Epidermal Differentiation in Barrier Maintenance and Wound Healing

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Significance: The epidermal barrier prevents water loss and serves as the body's first line of defense against toxins, chemicals, and infectious microbes. Disruption of the barrier, either through congenital disorders of barrier formation or through wounds, puts the individual at risk for dehydration, hypersensitivity, infection, and prolonged inflammation. Epidermal barrier disorders affect millions of patients in the United States, causing loss of productivity and diminished quality of life for patients and their families, and represent a burden to the health-care system and society.

Recent Advances: The genetic basis of many congenital barrier disorders has been identified in recent years, and great advances have been made in the molecular mechanisms of the formation and homeostasis of epidermal barrier, as well as acute and chronic wound healing. Progress in stem cell (SC) biology, particularly in induced pluripotent stem cells (iPSCs) and allogeneic mesenchymal stem cells (MSCs), has opened new doors for cell-based therapy of chronic wounds.

Critical Issues: Understanding of the molecular mechanisms of barrier homeostasis in health and disease, as well as contributions of iPSCs and allogeneic MSCs to wound healing, will lead to the identification of novel targets for developing therapeutics for congenital barrier and wound healing disorders.

Future Directions: Future studies should focus on better understanding of molecular mechanisms leading to disrupted homeostasis of epidermal barrier to identify potential therapeutic targets to combat its associated diseases.

SCOPE AND SIGNIFICANCE

AT THE INTERFACE between the organism and the external environment, skin serves as a protective barrier that prevents both the loss of moisture and entry of toxic or infectious agents. Much of this barrier function is provided by the exterior layers of the stratified epidermis, whose disruption can have dire consequences, resulting in defects of epidermal homeostasis and wound repair. This review will provide a framework for understanding epi-

dermal differentiation both through intrinsic mechanisms and through interactions with the environment, in barrier maintenance and wound healing.

TRANSLATIONAL RELEVANCE

Various forms of ichthyosis and atopic dermatitis (AD) are caused by defective epidermal barrier function. In addition, in chronic wounds, failure to restore barrier function fuels the vicious cycle of impaired

keratinocyte migration, abnormal differentiation, prolonged inflammation, hypoxia, and infection. A better understanding of epidermal barrier function in homeostasis and wound healing may lead to the identification of biomarkers and novel targets for developing more efficacious therapeutics for healing disorders and offering alternative therapies to certain forms of ichthyosis.

CLINICAL RELEVANCE

In the United States alone, chronic wounds affect millions of patients causing loss of productivity and diminishing quality of life. With an aging population, a sharp rise in the incidence of obesity and diabetes, and increasing health-care costs, the burden of treating chronic wounds is increasing rapidly. In addition, the costs of postsurgical wound care are also a great burden to the health-care system. Novel therapeutics to promote restoration of barrier function, either in wound healing or in congenital barrier defects, will improve patient quality of life and lower health-care costs.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Barrier formation and homeostasis

The epidermis is a stratified epithelium that undergoes continuous self-renewal in a basal to superficial direction. Approximately 90–95% of epidermal cells are keratinocytes organized into basal, spinous, granular, and cornified layers that correspond to progressive stages of differentiation.^{1,2} Basal keratinocytes, columnar in shape, consist primarily of mitotically active keratinocytes, including epidermal stem cells (SCs) and transient amplifying cells and a small population of postmitotic cells that express early differentiation

markers. Basal keratinocytes are structurally and functionally associated with components of the underlying basement membrane zone via specialized cell–extracellular matrix junction called hemidesmosomes (Fig. 1).

Terminal differentiation begins when the transient amplifying cells withdraw from the cell cycle and lose their ability to adhere to the basement membrane zone. In the intermediate spinous layers, cells contain large bundles of keratin filaments anchored to the desmosomes between adjacent keratinocytes to provide the mechanical strength essential for resistance to physical trauma. The spinous cells are polyhedral, larger, and more flattened. Different keratin genes are transcribed in the basal (keratins 5 and 14, K5 and K14) versus spinous cells (keratins 1 and 10, K1 and K10). The granular layer cells are recognized by characteristic basophilic keratohyalin granules in the cytoplasm composed primarily of keratin filaments, profilaggrin and loricrin. Through their association with mature filaggrin, keratin filaments aggregate and form disulfide bonds, and a cornified cell envelope is assembled directly underneath the plasma membrane. In addition, lipids accumulate inside lamellar bodies. During keratinocyte terminal differentiation, the plasma membrane and cellular organelles, including the nucleus, disintegrate. The subsequent calcium influx activates transglutaminase to catalyze crosslinking of proteins, such as involucrin and loricrin, resulting in a tough insoluble sac, called the cell envelope, surrounding the keratin fibers in the resulting corneocytes. In the meantime, lipids exuded into the intercellular space form a continuous lipid matrix, sealing the corneocytes together. This “bricks and mortar” structure provides most of the barrier function of the epidermis.^{3,4} Cell adhesions between adjacent keratino-

