



Could basement membrane alterations, resembling micro-wounds at the dermo-epidermal junction in psoriatic non-lesional skin, make the skin susceptible to lesion formation?

Renáta Bozó^{1,2} | Lili Borbála Flink¹ | Nóra Belső^{1,2} | Barbara Gubán¹ | Márta Széll^{3,4} | Lajos Kemény^{1,2,3} | Zsuzsanna Bata-Csörgő^{1,2,3}

¹Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary

²HCEMM-SZTE Skin Research Group, Szeged, Hungary

³MTA-SZTE Dermatological Research Group, Szeged, Hungary

⁴Department of Medical Genetics, University of Szeged, Szeged, Hungary

Correspondence

Renáta Bozó, Department of Dermatology and Allergology, University of Szeged, Korányi Fásor 6, Szeged, H-6720 Hungary. Email: bozo.renata@med.u-szeged.hu

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Abstract

Current data suggest that tissue microenvironment control immune functions. Therefore, understanding the tissue environment in which immune activation occurs will enhance our capability to interfere with abnormal immune pathology. Here, we argue that studying the constitutively abnormal functions of clinically uninvolved psoriatic skin in patients with plaque type psoriasis is very important to better understand psoriasis pathobiology, because non-lesional skin provides the tissue environment in which the psoriatic lesion develops. A key question in psoriasis is what initiates the abnormal, uncontrolled immune activation in the first place and the answer may lie in the skin. In light of this concept, we summarize abnormalities at the dermal-epidermal junction region which shows a special “non-healing-like” micro-wound phenotype in the psoriatic non-lesional skin that may act as a crucial susceptibility factor in the development of the disease.

KEYWORDS

basement membrane, dermal-epidermal junction, non-lesional skin, psoriasis, wound healing

1 | INTRODUCTION

Psoriasis is a complex inflammatory skin disease, which is mainly characterized by keratinocyte hyperproliferation and massive immune cell infiltration, primarily affecting the skin¹ with a wide-ranging clinical presentation.² However, not only the skin can show differences between patients, but some patients have arthritis^{3,4} while others may have psoriasis-related other organ involvements.⁵ Risk in developing the disease is based on multiple genetic and environmental

factors which differ in individuals and in different populations.⁶ Pustular psoriasis, the acute systemic generalized form, the chronic localized palmoplantar pustulosis and the acrodermatitis continua of Hallopeau represent a distinct group and have been linked to interleukin (IL)-36 receptor antagonist (IL36RN) mutations. Mutations were also found in that group in a gene encoding the adaptor protein 1 complex subunit (AP-1 complex subunit sigma-3, AP1S3) and a keratinocyte nuclear factor κB adaptor protein (the caspase recruitment domain-containing protein 14, CARD14).⁷ Guttate psoriasis is

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associated with streptococcal pharyngitis and HLA-Cw6, the most strongly associated psoriasis susceptibility allele.⁸ Psoriasis studies, including our own studies, usually focus on the most frequent, dominant plaque type psoriasis phenotype. An inherently abnormal immune regulation, both in innate as well as in adaptive responses, undoubtedly plays a central role in disease pathogenesis.⁹ However, it is also clear that the immune pathology is strongly influenced by the tissue environment.^{10,11}

An increasing body of evidence suggests that not only the lesional skin of patients is affected in psoriasis, but the seemingly healthy-looking non-lesional skin of patients contains disease-specific alterations as well. In 1995, Kadunce and Krueger suggested that in psoriasis the entire skin has the capacity to develop lesions, and control of expression is linked to a complex interaction of epidermal, dermal and immune cells. They considered psoriatic keratinocytes to have an inherent capacity for hyperproliferation and aberrant differentiation and advised to consider not only cytokines and growth factors, but also regulators of transcription, translation and modifications of cytokines and growth factors.¹² Data suggest that the psoriatic non-lesional skin could represent an intermediate stage between the healthy and lesional skin. Alterations in the non-lesional skin can reveal predisposing factors for lesion development and specific structural changes, or factors which help in the maintenance of the non-lesional stage.¹³

