

Peeling off the genetics of atopic dermatitis–like congenital disorders

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The epidermis forms during the course of a complex differentiation process known as cornification, which culminates with the formation of the epidermal barrier. The epidermal barrier serves as a vital line of defense against the environment and mainly consists of 3 elements: intracellular keratin filaments, intercellular lipids, and the cornified cell envelope. Adequate epidermal barrier function is also critically dependent on normal shedding of terminally differentiated keratinocytes, a process termed desquamation, which requires the dissolution of cell-cell junctions in the upper granular layers. Although much has been learned about epidermal differentiation through the deciphering of the molecular basis of various cornification disorders, less is currently known about the mechanisms regulating epidermal desquamation and disorders resulting from disruption of this process. Netherton syndrome, peeling skin syndrome type B, and skin dermatitis—multiple severe allergies—metabolic wasting syndrome are 3 autosomal recessive conditions resulting from aberrant regulation of epidermal desquamation. The deciphering of their pathogenesis has not only broadened our understanding of this process but has also shed new light on clinical and mechanistic links between allergic reactions and abnormal desquamation, substantiating the notion that allergic manifestations might, under some circumstances, be the sole consequence of a primary epidermal defect. (*J Allergy Clin Immunol* 2014;134:808–15.)

Key words: Netherton syndrome, peeling skin syndrome type-B, skin dermatitis, multiple severe allergies, and metabolic wasting syndrome, lymphoepithelial Kazal-type related inhibitor type 5, desmoglein 1, corneodesmosin

The epidermis forms during the course of a complex differentiation process known as cornification. Epidermal function is critically dependent on normal shedding of terminally differentiated keratinocytes, a process termed desquamation. Over the past few years, the study of rare disorders of cornification has shed new light on many aspects of this process, linking

Abbreviations used

CDSN:	Corneodesmosin
DSC:	Desmocollin
DSG:	Desmoglein
FTT:	Failure to thrive
KLK:	Kallikrein
LEKTI:	Lymphoepithelial Kazal-type related inhibitor type 5
LG:	Lamellar granule
NS:	Netherton syndrome
PKP:	Plakophilin
PSS-B:	Peeling skin syndrome type B
SAM:	Skin dermatitis, multiple severe allergies, and metabolic wasting
SC:	Stratum corneum
SG:	Stratum granulosum
SPINK5:	Serine protease inhibitor of Kazal-type 5
TSLP:	Thymic stromal lymphopoietin

epidermal dysfunction caused by abnormal desquamation with the pathogenesis of atopy and suggesting novel targeted therapeutic interventions for these rare, as well as more common, skin conditions.

EPIDERMAL HOMEOSTASIS: BETWEEN CORNIFICATION AND DESQUAMATION

The epidermis, the outer component of the skin, is involved in a number of pivotal physiologic functions, such as maintenance of a hermetic physical barrier, antioxidant defense, antimicrobial defense, maintenance of hydration, immune defense, and protection against UV damage.^{1,2}

The human epidermis develops from the primordial ectoderm and regenerates itself in cycles of 28 days in the course of a tightly regulated process during which keratinocytes, which represent the bulk of epidermal cells, progressively differentiate to form 4 successive cell layers: the proliferating stratum basale and 3 differentiated cell layers, the stratum spinosum, stratum granulosum (SG), and stratum corneum (SC).^{3–5} The most abundant epidermal proteins are keratins, which form the keratinocyte cell cytoskeleton.⁶ As cells migrate upward and become granular cells, they express proteins involved in formation of the cornified cell envelope, which gradually replaces the keratinocyte plasma membrane. These proteins include involucrin, loricrin, and a number of transglutaminases, the most important of which is transglutaminase 1, which catalyzes cross-linking of the cornified cell envelope proteins.⁷ Granular cells form keratohyalin granules containing filaggrin, a protein required for keratin filament aggregation, and also lamellar granules (LGs) containing proteases, protease inhibitors, antimicrobial peptides, and various lipids, which are secreted beneath the SC.⁷ LGs have been implicated in the pathogenesis of numerous diseases in human subjects, including atopic dermatitis.⁸ This graded

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differentiation process, known as cornification, culminates within the SC in formation of the epidermal barrier,⁷ which therefore comprises 3 major parts: intracellular polymerized keratin filaments, pericellular cornified cell envelope, and intercellular lipids.⁷