Figure 1. Schematic diagram of epidermal differentiation. Differentiation specific keratins K1, K10, K2e, and K9 are expressed in differentiating cells of suprabasal epidermal layers. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

cytes through tight junctions (TJs), adherens junctions, and desmosomes are also integral to the barrier function. Eventually, through the desquamation process, dissociated corneocytes are sloughed off into the environment.

Multiple signaling pathways essential for proper epidermal differentiation and barrier formation have been identified, mostly utilizing mouse models. These pathways involve Notch, C/EBP, MAPK, the AP2 family, NF- κ B, p63, IRF6, GRHL3, and KLF4, and crosstalk between these pathways continues to be investigated.⁵ Furthermore, recent studies on chromatin modifications and microRNAs have shown that these epigenetic regulators play an essential role in epidermal terminal differentiation.⁶ Although there are many differences between mouse and human skin (*e.g.*, thickness, hair follicle density, hair cycle, the role of contraction during wound healing), conservation between the genomes and gene pathways and similarities in skin components and structures make mice, especially genetic models carrying spontaneous or induced mutations (*e.g.*, knockout mice or transgenic mice), powerful tools for functional investigation (Fig. 2).

In humans, the epidermal barrier is not formed until ~34 weeks of gestation to allow rapid fetal growth. Consequently, premature babies with incomplete barrier formation may suffer from dehydration, electrolyte imbalance, poor thermoreg-

ulation, and be more susceptible to infection. Once a functional epidermal barrier is formed, the stratum corneum is continuously sloughed off into the environment and replenished through keratinocyte terminal differentiation. This process occurs throughout life and is part of epidermal homeostasis carried out by the SCs.

Congenital barrier disorders

Gene mutations of key components of the barrier or barrier formation process result in a variety of congenital disorders of abnormal epidermal differentiation and desquamation (Table 1), collectively termed ichthyoses.^{7–9} All types of ichthyosis have dry, thickened, scaly, or flaky skin.

In some types of ichthyosis, protein crosslinking or aggregation is affected. For example, in lamellar ichthyosis (LI), the loss of transglutaminase 1 activity leads to defective crosslinking of the cell envelopes,^{10,11} whereas in ichthyosis vulgaris, loss-of-function mutations in the filaggrin gene causes impaired keratinization.¹² Missense mutations in keratins 1, 10, and 2 have been found to cause bullous congenital ichthyosiform erythroderma^{13–15} and ichthyosis bullosa of Siemens.^{16–18} In Netherton syndrome, mutations in SPINK5 lead to increased proteolytic activity within the stratum corneum and its accelerated disintegration, resulting in impaired epidermal barrier.^{19,20} Additionally, a

Figure 2. Conserved expression of epidermal differentiation marker genes between the murine and human skin despite the differences in morphology. Basal keratinocytes express keratin 5 and keratin 14, and differentiation-specific markers, filaggrin and keratin 10, are expressed in suprabasal layers of murine as well as in human skin. Scale bar, 100 μ m. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