2 | INFLAMMATION IN THE NON-LESIONAL PSORIATIC SKIN

The number of several immune cell types are elevated in non-lesional skin, and the inducible T-cell co-stimulator, ICOS, a T-cell activation marker, is also detected.¹⁴ The characteristically sharp edges of psoriatic plaques are indicative of a very local, tissue-, if not cell-dependent effect. Cytokine signalling plays a key role in the pathomechanism of psoriasis. In psoriatic plaques, Th17 cytokines (mainly the IL-17A) stimulate the production of antimicrobial peptides which activate inflammatory cells, thus sustaining the inflamed state in the psoriatic skin. A large-scale study highlights the psoriasis specificity of IL-17A signature, the importance of cathelicidin (LL37) and an increase in foetal and other protein abundance, suggesting degradation deficiency.¹⁵ The presence of circulating LL37-specific T cells significantly correlates with disease activity.¹⁶ Dermal CD3⁺γδ T cells are the major source of IL-17A, and their number is increased in psoriatic skin.¹⁷⁻¹⁹ Meta-analysis on three gene array studies showed enhanced expression of IL-17 and IL-17 signature genes in non-lesional epidermis compared with normal. The transcription factor C/EBPδ also showed elevated expression¹⁴ and it is believed to mediate the IL-17 signalling and it could enhance the sensitivity of non-lesional keratinocytes to IL-17 stimuli.²⁰ Elevated expression of IL-22 in non-lesional versus healthy skin is associated with an upregulation of antimicrobial peptides.¹⁴ In psoriasis, interferon-γ (IFNγ) is known to take part in the immune induction of the keratinocyte cell cycle progression.²¹ In the above-mentioned gene array, the expression

level of IFNγ and the IFNγ-related genes also showed higher expression in non-lesional versus healthy skin. It is also interesting to note that some genes, which are known to mediate keratinocyte differentiation processes, are also upregulated in the non-lesional skin.¹⁴ Furthermore, proinflammatory mediators, namely IL-1α and IL-1β, have been reported to show lower expression level in non-lesional skin.²² According to a recent study, in the clinically resolved lesions epidermal tissue, resident memory T cells are retained in the tissue and can produce cytokines indicating a site-specific T cell-driven disease memory.²³ Besides alterations in the resolved psoriatic skin, epidermal resident T cells in never-lesional skin from patients with psoriasis can trigger psoriasiform tissue responses.²⁴ These changes in the non-lesional skin affect the professional and non-professional immune cells, and the expression levels of the different cytokines suggest an altered inflammatory state of the clinically asymptomatic skin.

3 | SIGNS OF TISSUE STRESS IN PSORIATIC NON-LESIONAL SKIN

One of the first indications of the altered stress response of the non-lesional skin is the Koebner phenomenon, which means that psoriatic lesions can develop on non-lesional skin after various injuries.²⁵ Tape stripping is one standard method to induce mechanical stress on the epidermis which results in enhanced proliferation rate²⁶ and overexpression of transforming growth factor (TGF) alpha in the non-lesional vs. healthy epidermis.²⁷

Previously, we compared the expression profiles of non-lesional psoriatic and healthy epidermis, and we identified a long non-coding RNA induced by stress which we named Psoriasis Susceptibility-Related RNA gene induced by stress (PRINS). In our studies, tissue samples are taken from the trunk of healthy and plaque type psoriatic individuals. Interestingly, PRINS is highly expressed in non-lesional psoriatic tissue, but not in healthy or psoriatic lesional epidermis.²⁸ Later it was shown that PRINS can downregulate inflammation due to destabilization of IL-6 and the chemokine ligand 5 (CCL-5, RANTES) messenger RNAs.²⁹ Moreover, PRINS can act as an apoptotic function regulator by influencing interferon alpha inducible protein 6 (G1P3) gene expression³⁰ and by interacting with miR-491-5p³¹ and nucleophosmin.³² Our data indicated that similar to other known stress induced factors,³³ PRINS had a protective effect on cells. Enhanced PRINS production by non-lesional keratinocytes can alter the stress response of the non-lesional epidermis thereby contributing to the pathogenesis of psoriasis.³⁴

Further evidence that demonstrates the altered stress/inflammatory state of the non-lesional skin is the elevated expression of the psoriasis-associated danger signal induced caspase recruitment domain family member 18 (CARD18), which has a negative role in keratinocyte inflammatory signalling.³⁵ Bioinformatic comparison of the gene expression profile of psoriatic non-lesional and healthy epidermis exposed to the same lymphokines suggested altered regulation of cell morphology, development, cell death and

metabolism of small molecules and lipids in psoriatic non-lesional epidermis. Data suggest that differential regulation of IL-23A and IL-1 β genes in keratinocytes of psoriatic patients are important in lesion development.³⁶