In parallel, epidermal cell differentiation and barrier formation are critically dependent on the proper organization of several dynamic intercellular structures.^{8,9} The desmosome, a key intercellular transmembrane structure connecting the cell surface to the intermediate filament cytoskeleton, is formed by heterodimers of desmosomal cadherins, desmogleins (DSGs) 1 to 4, and desmocollins (DSCs) 1 to 3, which interact within the intercellular space. The intracytoplasmic part of the desmosomal plaque contains 2 members of the armadillo protein family, plakoglobin and plakophilin (PKP), which interact with desmoplakin and thereby link the cell membrane to the keratin cytoskeleton.¹⁰⁻¹³ Desmosomal cadherins are widely expressed in human tissues and demonstrate a relatively complex pattern of distribution.¹⁴ Although isoforms 2 and 3 of DSGs, DSCs, and PKP1 are expressed in the basal layer of the epidermis, the suprabasal cells contain mainly DSG1, DSC1, and PKP1.¹⁵⁻¹⁸ Although desmosomes were initially considered primarily as structural elements responsible for ensuring mechanical cell-cell adhesion in the epidermis, recent studies now suggest that they might also regulate various intracellular signaling processes.¹⁹⁻²⁹

Epidermal desquamation, which leads to the shedding of dead corneocytes from the outermost layers of the SC, plays an essential role in regulating the process of cornification. Desquamation mainly depends on controlled degradation of specialized desmosomes found in the SC (ie, corneodesmosomes), the extracellular component of which mainly consists of DSG1, DSC1, and corneodesmosin (CDSN).³⁰⁻³³ Under normal circumstances, corneodesmosome degradation entails cleavage of DSG1, DSC1, and CDSN by various LG-secreted proteases, including kallikreins (KLKs) and cathepsins. This process is regulated by protease inhibitors expressed in the SG and transported by the LGs.³⁴⁻³⁶ Accordingly, accelerated desquamation and degradation of corneodesmosomes caused by either overexpression of proteases or downregulation of their inhibitors were shown in various mouse models³⁷⁻⁴⁰ to result in increased shedding of keratinocytes and epidermal barrier dysfunction.

Although allergic diseases have been traditionally considered as primarily resulting from immunologic dysregulation,⁴¹ it is now clear that impaired epidermal barrier function might also contribute to the development of this group of disorders,⁴² as shown by the fact that deficiency of filaggrin, a major component of the epidermal barrier, is a strong risk factor for atopic diseases and a wide range of allergic disorders.⁴³⁻⁴⁸ Most of the data that have led to this conceptual change have been gleaned over the past decade through the study of a group of phenotypically and etiologically related genodermatoses, featuring severe dermatitis associated with multiple allergies and atopic dermatitis-like characteristics, with histopathologic evidence of increased desquamation.

NETHERTON SYNDROME

Netherton syndrome (NS; MIM 256500) is transmitted as an autosomal recessive trait. It is characterized by congenital

ichthyosiform erythroderma, hair shaft abnormalities, and atopic manifestations.⁴⁹ Affected newborns present with erythroderma commonly complicated by hypernatremic dehydration and sepsis that evolves into confluent erythroderma with scaling or develops into a widespread eruption consisting of serpiginous plaques with typical double-edged scales, known as ichthyosis linearis circumflexa.⁴⁹⁻⁵³ Moreover, most patients display eczematous atopic dermatitis-like lesions with a predilection for the popliteal and antecubital fossae associated with pruritus and secondary infection.

The hair abnormalities involving the scalp, eyebrows, and eyelashes might be present at birth but more commonly develop after the first year of life. The most characteristic and specific hair abnormality in patients with NS is trichorrhexis invaginata, also known as bamboo hair,⁵⁴⁻⁵⁶ which results from the invagination of the distal hair shaft into its proximal part with formation of a golf-tree hair shaft deformity after trichorrhexis invaginata hair breakage. Additional hair abnormalities have also been reported, such as trichorrhexis nodosa. Most patients also complained of noncutaneous atopic manifestations, including asthma, allergic rhinitis, urticaria, angioedema, and often severe reactions to food and airborne allergens. Systemic complications include failure to thrive (FTT), short stature, systemic infections, diarrhea, pancreatitis, and pulmonary hypertension.⁵⁷⁻⁶⁴ Eosinophilia and increased IgE levels⁶⁵ are often found. Histopathologic electron microscopic examination of skin biopsy specimens revealed features typical of abnormal differentiation and accelerated desquamation, including a diminished granular layer, nuclei in the SC, subcorneal separation, and premature lamellar body secretion.^{66,67}