Table 1. Molecular genetics of epidermal barrier defects

Disorder	Inheritance	Phenotype MIM No.	Gene	Protein	Gene/Locus MIM No.	Mechanism	References
LI	Autosomal recessive	242300	TGM1	Transglutaminase-1	190195	Impaired protein cross-linking and esterification of epidermis-specific ceramides during formation of the cell envelope	10,11
Ichthyosis vulgaris	Autosomal recessive	146700	FLG	Filaggrin	135940	Defective keratohyalin granules	12
Bullous congenital ichthyosiform erythroderma	Autosomal dominant	113800	K1, K10	Keratin 1; keratin 10	139350; 148080	Defective keratin filaments	13–15
Ichthyosis bullosa of Siemens	Autosomal dominant	146800	K2e	Keratin 2e	600194	Impaired keratinization	16–18
Loricrin keratoderma (Vohwinkel's syndrome)	Autosomal dominant	604117	LOR	Loricrin	152445	Thinner cell envelope and barrier defects	22
Vohwinkel's syndrome	Autosomal dominant	124500	GJB2	Connexin 26	121011	Premature keratinocyte programmed cell death	21
LI	Autosomal recessive	601277	ABCA12	ATP-binding cassette transporter	607800	Impaired epidermal lipid trafficking	23
Harlequin ichthyosis	Autosomal recessive	242500	ABCA12	ATP-binding cassette transporter	607800	Defective lipid transport	27,28
NCIE	Autosomal recessive	606545; 242100	ALOXE3, ALOX12B	Lipoxygenase-3, 12(R)-lipoxygenase	607206; 603741	Impaired epidermal lipid barrier formation	25
LI	Autosomal recessive	604777	CYP4F22	Cytochrome P450 gene	611495	Impaired epidermal lipid barrier formation	24
Netherton syndrome	Autosomal recessive	256500	SPINK5	Serine protease a inhibitor	605010	Increased proteolytic activity in the stratum corneum leading to accelerated disintegration	19,20
NCIE	Autosomal recessive	612281	ICHYN	Ichthyin	609383	Abnormal lamellar bodies and elongated membranes in the granular layer	26
Recessive X-linked ichthyosis	Recessive X-linked	308100	STS	Steroid sulphatase	300747	Malformation of barrier lipid layers and corneocyte retention	29–31
Atopic dermatitis	Autosomal recessive	605803	FLG	Filaggrin	135940	Defective keratohyalin granules, accelerated desquamation, <i>Staphylococcus aureus</i> colonization	33,35

FLG, filaggrin; LI, lamellar ichthyosis; NCIE, nonbullous congenital ichthyosiform erythroderma.

dominant mutation in the gap junction protein connexin 26 led to premature keratinocyte programmed cell death and marked thickening of the cornified layers in Vohwinkel's syndrome.²¹ A dominant mutation in the loricrin gene was found to cause a variant of Vohwinkel's syndrome (Table 1).²²

Other mutations involved in congenital barrier defects affect lipid modification, transport, or degradation. Mutations in lipid transporter ABCA12 or cytochrome P450 gene CYP4F22 result in aberrant lipid extrusion and barrier defects in LI,^{23,24} whereas mutations in other proteins involved in this metabolic pathway underlie nonbullous congenital ichthyosiform erythroderma.^{25,26} Complete loss of ABCA12 function results in the devastating Harlequin ichthyosis.^{27,28} In recessive X-linked ichthyosis, loss of steroid sulphatase activity results in abnormal accumulation of cholesterol sulphate in the stratum corneum and corneocyte retention (Table 1).^{29–31} Furthermore, recent studies in mutant mouse models have shown other genes playing critical roles in establishing the epidermal barrier.³²

Skin inflammatory disorders with barrier defects

In addition to congenital barrier defects, impaired barrier function is the hallmark of two of the most common chronic skin inflammatory disorders, AD, and psoriasis. Both AD and psoriasis have genetic and environmental components underlying their pathogenesis and exhibit abnormal keratinocyte differentiation, disrupted barrier function, and/or abnormalities of immunocytes. Linkage of both AD and psoriasis susceptibility to the epidermal differentiation complex on chromosome 1q21, which encodes at least 30 proteins involved in barrier formation, strongly suggests a role for barrier function in these inflammatory disorders. Two of the most striking results of barrier perturbation are stimulated DNA synthesis/epidermal hyperplasia, and cytokine production, including TNF- α , IFN- γ , interleukin (IL)-1, and GM-CSF.³² This cytokine release not only acts in an autocrine fashion to induce differentiation and growth of keratinocytes but also functions in a paracrine and endocrine fashion to stimulate both

local and systemic inflammatory and immune responses.