4 | ABNORMALITIES AT THE DERMAL-EPIDERMAL JUNCTION (DEJ) REGION OF PSORIATIC NON-LESIONAL SKIN

Cell-cell and cell-extracellular matrix contact abnormalities, such as the basement membrane (BM) abnormality at the DEJ, can result in cell-extrinsic stress and defense responses, that is a tissue level response, and although it involves innate immune responses, it is not equivalent to the classical acute inflammatory response (para-inflammation).³⁷ Para-inflammation is an adaptive response to stress and malfunction in tissues that develops for restoration of homeostasis. It is an innate response that can evolve into classic inflammation due to additional or persistent stress or malfunction. Para-inflammation relies mainly on tissue resident macrophages, and indeed activated macrophages was observed in non-lesional psoriatic tissue.³⁸

Altered integrin-mediated adhesion of psoriatic keratinocytes can be seen not only in the lesional but also in non-lesional skin. The polarized distribution of α 2 β 1, α 3 β 1 and α 6 β 4 integrins is lost, the β 1 integrin subunit is localized to the basal surface of basal keratinocytes and is in contact with the BM, while β 4 integrin is detected all around basal and suprabasal keratinocytes.³⁹ Furthermore, keratinocytes in non-lesional epidermis overexpress the main fibronectin (FN) receptor α 5 β 1 integrin compared with normal skin.^{39,40}

In the BM of non-lesional psoriatic skin, discontinuous and uneven laminin-1 distribution was observed.⁴¹ Compared with normal skin, both non-lesional and lesional skin lack the expression of laminin- α 1 and there is evidence that without α -chain, there is no distinct BM formation.⁴² In another study, gaps, folding and reduplication were described with collagen type-IV α 1, α 2 chains and laminin- α 2, α 5, β 1 and γ 1-chains.⁴³ A synthetic C16 peptide (KAFDITYVRLKF) that deputizes the functional domain of the laminin- γ 1-chain was shown to have an anti-inflammatory effect, including leucocyte infiltration reduction, in a rat acute allergic encephalomyelitis model suggesting an important role of the BM proteins in inflammation.⁴⁴

Two major forms of FN exist, a soluble, found in the serum and synthesized by hepatocytes, and the so-called cellular form, synthesized by fibroblasts, epithelial cells and others.⁴⁵ We found that as opposed to normal skin, in psoriatic non-lesional skin, there was serum FN present around basal keratinocytes, which could be explained by a leaky BM.⁴⁰ In vivo, the alternatively spliced, extra domain A containing FN (EDA⁺FN) variant is poorly expressed in adult tissue; however, it is overexpressed in developing embryos, in tumors (it is also called oncofoetal fibronectin), and in highly proliferating tissues, such as wounds. The exact regulation of EDA⁺FN splicing is not completely clear, but TGF β 1 is known to enhance EDA⁺FN production in wounded tissue.⁴⁶ We have evidence that keratinocytes are able to produce FN and its EDA⁺ isoform, and

psoriatic non-lesional keratinocytes are more readily capable of EDA⁺FN production in response to signals of activation compared with normal cells.⁴⁷ We recently also reported that signal transducer and activator of transcription 1 (STAT1) negatively regulate both FN and EDA⁺FN expression in healthy fibroblasts and this regulation is compromised in fibroblasts derived from non-lesional psoriatic dermis. We observed that in the non-lesional skin, STAT1 activation was absent in tissues far away from lesions.⁴⁸ This is in line with known alterations of psoriatic keratinocytes in the IFN–interferon regulatory factor-1–STAT1–suppressor of cytokine signalling-1 regulatory pathway.^{49,50} Recombinant EDA⁺FN, but not other recombinant FN domains, is known to activate human Toll-like receptor-4 (TLR4) in human embryonic kidney 293 cells. EDA stimulation of TLR4 was dependent upon co-expression of MD-2, a TLR4 accessory protein.⁵¹ This indicates a mechanism by which EDA-containing FN fragments promote an innate inflammatory response.

