly, and on buccal mucosa, which healed more quickly, and elegantly characterized transcriptional profiles of these wounds at baseline and over time using next-generation RNA sequencing. Interestingly, the investigators found that baseline gene expression in human buccal mucosa differed dramatically from that of skin; many of the genes found to be expressed more abundantly at baseline in buccal mucosa compared with skin encoded epithelial differentiation markers and inflammatory genes. This suggests that the baseline epithelial transcriptional state of buccal mucosa was conducive to driving a rapid, early resolving inflammatory response in wounded mesenchymal tissue, leading to superior healing outcomes compared with skin wounds. Accordingly, transcriptional profiling of buccal mucosa elucidated a response characterized by early inflammation that resolved rapidly over the course of wound
healing. In contrast, transcriptional profiles of skin showed a delayed inflammatory signature that was sustained until later in the healing process. As a follow-up experiment, investigators showed that epidermal-specific overexpression of Sox2, the gene encoding a transcription factor shown to be highly enriched in buccal versus skin epithelia, was sufficient to accelerate healing of murine excisional skin wounds.\(^48\) The investigators elaborated upon this finding in a subsequent article by showing that Sox2 overexpression promoted a wound healing—like transcriptional state in unwounded epidermis, accompanied by accelerated keratinocyte proliferation. Epidermal-specific overexpression of Sox2 also promoted granulation tissue formation and angiogenesis in wounded skin, suggesting that Sox2-associated transcriptional networks positively influenced wound healing phenotypes in the dermis.\(^49\) Taken together, these data show that intrinsic differences in mucosa and skin, as shown by basal transcriptional states, likely contribute to divergent wound healing outcomes in part through regulation of epidermal—dermal interactions. Some of the differences contributing to the improved healing of mucosal wounds versus skin wounds may be linked to the hydrated, mucosa-specific environment, lending support to the purported mechanisms underlying the positive effects of occlusion on skin wound healing. This also is consistent with demonstrated adverse effects of desalivation on wound healing in rodents.\(^50\text{--}52\)

In addition to differences in hydration and baseline variations in transcriptional profiles, other differences contributing to the improved healing of mucosal wounds appear to be independent of the healing environment, and thus are intrinsic to mucosal tissues.\(^53\) Likely endogenous contributors to divergent wound healing outcomes between mucosal and skin wounds are differences in tissue mechanical properties, including tension. It has long been appreciated that skin is anisotropic and experiences different degrees of tension, depending on anatomic location. For example, the nonuniform incidence of keloid formation across different body sites, as well as the distinct shapes characteristic of keloids occurring at these locations, has lent further support to the idea that tension is a critical factor underlying tissue fibrosis.\(^54,55\) Understanding the relationship between tension and scarring has led surgeons to apply strategies to minimize fibrosis resulting from incisions, such as offloading and making incisions along, rather than across, resting tension lines within the skin.\(^56,57\) In addition, recent research has shown the potential of pharmacologic disruption of mechanotransduction to inhibit fibrosis.\(^58,59\) Given the clear influence of tension on fibrosis, it makes sense to hypothesize that differences in tension might contribute to divergent wound healing outcomes in different tissues. Fetal skin, for example, shows decreased dynamic resting tension and stiffness compared with adult skin,\(^60\text{--}61\) likely contributing to the Scarless nature of fetal healing, while cadaveric analysis determined notable differences in rigidity and extensibility between vaginal tissue and abdominal skin.\(^62\) Therefore, it is likely that resting mechanical properties, as well as variations in the mechanical environment, contribute to the different healing outcomes realized in skin and mucosal wounds. In addition, innate stiffness and other material properties vary among different mucosal tissues, as do the realized forces experienced (eg, as a result of mastication, peristalsis, childbirth, and so forth), potentially contributing to differences in healing outcomes in response to wounding among these tissues.\(^63\text{--}66\) A more complete understanding of which factors are critical to mucosal healing and which factors are dispensable will enable us to focus our efforts more productively on therapeutic modalities that seek to simulate superior outcomes in the skin that generally are characteristic of mucosal wounds.