AD is a complex disorder clinically characterized by dry skin, defective epidermal barrier, susceptibility to cutaneous bacterial colonization and infection, and cutaneous inflammation driven by type 2 helper T cells.^{33,34} AD is strongly associated with food allergies, asthma, and allergic rhinitis in later life. Recent studies established strong associations of AD with filaggrin (*FLG*) mutation.^{33,35} Filaggrin deficiency may contribute to defective epidermal differentiation and AD pathogenesis in several ways by impairing filament aggregation, and subsequently, maturation and release of lamellar bodies.^{33,34} It is also associated with increased pH in the stratum corneum, resulting in increased activity of serine proteases, such as kallikreins. This leads to accelerated degradation of the corneodesmosomes (the cell-cell junction that holds neighboring corneocytes together), and consequently, accelerated desquamation, and may also downregulate lamellar body secretion, resulting in reduced extracellular lipids in AD.³⁴ Additionally, increased serine protease activity may increase the generation of IL-1 α and IL-1 β , which are considered the first step in the cytokine cascade leading to inflammation in AD.³⁴ Furthermore, elevated pH may lead to enhanced *Staphylococcus aureus* adhesion and multiplication. This situation may be exacerbated by the observation that lesional skin in AD patients has reduced antimicrobial peptides.

Psoriasis afflicts 2–3% of the world population. It persists for life with spontaneous remissions and exacerbations. Lesional plaque-stage skin is significantly thickened, with parakeratotic scale. The epidermis is hyperplastic, whereas the granular layer is absent. T cells are present in the dermis, and epidermis accompanied by increased numbers of dermal dendritic cells, macrophages, mast cells, and neutrophils is detected. In addition to skin manifestation, some patients present nail dystrophy and psoriatic arthritis. Patients may also develop inflammatory bowel disorder.³⁶ Although several psoriasis susceptibility loci have been identified, no specific gene has been validated as a definite cause for psoriasis. A characteristic abnormality of lesional skin in psoriasis is the excessive production of antimicrobial peptides. They had been thought to worsen psoriatic lesions, but recent evidence has suggested that the induction of antimicrobial peptides may improve aspects of the disease by modifying host inflammatory responses.³⁷

Cell adhesion in epidermal barrier

In addition to the “bricks and mortar” consisting of corneocytes and lipids, cell adhesion between keratinocytes through TJ, adherens junctions, and desmosomes is an integral part of the epidermal barrier. Adhesion of keratinocytes to each other and the underlying basement membrane as well as interactions between keratinocytes and other cells found in the epidermis (melanocytes, Langerhans, and Merkel cells) are all involved in the structural integrity and function of the epidermis. Since the epidermis is a self-renewing tissue with a continuous upward movement of differentiating cells, to maintain the barrier properties, the intercellular junctions must be dynamically rearranged without losing their adhesive strength. Functional deletions of various adherens junction components in mice have resulted in impaired intercellular adhesion, blistering, hair loss, and inflammatory response.³⁸ Furthermore, viruses and bacteria may gain entry into cells by binding to or modulating junctional structures, causing infection.³⁸ Conversely, dissolution of the corneodesmosomes is an integral step of the desquamation process.

Whereas TJs had been extensively studied in simple epithelium and had been observed in the granular layer of the epidermis,³⁹ its role in stratified epithelium such as the epidermis did not become clear until the observation that TJ component claudin-1 knockout mice died after birth from dehydration of the wrinkled skin.⁴⁰ In claudin-1-deficient mice, although the stratum corneum appeared to function normally, the epidermal barrier was severely impaired.⁴⁰ Other TJ components have also been implicated in epidermal barrier function.³⁸ The distribution of functional TJs in the epidermis suggested that they are not static but form and degrade dynamically with turnover of keratinocytes.⁴¹ Furthermore, expression of TJ-associated molecules was found to be altered in psoriasis.⁴² These observations suggest that defective TJ structures impair the epidermal barrier function and, vice versa, a rapid turnover and impaired differentiation of keratinocytes in skin disorders such as psoriasis influence the dynamics of the formation of TJs in the epidermis.³⁸

Barrier restoration in acute and chronic wounds

Acute wounds. Damage to the barrier upon wounding activates a cascade of molecular and cellular events aimed at restoration of the barrier structure and function. After the initial hemostasis, acute wound healing proceeds through independent, yet overlapping phases: inflammatory,