At the DEJ, α 5 β 1 integrin can mediate FN-mediated proliferative signals and can help in the cell adhesion process as well.^{39,50} In addition, together with EDA⁺FN, α 5 β 1 integrin is overexpressed by basal keratinocytes, when the BM is disrupted, for example at psoriatic non-lesional skin sites or in wounds⁵² and binding of α 5 β 1 integrin to EDA⁺FN is a provisional anchoring mechanism.⁵³ The recently discovered short laminin peptide C16, representing the laminin- γ 1 functional domain, targets the α 5 β 1 integrin and could block the association of α 5 β 1 integrin to FN, thus suppressing FN-mediated proliferative, cytoskeletal, and inflammatory responses in HaCat keratinocytes. Furthermore, in imiquimod-induced psoriasis-like mouse model, C16 could reduce epidermal hyperproliferation and immune cell infiltration.⁴⁴

Recent evidence indicates further abnormalities at the DEJ in psoriatic non-lesional skin suggesting a key role of this site in the pathomechanism of psoriasis. We have previously described that the cartilage oligomeric matrix protein (COMP) is also overexpressed in the psoriatic non-lesional skin.⁵⁴ COMP is a structural component of the healthy skin, and it provides the cohesion between the anchoring plaques of the upper dermis and the BM.⁵⁵ We found that COMP formed a continuous layer below basal keratinocytes in non-lesional skin and could interact with the α 5 β 1 integrin and EDA⁺FN due to the disrupted distribution of the laminin- α 1. In addition, COMP helps in the maintenance of the non-lesional state by suppressing the proliferation of keratinocytes via interaction with α 5 β 1 integrin despite the overexpression of EDA⁺FN. COMP may also be involved in influencing keratinocyte proliferation through its direct interaction with EDA⁺FN.⁵⁴

Matrix metalloproteinases (MMPs) play an important role in the stability and homeostasis of the extracellular matrix (ECM).⁵⁶ MMP-2 has the ability to modify the ECM and the BM, as it contributes to cell migration and tissue remodelling and has several substrates including type IV collagen, laminin-1 and FN.^{57,58} Both MMP-2 and tissue inhibitor of matrix metalloproteinases (TIMP)-2 are elevated in non-lesional psoriatic skin.⁵⁹ MMP-9 also showed higher expression in non-lesional versus healthy skin,¹⁴ and it shares similar functions with MMP-2.⁵⁶

5 | PSORIATIC NON-LESIONAL SKIN EXHIBITS CHANGES THAT RESEMBLE WOUND HEALING

Several studies have provided evidence that psoriasis demonstrates many characteristics of wound repair. Both lesional and non-lesional skin of individuals with psoriasis show significantly faster healing than skin of healthy individuals.⁶⁰ Hyperproliferation of keratinocytes, infiltration of inflammatory cells and neovascularization are common processes both in wound repair and in psoriasis. Further similarities are in filaggrin, transglutaminase and involucrin expression in both conditions. Antimicrobial peptides and specifically the antimicrobial protein REG3A, which is largely responsible for keratinocyte proliferation and differentiation after skin injury, are expressed not only following skin injury, but also in psoriasis.⁶¹ Keratin-1 and keratin-10 show reduced, while keratin-6 and keratin-16 show increased expression in both conditions.⁶²

Mechanisms similar to the wound healing process can also be observed in the psoriatic non-lesional skin. The EDA⁺FN and its receptor, the $\alpha 5\beta 1$ integrin, is overexpressed not only in psoriasis, but also in wounded tissue.⁶³⁻⁶⁵ The level of COMP in normal healing wounds is minimal; however, in chronic non-healing wounds, such as venous leg ulcer, it is overexpressed,⁶⁶ similar to its overexpression in non-lesional skin. High dose recombinant human COMP protein treatment results in a delay in the wound healing in an *ex vivo* wound healing model.⁵⁴ The BM is also affected in regeneration of the tissue following injury.⁶⁷ In the wound bed, the BM is often not intact, similar to areas of non-lesional skin where the laminin layer within the BM is discontinuous and the EDA⁺FN, $\alpha 5\beta 1$ integrin and COMP show elevated expression. It has long been known that fenestration of the BM is part of the lesion formation process in psoriasis^{68,69} and a soluble form of FN could infiltrate into the epidermis evolving a micro-wound stage.^{70,71}