### Fibrotic Dermis Is Associated with Epidermal Aberrations

Thus far, the above evidence suggests that, among other contributing factors, loss of homeostasis in the epidermal barrier leads to pathologic inflammatory signaling, exacerbating the formation of dermal fibrosis. If epidermal malfunction is indeed a contributing factor to initiation and/or maintenance of fibrosis, then one would expect to find aberrations in the structure and function of the epidermis in fibrotic skin tissue compared with healthy skin. Indeed, there are several lines of evidence in support of this hypothesis. Gardien et al\(^67\) described a prolonged increase in TEWL of burn scars compared with adjacent control skin. Suetake et al\(^68\) showed persistent increases in TEWL of HTSs and keloids for months after the initiating wound, indicative of prolonged defects in epidermal barrier function, compared with normal skin or atrophic scars. Sogabe et al\(^69\) showed increases in skin surface high-frequency conductance and TEWL in hypertrophic scar and keloid tissue compared with control skin. In a proteomic analysis, Li et al\(^70\) compared whole-skin peptide composition of hypertrophic scars and patient-matched control skin tissues. Among many peptides expected to be dysregulated in fibrosis, such as those derived from type I collagen, the investigators also identified a dramatic decrease of filagrin-derived peptides in HTS, suggesting defective epidermal structure in HTS as well. These findings are consistent with other reports of abnormal epidermal differentiation in HTS tissue.\(^71\text{--}73\) Niessen et al\(^74\) described heightened numbers of Langerhans cells in the epidermis of hypertrophic scars compared with normal scars, suggesting persistent differences in tissue-resident sterile inflammation. Durcanska et al\(^75\) reported modestly increased TEWL in localized scleroderma plaques compared with control healthy skin as well. Jumper et al\(^76\) showed that keloid epidermis is characterized by defective retinoic acid synthesis and dampened retinoic acid—receptor signaling. This leads to a profibrotic secretory profile emanating from keloid keratinocytes, resulting in potentiation of dermal fibrosis through epidermal—dermal interaction.
together, these reports show that dermal fibrosis is accompanied frequently by structural and functional aberrations in the epidermis, suggesting that epidermal malfunction may contribute to the development and/or maintenance of fibrotic dermal phenotypes (Figure 1).

Notably, the aforementioned associations of aberrant epidermal barrier function with development or maintenance of dermal fibrosis (presented in the previous paragraph) do not definitely prove that deficient barrier function is upstream of pathologic dermal phenotypes of fibrotic skin, particularly in human patients with fibrotic conditions. Therefore, future research should seek to better understand whether aberrant epidermal barrier function is implicated causally in the development of fibrosis and, if so, to delineate the mechanisms that underlie this causality. Nevertheless, circumstantial evidence exists suggesting that loss of epidermal barrier function may be strictly sufficient to potentiate dermal fibrosis. Several reports have described changes in proinflammatory epidermal gene expression in direct response to acute barrier disruption, suggesting that loss of barrier function plausibly could induce or exacerbate dermal fibrosis either directly or indirectly via paracrine signaling. Observations that up-regulation of proinflammatory genes upon acute barrier disruption are partially dampened by occlusion and tend to resolve as barrier function recovers provide further evidence that loss of barrier function may contribute causally to skin fibrosis and other dermal pathologies. Takahashi et al reported that an epithelial-specific Fli1 knockout mouse spontaneously developed epidermal pathology resembling that of scleroderma epidermis, followed by spontaneous development of fibrosis in the skin, esophagus, and lung. Similarly, Rana et al recently showed that epithelial-specific Snail overexpression spontaneously induced scleroderma-like phenotypes in the mouse via stimulation of dermal fibroblast inflammatory signaling by epidermal-derived mindin. Taken together, these reports suggest that aberrant epidermal structure and function may be sufficient to induce or exacerbate dermal fibrosis. However, further research is needed to elucidate particular epidermal–dermal interactions that occur in individual human skin pathologies and the nature of their pathophysiological contributions to these conditions.