proliferative, and remodeling.⁴³ During the inflammatory phase, bacteria and debris are phagocytosed and removed, and leukocytes infiltrate the wound, releasing antimicrobials and cytokines, which cause the migration and proliferation of cells involved in the proliferative response. The proliferative phase is characterized by keratinocyte migration over the wound bed (re-epithelialization), angiogenesis, collagen deposition, granulation tissue formation, and wound contraction. Keratinocytes at the wound edge switch their phenotype from differentiating to activated, start expressing keratins 6, 16 and 17. They migrate to cover the wound by forming a cell monolayer over denuded dermis. To restore functional epidermal barrier, proliferation is followed by differentiation, which is represented by a switch of keratin expression back to K5/K14 in basal and K1/K10 in suprabasal layers.⁴⁴ Activated and differentiating phenotypes are controlled by many cytokines and growth factors secreted by multiple cell types in a wound.⁴⁵ These include epidermal growth factor, fibroblast growth factor, ILs (IL-1 and IL-6), and cortisol among others.^{44,46} Once closure is achieved, collagen is remodeled and realigned in the scar tissue, whereas excess of cells is removed by apoptosis, and barrier epidermal keratinocytes resume their role to properly restore barrier.

An elegant study by Segre and colleagues showed that re-epithelialization and the subsequent barrier formation are controlled by different mechanisms. Mice overexpressing the gap junction protein connexin 26 in the epidermis underwent normal re-epithelialization after excisional wounds but failed to restore normal epidermal structure and barrier function.⁴⁷ Interestingly, the re-epithelialized areas of these mice shared many similarities with human psoriatic plaques, such as hyperproliferation of the keratinocytes and a significant infiltration of inflammatory cells including neutrophils and lymphocytes. Yet contrary to the impaired wound healing in these mice, significantly more rapid acute wound healing was observed in both involved and uninvolved skin in psoriatic patients than controls.⁴⁸ Thus, disruption of the epidermal barrier may be sensed by the epidermal cells, leading to increased DNA synthesis and epidermal hyperplasia. These observations suggest that the impaired barrier in psoriatic lesions may contribute to keratinocyte hyperproliferation and also cytokine activation, and that restoration of the barrier after re-epithelialization is important for the balance between proliferation and differentiation.³²

Chronic wounds. Deficiency in successful barrier restoration leads to chronic wound. Failed re-

epithelization is one of the major reasons for the lack of barrier formation in chronic wounds. Keratinocytes at the wound edge fail to migrate over a wound bed, increasing potential for bacterial colonization. This in turn triggers continuous immune response to bioburden, leading to prolonged inflammation, delayed healing, and tissue damage. Keratinocytes at the edges of a nonhealing wounds sustain a proliferative phenotype.^{49,50} In addition to impairment in migration, keratinocytes do not fully differentiate, as represented by the presence of nuclei in a thick cornified layer.⁴⁹ Some of early as well as late differentiation markers, keratins K1/K10 and filaggrin, subset of small proline-rich proteins, are found suppressed, whereas late differentiation markers, involucrin, transglutaminase 1, and another subset of small proline-rich proteins, are found induced in nonhealing edges of chronic venous ulcers, reflecting loss of control in differentiation and barrier formation.⁴⁹ Diabetic foot ulcer keratinocytes are also highly proliferative, show a reduced expression of K10 and K2, uncleaved precursor of the alpha3 chain of laminin (a molecule present on migrating epithelium), indicating keratinocyte inability to migrate and differentiate properly.⁵¹ All these findings indicate the inability of keratinocytes to revert to a normal differentiation pathway in the setting of chronic wounds, leading to defect in wound closure and barrier restoration. Interestingly, in hypertrophic scars, another pathological process where normal cutaneous wound healing fails, although the epithelium regenerates, the barrier function of the stratum corneum is altered, displaying high rates of water loss.⁵²

Stem cells in barrier formation and restoration

Keratinocyte SCs within the skin. Keratinocyte SCs residing in the basal layer are responsible for the homeostasis of the epidermis throughout life, as they give rise to daughter cells that are destined for terminal differentiation and barrier formation. However, it has long been observed that hair follicle cells contribute to healing of the epidermis after wounding, both in the clinic and in animal models.⁵³ A significant keratinocyte SC reservoir resides in the bulge of the hair follicles and maintains the hair follicle homeostasis through activation during each hair cycle.⁵³ The bulge cell progeny migrate into excisional and incisional wounds, as well as into the epidermis after tape stripping. Interestingly, experiments using neonatal versus adult skin have suggested that the wound healing potential of bulge SCs may decline with age,⁵ although the bulge SCs have been shown to

be retained throughout skin aging.⁵⁴ Additionally, despite the presence of bulge-derived cells in the basal layer of the re-epithelialized epidermis, the majority of the bulge-derived cells did not persist in the regenerated stratified epidermis. This observation suggests that bulge-derived cells and epidermal SCs are intrinsically different and that the epidermis-derived cells seem better suited for the long-term maintenance of the epidermis.⁵⁵