MMPs are also important factors in wound healing; however, they can negatively affect healing if they are not present in the appropriate amount.^{72,73} MMP-2 and MMP-9 play a crucial role in wound healing due to their ability to remodel the ECM. The MMP-2 expression is linked with the expression of laminin-332 and increased keratinocyte migration at the edge of acute wounds, while MMP-9 is expressed at the leading edges of migrating keratinocytes during wound closure.⁷⁴ During wound healing, MMP-2 and the pro-MMP-2 activator MT1-MMP⁵⁹ create a fragment that triggers cell migration by cleaving the gamma-2 chain of laminin-332.⁷⁴ In chronic skin wounds, or non-healing wounds, the balance between MMPs and TIMPs is disrupted, which results in a delayed or absent wound closure. In chronic wounds the level of TIMPs are decreased, while the activity of MMPs are upregulated and this imbalance influences the turnover of the ECM.⁷² The induction of MMP-2 and MMP-9 occurs via the $\alpha 3$ chain of laminin-5.⁷⁵ In contrast, elevated MMP-9 is able to suppress the mobility of fibroblasts and keratinocytes^{76,77} and this phenomenon can also lead to a delayed re-epithelization.⁷⁸

Recently, we showed that in the psoriatic non-lesional skin, there is an overexpression of keratinocyte growth factor (KGF) and its

receptor KGFR (also known as FGFR2), indicating the activation of a wound healing process. Tape stripping of the skin did not lead to any obvious changes in $\alpha 5$ integrin, EDA⁺FN, KGF or KGFR expression or distribution at 24 and 48 h after tape stripping in non-lesional skin, while in the healthy controls a slight increase in all protein expression was detected based on immunostaining.⁴⁸ KGF is known for its effect on keratinocyte proliferation and differentiation, and since it is not present in normal skin, but is induced in wound healing, it is regarded as a major player in the wound healing processes of epithelial tissues.⁷⁹ KGF in the skin is produced mainly by fibroblasts, but through the release of IL-1, keratinocytes induce KGF expression and release in fibroblasts.⁸⁰ In an *in vitro* co-culture composed of keratinocytes and fibroblasts, Jun and JunB antagonistically regulated the synthesis of fibroblast-derived KGF and GM-CSF.⁸¹ Psoriatic keratinocytes derived from non-lesional epidermis produce significantly higher proinflammatory IL-1 in the presence of IL-17, compared with healthy skin keratinocytes, indicating an intrinsic feature of psoriasis epithelium.²²

6 | BULLOUS PEMPHIGOID AND PSORIASIS

The coexistence of autoimmune bullous diseases, particularly the anti-laminin- $\gamma 1$ (p200) pemphigoid, has been well documented in psoriasis.⁸² Autoimmune diseases are characterized by autoantibodies, and autoreactive T cells specific for self-antigens. How exactly they contribute to any given pathological process is not always clear, and some may not play any role in disease pathology, they may only reflect abnormal processes taking place in tissues.⁸³

Data indicate that protein complexes that are formed when cells are under stress could possess immunological features that can modulate the host's immune response and induce autoantibody production. In the psoriatic non-lesional tissue, abnormal BM proteins may expose novel epitopes to immune cells and this, together with other immune activating factors, can induce autoantibody formation.⁸⁴ It is presently not completely understood how much autoimmunity contributes to psoriasis, and although no particular autoantibody could be linked to the disease so far, one cannot rule out the possibility that autoantibodies may participate in the maintenance of chronic inflammation. Homology between the streptococcal M-protein and keratin 17 raises the possibility of molecular mimicry taking place.⁸⁵ Indeed, cross-reactive CD8⁺ T cells can be detected in patients with psoriasis, especially in patients with HLA-Cw*0602.⁸⁶ Circulating LL37-specific T cells correlates with disease activity¹⁶ and ADAMTS-like protein 5 was also proposed in psoriasis as an autoantigen that can contribute to the pathogenesis.⁸⁷