### Epidermal Cells from Fibrotic Pathologies Drive Activation of Dermal Fibroblasts

Further evidence that pathologic epidermal cells drive the profibrotic activity of dermal fibroblasts has implicated numerous cellular and molecular pathways in these effects. Several reports have described that keratinocytes derived from HTS or keloid epidermis can activate fibroblasts through paracrine signaling. Lim et al showed that keloid-derived keratinocytes induced proliferation of co-cultured fibroblasts, more potently than normal skin-derived keratinocytes, suggesting that factors secreted from keloid keratinocytes promote fibroblast proliferation. Phan et al also used co-culture experiments to show that keloid-derived keratinocytes induced proliferation in healthy skin-derived and keloid-derived fibroblasts, at least in part through regulation of insulin-like growth factor signaling in fibroblasts. Funayama et al described increased proliferation and decreased apoptosis in fibroblasts upon co-culture with, or treatment with conditioned media from, keloid-derived keratinocytes, compared with the effects of normal keratinocytes. Co-culture with keloid-derived keratinocytes also resulted in heightened transforming growth factor-β1 expression in fibroblasts, and keloid keratinocytes also have been shown to increase secretion of types I and III collagen in co-cultured fibroblasts. Production of human reconstructed skin equivalents using keratinocytes derived from HTS resulted in increased dermal thickness compared with the use of normal keratinocytes. HTS keratinocytes were found to
express more tissue inhibitor of metalloproteinase-1 protein both in vitro and in vivo compared with normal keratinocytes, suggesting that this may be another epidermis-derived factor contributing to dermal hypertrophy in HTS.89 Similarly, Bellemare et al90 reported increases in dermal thickness, fibroblast proliferation, and collagen secretion, and a decrease in matrix metalloproteinase-1 production, when wound myofibroblasts or HTS myofibroblasts were used to construct reconstructed skin equivalents with keloid-derived keratinocytes compared to normal skin-derived keratinocytes. Gauglitz et al91 detected decreased expression of keratinocytes compared to normal skin-derived keratinocytes. Do et al93 detected up-regulation of IL-18 and its co-receptors (IL-18Rα and IL-18Rβ) in epidermis and dermis of keloids compared with healthy epidermis. Co-culture or conditioned medium experiments between keratinocytes and fibroblasts showed that keloid keratinocytes induced pro–IL-18 expression in fibroblasts, and that keloid fibroblasts induced pro–IL-18 expression and processing to mature IL-18 in keratinocytes, compared with their normal skin-derived counterparts. This suggests that, in keloids, fibroblasts and keratinocytes maintain IL-18 signaling through mutual bidirectional stimulation of protein expression and processing. Keloid fibroblast/keratinocyte co-cultures were found to secrete less anti-inflammatory IL-10 than normal fibroblast/keratinocyte co-cultures as well, potentially explaining the increased expression of IL-18 and other proinflammatory cytokines in keloid tissue. Consistent with this, recombinant IL-18 induced expression of IL-6 and IL-8 proteins, as well as collagen secretion, in keloid-derived fibroblasts. This demonstrates a direct profibrotic effect of IL-18 signaling on fibroblasts.