NS was found to be caused by loss-of-function mutations in the serine protease inhibitor of Kazal-type 5 (*SPINK5*) gene, encoding a 1094-amino-acid serine protease inhibitor called lymphoepithelial Kazal-type related inhibitor type 5 (LEKTI).⁶⁸⁻⁷⁰ More than 70 mutations have been described in *SPINK5* to date, the majority of which lead to a premature stop codon, with null mutations resulting in complete absence of LEKTI expression in the epidermis.^{50,71-78}

LEKTI is expressed in the spinous and granular layers of the epidermis.^{68,69} In addition, it was found to be expressed in other epithelial tissues, including the thymus, oral mucosa, tonsils, parathyroid, and Bartholin glands.^{69,70} Keratinocytes synthesize the unprocessed LEKTI protein, which is proteolyzed into active subdomains and secreted into the extracellular space. LEKTI-derived peptides have the ability to inhibit different serine proteases, including plasmin, trypsin, elastase, and tissue KLKs, in particular KLK5 and KLK7.⁷⁹⁻⁸² Overexpression of serine proteases in a mouse model of NS was shown to lead to both SC detachment, epidermal barrier dysfunction,³⁹ and heightened inflammation caused by KLK proteolytic activation of antimicrobial and anti-inflammatory mediators.⁸³

Moreover, it was recently shown that transgenic KLK5 mice reproduce most of the cutaneous and systemic hallmarks of NS, including exfoliative erythroderma, scaling, allergic manifestations in concert with SC detachment, increased IgE levels, and T_H2 immune response.⁴⁰ KLKs are a family of 15 trypsin- or chymotrypsin-like secreted serine proteases expressed in various tissues, 8 of which have been identified in the SC and regulate epidermal desquamation.⁸⁴⁻⁸⁶ KLKs play a crucial role in controlling epidermal desquamation through degradation of the extracellular domain of DSG1. This might explain the reduced

expression of DSG1, DSC1, and desmoplakin (DSP) in the skin of patients with NS, which in turn is likely to underlie subcorneal separation caused by desmosomal cleavage.

LEKTI forms a complex with KLK5 that dissociates under acidic pH, leading to activation of free KLK5 by the serine protease matriptase, KLK5 upregulation, and degradation of corneodesmosomes.^{79,87} In patients with NS, LEKTI deficiency is associated with increased expression of free KLK5. LEKTI deficiency also results in abnormal epidermal differentiation and lipid metabolism, with increased expression of loricrin, decreased expression of filaggrin in the granular layer, reduced keratohyalin granule numbers, lipid droplets, and abnormal processing of lamellar bodies.^{32,37,88} This might also in part be due to increased KLK activity because activated KLK5 also upregulates elastase 2, which increases proteolytic processing of profilaggrin and impairs lipid metabolism, both of which contribute to the abnormal epidermal barrier seen in patients with NS.⁸⁸

Unopposed KLK5 activity is also related to increased inflammation and allergic reactions seen in patients with NS, which further aggravate the skin barrier defects.^{32,38,49,89} KLK5 activates KLK7 (which activates IL-1 β) and protease-activated receptor 2.^{38,90} Protease-activated receptor 2 is expressed on the keratinocyte cell surface and upregulates nuclear factor κ B activity, leading to increased levels of the T_H2 cytokine thymic stromal lymphopoietin (TSLP) and other proinflammatory cytokines (eg, TNF- α).⁹¹⁻⁹⁴ TSLP has been shown to drive T_H2 differentiation and T_H2 cytokine production, including IL-4, IL-5, and IL-13, which induce mast cell and eosinophil activation in concert with B-cell IgE switch.^{38,95}