7 | CONCLUSIONS AND PERSPECTIVES

Here, we propose that the seemingly normal looking skin of psoriatic patients represents a balanced, "non-healing-like" micro-wounded

skin phenotype mainly due to its structural abnormalities (Figure 1). Environmental factors (infection, wounding etc.) can easily tip the tissue out of its abnormal, but still visibly balanced state and induce an overt wound reaction (lesional skin). The keratinocyte proliferation rate in the clinically uninvolved epidermis of psoriatic patients is almost the same, as in the healthy epidermis²⁶ despite the overexpression of KGF and its receptor,⁴⁸ but, the psoriatic non-lesional keratinocytes are more sensitive to stress³⁶ and proliferative signals²¹ and the non-lesional skin shows a special para-inflammation state.³⁷ An intact DEJ region below the basal keratinocytes is crucial to the functional integrity of the skin. Abnormalities of the BM zone within the DEJ will have an effect both on the dermis and the epidermis.⁶⁷

In the psoriatic non-lesional skin, the laminin layer within the BM is disrupted,⁴¹⁻⁴³ EDA⁺FN is overexpressed^{47,88} and the expression of its receptor, the $\alpha 5\beta 1$ integrin, on the surface of basal keratinocytes is also elevated without any observed hyperproliferation.^{39,40} COMP could be one component, which despite these alterations

can restrain the proliferation of basal keratinocytes and help to maintain the uninvolved, non-hyperproliferative phenotype of the non-lesional psoriatic skin.⁵⁴ MMPs and their inhibitors may play an essential role in the regulation of the ECM proteins in the DEJ region.⁵⁶ MMP-2 and MMP-9 overexpression in non-lesional psoriatic skin^{14,59} suggest a potential connection with the altered laminin layer within the BM.

Wound healing on surfaces in direct contact with the external environment is tied to innate immune functions, because an intact barrier is essential for defending the body against microbes and other damaging environmental factors. Barrier tissues are highly equipped with numerous machineries to respond to noxa, and as suggested by Matzinger et al., they control immune functions.⁸⁹ Barrier dysfunction is not unique to psoriasis; other chronic inflammatory skin diseases are known to have various structural defects in the epidermis. These structural abnormalities may be inherent to the tissue (e.g., mutations in the gene encoding