In addition to keloid and HTS keratinocytes, several reports have detailed pathologic profibrotic effects of sclerodermaderived keratinocytes on fibroblasts as well. Russo et al94 generated epidermal equivalents using keratinocytes derived from healthy donors and from patients with scleroderma. Treatment of healthy human dermal fibroblasts with conditioned media from scleroderma patient-derived epidermal equivalent cultures resulted in significant up-regulation of IL-6 and CXCL8 expression compared with conditioned medium from culture of healthy patient-derived epidermal equivalents. McCoy et al95 reported that culture of human fibroblasts with conditioned media from scleroderma keratinocytes resulted in fibroblast activation, even though no transforming growth factor-β could be detected in the media. Instead, the investigators noted transcriptional signatures in scleroderma keratinocytes consistent with increased NF-κB signaling, the expression of which correlated positively with clinical scaling of disease severity in the tissue donors. Aden et al96 showed heightened levels of IL-1α in scleroderma epidermis compared with healthy epidermis. Co-culture of normal human fibroblasts with scleroderma keratinocytes, but not normal keratinocytes, resulted in significant stimulation of collagen lattice contraction, in a manner dependent on IL-1α signaling. The investigators also showed activation of stress-associated mitogen-activated protein kinases (c-Jun N-terminal kinase and p38) in scleroderma keratinocytes in vivo and in vitro, as well as downstream activation of endothelin and transforming growth factor-β signaling in fibroblasts, which likely was responsible at least in part for their increased contractile activity. Nikitorowicz-Buniak et al97 showed that scleroderma skin expressed heightened levels of connective tissue growth factor [also referred to as cellular communication network factor-2 (CCN2)] in the epidermis and at the epidermal–dermal junction, as well as dramatically increased epidermal S100A9. Treatment of dermal fibroblasts with recombinant S100A9 resulted in increased expression of CCN2 in a TLR4-dependent manner. This suggests that scleroderma epidermis may support fibroblast activation through inducing TLR4 signaling via S100A9, consistent with subsequent work identifying S100A9/TLR4 signaling as an inducer of fibroblast activation in the context of HTS and keloid as well.42 Russo et al98 recently showed that IL-25 expression was decreased in the epidermis of fibrotic skin from scleroderma, morphea, and eosinophilic fasciitis patients compared with healthy skin. Exposure of dermal fibroblasts to conditioned media of IL-25–stimulated keratinocytes led to increased matrix metalloproteinase-1 secretion compared with conditioned media of unstimulated keratinocytes. Direct exposure of human dermal fibroblasts to exogenous IL-25 also modestly suppressed fibroblast activation. This suggests that a reduction of IL-25 in fibrotic epidermis may contribute to persistence of dermal fibrosis either indirectly through modulating the epidermal secretome or directly via effects on dermal fibroblasts. Kudo et al99 showed that epidermal expression of the IL-35 subunit Epstein-Barr virus induced gene-3 (EBI3) was decreased in lesional scleroderma skin compared with normal skin. The addition of exogenous EBI3 decreased deposition of collagen I in normal skin—derived and scleroderma-derived
fibroblasts in vitro, and local administration of EBI3 antagonized bleomycin-induced dermal fibrosis in a mouse model in vivo. This suggests that suppressed EBI3 expression in scleroderma epidermis may contribute to exacerbation of dermal fibrosis via modulation of epidermal–dermal crosstalk. Canady et al. described a mechanism by which keratinocyte growth factor, which they found to be overexpressed in dermal fibroblasts derived from both scleroderma lesions and from keloids, activates epidermal keratinocytes in a paracrine manner. Stimulation of keratinocytes by keratinocyte growth factor subsequently leads to secretion of oncostatin M, which activates fibroblasts through STAT3-mediated signaling. This report suggested a mechanism of bidirectional crosstalk initiated by fibrotic dermal fibroblasts that ultimately leads to their own activation via intermediate keratinocyte stimulation. Literature describing the effects of epithelial cell–derived microvesicles and their demonstrated ability to induce paracrine signaling in dermal cells shows an additional likely paradigm at work in pathologic epidermal–dermal crosstalk.

Conclusion

Epidermal contributions to dermal fibrosis remain incompletely understood, limiting our understanding of the basic science of fibrotic diseases, as well as of potential therapeutic targets and strategies to treat them. Here, the current review focused on evidence that defective epidermal barrier function drives pathologic fibrotic signaling in the dermis, as well as some of the mechanisms through which this crosstalk operates. It also touched upon evidence showing that this signaling can be dampened through occlusion. A more comprehensive understanding of the signals regulated by occlusion, and thus the mechanisms through which occlusion limits scarring, will lead to a more complete understanding of the pathologic processes involved in the formation and exacerbation of fibrosis. This, in turn, may lead to additional targets for pharmacologic intervention or therapeutic strategies to limit dermal scarring, as well as provide potential avenues for treating fibrotic conditions more generally. Furthermore, a more comprehensive understanding of the paradigms underlying epidermal–dermal crosstalk in specific fibrotic diseases may aid in designing new strategies for treatment or drug discovery.

Author Contributions

All authors conceived the idea; D.M.D. and L.S.S. searched for relevant literature; D.M.D. wrote the article and generated the figure; A.E.R., R.D.G., T.A.M., and S.J.H. provided expert opinions and feedback on the article; and all authors revised the article and have approved the final version of the article.

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