Although these observations collectively provide a comprehensive explanation for the phenotype displayed by patients with NS, novel data suggest additional levels of complexity. For example, mesotrypsin, a protein found in granular cells and intercellular spaces of the SC, was recently found to regulate desquamation through activation of KLKs and degradation of LEKTI.⁹⁶ In addition, several cytokines involved in the abnormal inflammatory response seen in patients with NS are not regulated by PAR-2, such as thymus and activation-regulated chemokine and macrophage-derived chemokine.^{32,38,89,91,97}

PEELING SKIN SYNDROME TYPE B

Peeling skin syndrome type B (PSS-B; MIM 270300) is a rare autosomal recessive genodermatosis featuring spontaneous and widespread peeling of the skin associated with ichthyosiform erythroderma starting at birth or during early infancy. Additional major features are severe pruritus and food allergies, repeated episodes of angioedema and urticaria, asthma, increased IgE levels, and eosinophilia. The patients exhibit FTT and recurrent skin infections, especially with *Staphylococcus aureus*.⁹⁸⁻¹⁰⁰ The phenotypic resemblance between PSS-B and NS is striking, except for the fact that hair abnormalities are absent in patients with PSS-B.

PSS-B results from loss-of-function mutations in *CDSN* encoding CDSN, which lead to complete loss of protein expression in the epidermis.⁹⁸⁻¹⁰¹ Lately, a genomic deletion at the psoriasis susceptibility 1 (*PSORS1*) locus, removing the entire *CDSN* gene, has been reported as the cause of PSS-B.¹⁰²

Skin biopsy specimens demonstrate subcorneal separation with mild inflammatory infiltrate in the upper dermis associated with

ultrastructural evidence of split formation between the keratinocytes of the SG and corneocytes of the SC because of loss of corneodesmosomes.⁹⁹ Immunohistochemistry analysis reveals total absence of CDSN expression in the epidermis.

CDSN is an extracellular 52- to 56-kDa glycoprotein that contributes to corneodesmosome formation. These cellular junctions derived from desmosomes were first identified by using mAbs produced by immunizing BALB/c mice with human plantar SC proteins.¹⁰³ CDSN is expressed in the extracellular part of the desmosomes and corneodesmosomes at the interface between the SG and the SC and in the inner root sheath of the hair follicles.¹⁰⁴ CDSN molecules have been shown to interact through their glycine loop domains in a homophilic fashion to mediate adhesive interactions between corneocytes.¹⁰⁵ The precursor protein is synthesized in keratinocytes; stored, transported, and secreted by LGs at the apical cell surface of granular cells; and then covalently cross-linked to the cornified cell envelope. The protein plays a role in reinforcing cell-cell adhesion in the upper epidermis and SC, and its degradation by KLK5 and KLK7 is essential for normal desquamation.^{31,35}

Knockout mouse studies showed that CDSN is essential for maintaining desmosome integrity in the epidermal upper layers, for the proper development and function of the skin barrier in adult skin, and for normal hair follicle formation.^{106,107} Similar to inactivation of CDSN in mouse skin, which results in early postnatal death caused by epidermal barrier breakdown and increased transepidermal water loss,^{106,107} CDSN absence in patients with PSS-B results in impaired cell-cell coherence in the upper epidermis, which increases its permeability to allergens and microbes, predisposing to atopic manifestations and possibly leading to activation of epidermal proteases. It has been shown that KLKs are upregulated in patients with PSS-B as in patients with NS, despite normal LEKTI expression, suggesting that increased protease activity overrides the inhibitory capacity of LEKTI domains, resulting in degradation of adhesion molecules and increased corneocytes desquamation.¹⁰⁸

SKIN DERMATITIS, MULTIPLE SEVERE ALLERGIES, AND METABOLIC WASTING SYNDROME

Skin dermatitis, multiple severe allergies, and metabolic wasting (SAM) syndrome (MIM615508) is a recently described genodermatosis caused by homozygous mutations in *DSG1*. Dermatologic manifestations consist of congenital erythroderma (reminiscent of congenital ichthyosiform erythroderma); striate palmoplantar keratoderma with yellowish papules and plaques arranged at the periphery of the palms, along the fingers, and over weight-bearing areas of the feet; skin erosions; scaling; and hypotrichosis. The tendency toward severe allergies is manifested by food allergies and increased IgE levels. Additional features include recurrent skin and respiratory tract infections, eosinophilic esophagitis, esophageal reflux, minor cardiac defects, FTT, and growth retardation.²⁵