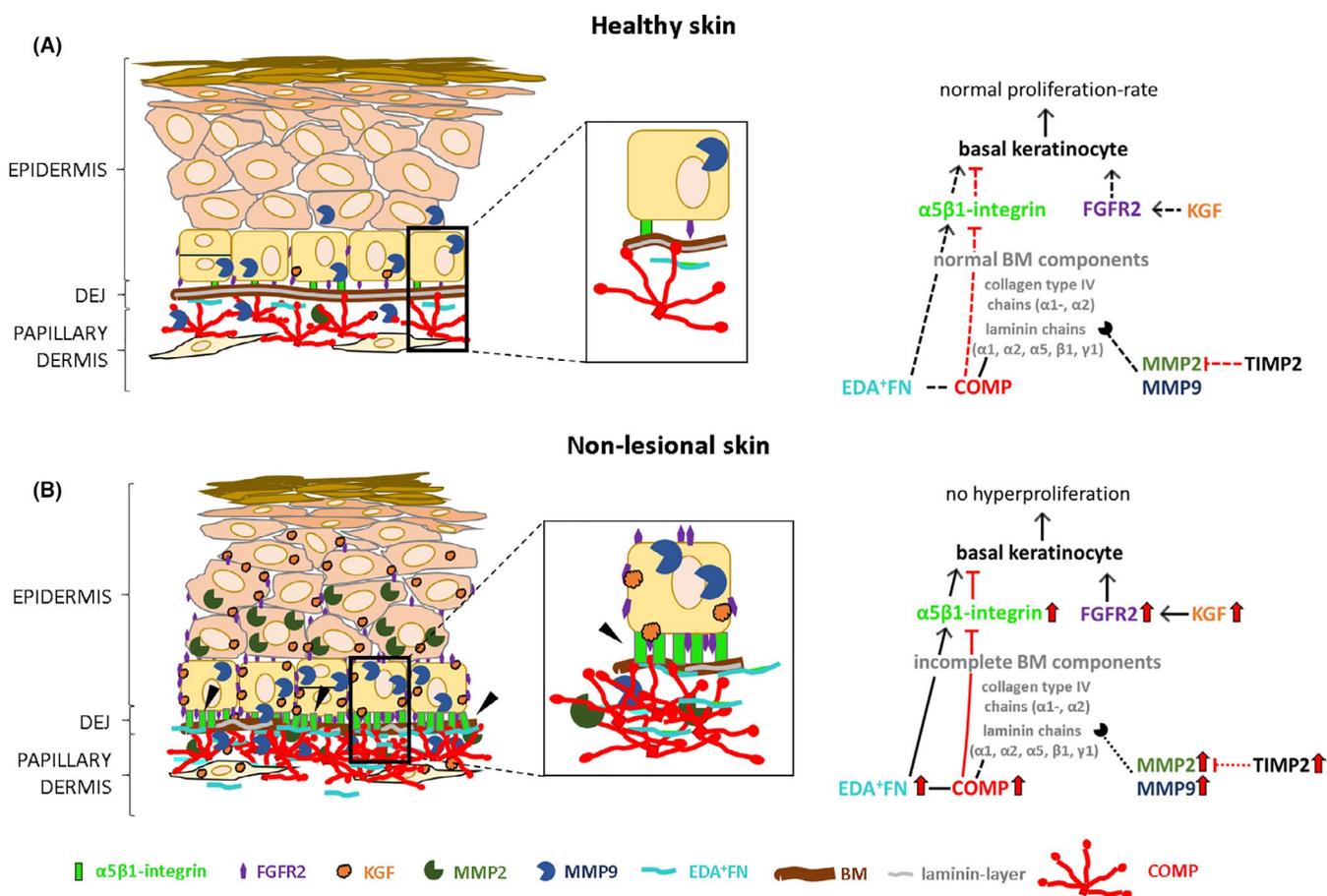


FIGURE 1 Micro-wounds at the dermal-epidermal junction in psoriatic non-lesional skin. Schematic representation of (A) healthy and (B) psoriatic non-lesional skin. The incompleteness of the basement membrane and elevated cartilage oligomeric matrix protein level indicates the “non-healing-like” micro-wounds at the dermal-epidermal junction region of the non-lesional skin. These sites are labelled with black arrowheads. Framed areas show enlarged regions. Straight lines indicate direct, and dashed lines indicate partial relationship between the components. Literature data indicate potential relationship between the dotted line marked components. Red arrows represent the elevated expression of the proteins. (Abbreviations: BM, basement membrane; COMP, cartilage oligomeric matrix protein; DEJ, dermal-epidermal junction; EDA⁺FN, fibronectin splice variant containing the extra domain A; FGFR2, fibroblast growth factor receptor 2; KGF, keratinocyte growth factor; MMP2, matrix-metalloproteinase 2; MMP9, matrix-metalloproteinase 9; TIMP2, tissue inhibitor of matrix metalloproteinases 2.)

filaggrin in atopic dermatitis)⁹⁰ or induced by inflammation (e.g., lichen planus or drug induced reactions where basal keratinocytes are destroyed by cytotoxic T cells).⁹¹ The nature of the barrier dysfunction (e.g., abnormal differentiation of keratinocytes, tight junction, desmosomal, hemi-desmosomal deficiency) and the nature of the dominant inflammation characterize the disease. For example, data suggest that atopic dermatitis is primarily an IL-13 dominant disease, while in psoriasis the dominant immune reaction is polarized towards the IL-17 response.⁹² In the chronic phase of inflammation common features of the wound healing immune response may be seen, such as in atopic dermatitis, where in the chronic phase of the disease a prominent activation of skin barrier repair signature can be detected in transcriptomic profiling using RNA-sequencing.⁹³

Understanding the contribution of the tissue factors in the pathomechanism of psoriasis will be essential to design therapies that give longer term relief from the disease than presently available treatments.

If, as indicated by our current knowledge, psoriasis is indeed genetically determined, the non-lesional tissue is the place to look for the primary effects of the inherent susceptibility factors. In future studies of the non-lesional psoriatic tissue, it will be important to better characterize the investigated tissue samples. HLA-Cw*0602 association, previous lesional versus never lesional status and severity of the disease based on PASI scores may influence the structural changes and its importance in disease pathophysiology.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

ZBC and RB have made substantial contributions to conception. ZBC, RB, LBF, NB and BG involved in drafting the manuscript. ZBC, MS and LK involved in revising critically for important intellectual content and given final approval of the version to be published. All authors have read and approved the final manuscript.

ORCID

Renáta Bozó  <https://orcid.org/0000-0003-4242-2474>

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