Besides the bulge cell progeny, several other cell populations within the hair follicle/sebaceous gland expressing different lineage markers (such as K15, Blimp1, Lgr5, Lgr6, Lrig1, MTS24, and Nestin) have also been shown to integrate into the regenerating epidermis in the wound.⁵⁶ Such observations are suggestive of the activation and significant plasticity of these cells in response to wounding, which may be explored for the purpose of promoting wound healing and regeneration.

Induced pluripotent stem cells. The discovery that both mouse and human somatic cells can be reprogrammed has had a great impact on the fields of SC biology and regenerative medicine.^{57–59} This was initially achieved by transduction with a viral vector encoding reprogramming factors, such as Oct3/4, Sox2, Klf4, and c-Myc, or alternatively, Oct3/4, Sox2, Nanog, and Lin28. However, recent progress in generating transgene-free human induced pluripotent stem cells (iPSCs) has advanced their potential application closer to the clinic.^{60–62} The therapeutic potential of iPSCs for tissue repair and regeneration is enormous. iPSC technology can be used for the development of customized, autologous cell-based therapies to treat human diseases and tissue/organ repair and regeneration. In fact, procedures have been developed to effectively differentiate iPSCs into various cell types, including functional keratinocytes capable of reconstituting a normal stratified epidermis, hair follicles, and sebaceous glands.⁶³

Mesenchymal stem cells. In addition to resident SCs in the skin, mesenchymal stem cells (MSCs) derived from either the bone marrow or adipose tissue have been shown to accelerate cutaneous wound regeneration.^{64,65} MSCs likely participate in wound healing through several mechanisms, including their multipotential differentiation and secretion of cytokines to promote tissue growth and angiogenesis. For example, adi-

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- The barrier function of the skin, which prevents both the loss of moisture and the entry of toxic or infectious agents, is provided by the stratified epidermis.
- The epidermis undergoes continuous self-renewal in a basal to superficial direction. SCs are only found in the basal layer. The outermost layer, the stratum corneum, forms the “bricks and mortar” barrier.
- Gene mutations of key components of the barrier or barrier formation process result in a variety of congenital disorders collectively termed ichthyosis.
- Impaired barrier function is also the hallmark of two of the most common chronic skin inflammatory disorders, AD and psoriasis.
- Chronic wounds show deregulation of keratinocyte proliferation and differentiation markers indicating inability of wound edge keratinocytes to form proper barrier and close the wound.
- Whereas keratinocyte SCs residing in the basal layer are responsible for the homeostasis of the epidermis throughout life, SCs in the hair follicles and sebaceous glands have also been shown to contribute to proper epidermal wound healing. In addition, iPSCs have been shown capable of reconstituting a normal stratified epidermis, hair follicles, and sebaceous glands.
- The recent advances may provide a promising option for treating chronic wounds using allogeneic MSCs.

pose-derived MSCs injected directly into excisional wounds were shown to differentiate directly into endothelial and epithelial cell types as well as secrete growth factors to enhance neovasculogenesis, thus accelerating the time for wound closure.⁶⁶ MSCs are also rapidly mobilized in response to hypoxia, which is commonly found in chronic wounds with poor vascularization.⁶⁷ Although their progeny can contribute to the regenerated tissue, perhaps more important is that MSCs can orchestrate tissue repair (sometimes with reduced scar formation), even at distant sites. Yet the most unique and prospectively useful aspect of MSCs for treating chronic wounds is their low immunogenicity and immunosuppressive features. These properties, combined with the availability of MSCs and the ease of propagation and storage, allow allogeneic grafting from healthy donors. This is particularly important for treating nonhealing wounds in older individuals, patients with diabetes and autoimmune diseases with compromised MSCs.^{67,68}

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Abbreviations and Acronyms

AD = atopic dermatitis
 FLG = filaggrin
 HI = harlequin ichthyosis
 IL = interleukins
 iPSC = induced pluripotent stem cell
 LI = lamellar ichthyosis
 MSC = mesenchymal stem cell
 SC = stem cell
 TGM = transglutaminase
 TJ = tight junction