To date, 2 homozygous mutations in *DSG1* resulting in *DSG1* loss of function were described in 2 consanguineous families.²⁵ One mutation resulted in cytoplasmic mislocalization of DSG1 with lack of expression of the protein at the cell membrane; the other mutation led to complete absence of DSG1 expression. In both cases the absence of membrane expression of DSG1 resulted in abnormal cell-cell adhesion and malformed desmosomes in the upper epidermal layers.²⁵ Accordingly, histopathologic

TABLE I. Clinical, histopathologic, and pathogenetic features of NS, PSS-B and SAM syndrome

	NS	PSS-B	SAM syndrome
Inheritance	AR	AR	AR
Gene	<i>SPINK5</i>	<i>CDSN</i>	<i>DSG1</i>
Protein	LEKTI	CDSN	DSG1
Clinical features			
Skin manifestations	Congenital erythroderma, ichthyosis linearis circumflexa, eczematous AD-like lesions	Ichthyosiform erythroderma, superficial peeling of the skin	Congenital erythroderma, striate PPK, erosions, scaling
Hair abnormalities	Trichorrhexis invaginata	—	Hypotrichosis
Allergic manifestations	Asthma, allergic rhinitis, urticaria, angioedema	Food allergies, asthma, urticaria, angioedema	Severe food allergies
Complications	FTT, short stature, recurrent infections, diarrhea, pancreatitis, pulmonary HTN	FTT, recurrent skin infections	FTT, metabolic wasting, recurrent skin and respiratory tract infections, eosinophilic esophagitis, esophageal reflux, minor cardiac defects
Increased IgE level	+	+	+
Histopathologic and EM findings	Abnormal differentiation and desquamation, diminished granular layer, parakeratosis, subcorneal separation, premature lamellar body secretion	Subcorneal separation, inflammatory infiltrate in the upper dermis, split formation between the keratinocytes of the SG and corneocytes of the SC	Acantholysis with subcorneal and intragranular separation, abnormal structure of desmosomes
Immunologic characteristics	Upregulation of KLKs, ELA2, PAR2, NF-κB, T _H 2 cytokines (eg, TSLP, TNF-α, IL-4, IL-5, IL-13)	Upregulation of KLKs	Upregulation of proinflammatory cytokines (TSLP, TNF-α, IL-5)

AR, Autosomal recessive; ELA2, elastase 2; EM, electron microscopy; HTN, hypertension; NF-κB, nuclear factor κB; PAR2, protease-activated receptor 2; PPK, palmoplantar keratoderma.

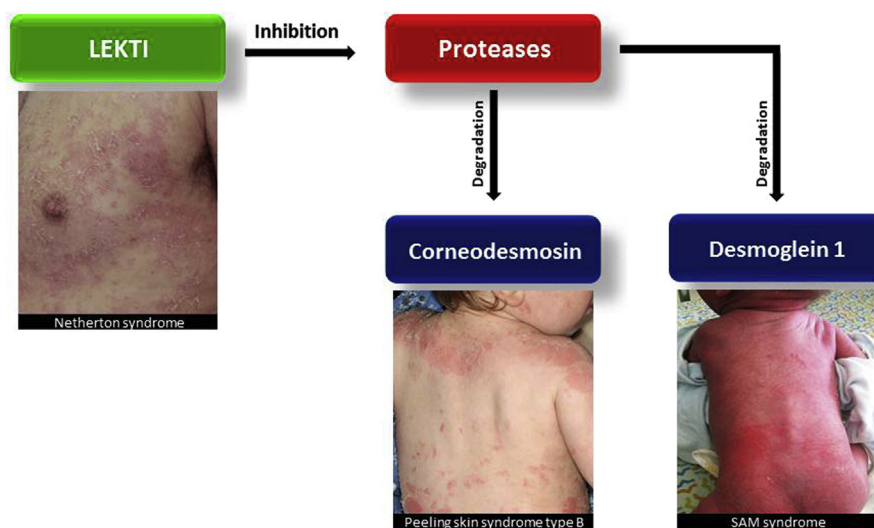


FIG 1. Clinical and pathogenetic overlap among NS-like disorders. NS, PSS-B, and SAM syndrome share numerous clinical features, including congenital erythroderma, skin fragility, recurrent infections, and allergic diathesis. These phenotypic resemblances reflect the fact that the proteins defective in each of these 3 syndromes function along the same biological pathway: LEKTI, which is deficient in patients with NS, inhibits serine proteases that normally degrade in the upper epidermal layers, both CDSN and DSG1, which are the proteins defective in patients with PSS-B and those with SAM syndrome, respectively. In the absence of LEKTI, uncontrolled degradation of CDSN and DSG1 leads to an impaired epidermal barrier, desquamation, and subcorneal separation associated with allergic manifestations.

examination of skin biopsy specimens obtained from patients with SAM syndrome demonstrate widespread acantholysis (loss of adhesion between keratinocytes) within the SS and SG leading to subcorneal and intragranular separation.²⁵

Abnormal DSG1 expression is expected to lead to aberrant epidermal differentiation given the recently demonstrated role of

this protein in the regulation of various aspects of cornification. DSG1 was shown to promote epidermal differentiation by inhibiting extracellular signal-regulated kinase (ERK) through Erbin, which interacts with Shoc2 and disrupts Ras-Raf scaffolding.¹⁰⁹ Therefore DSG1 deficiency is expected to result in unopposed ERK activation, which promotes keratinocyte proliferation and

inhibits keratinocyte differentiation.⁹⁰ This in turn might compromise epidermal barrier formation and function. A leaky barrier could then allow foreign antigens to gain access to the immune system and evoke an abnormal immune response, which would manifest as allergic reactions seen in the skin and elsewhere in patients with SAM syndrome.

However, additional data suggest that DSG1-deficient keratinocytes might also directly contribute to skin inflammation in patients with SAM syndrome. Indeed, cytokine gene expression analysis in keratinocytes isolated from the skin of patients with SAM syndrome revealed upregulation of a number of proinflammatory genes, including *TSLP*, *IL5*, and *TNFA*.^{25,110,111} Thus allergic diathesis in patients with SAM syndrome seems to result from combined abnormal barrier function and epidermal secretion of proinflammatory cytokines.

NS-LIKE INHERITED DISORDERS: A COMMON PATHOMECHANISM

As mentioned above, NS, PSS-B, and SAM syndrome share a common phenotype consisting of combined inflammatory erythroderma, atopic manifestations, an inappropriately active T_H2 immune response,^{25,69,99} and superficial intraepidermal detachment or subcorneal separation on histology (Table I). LEKTI, which is deficient in patients with NS, inhibits the proteolytic degradation of CDSN and DSG1,⁴⁹ which are missing in the skin of patients with PSS-B and those with SAM syndrome, respectively, and are major components of the corneodesmosomes, which are responsible for ensuring cohesiveness within the SC.¹¹² The marked phenotypic overlap among these 3 disorders thus results from the fact that they feature defective expression, function, or both of proteins functioning along the same physiologic pathway (Fig 1).

In addition, these observations collectively demarcate a novel group of disorders (which is likely to further expand over the next few years) characterized by excessive desquamation, compromised cell-cell adhesion, and an inflammatory phenotype caused by a defect residing primarily within the epidermis.

Finally and more importantly, by shifting our attention to the importance of the epidermal barrier in the development of allergic and inflammatory dermatoses, these disorders suggest new ways to explain the benefit of existing therapies and raise the possibility of translating these new data into novel therapeutic approaches.

For example, because it has been shown that proinflammatory cytokines, such as IL-4 and TNF- α , compromise epidermal barrier function¹¹³ and modulate the expression of differentiation markers in keratinocytes,^{114,115} the use of strategies targeting immune responses (including biologic agents, such as TNF- α inhibitors [eg, infliximab] or IL-4 and IL-5 blockers [eg, mepolizumab]) might in fact benefit atopic patients by directly contributing to the restoration of the epidermal barrier. Similarly, increased numbers of mast cells with high levels of secreted histamine are evident in the skin of patients with atopic dermatitis; because histamine attenuates the expression of differentiation-mediating tight junction and desmosomal proteins (CDSN and DSG1),¹¹⁶ antihistamine drugs might be of benefit because of their effect on epidermal differentiation.¹¹⁶ On the other hand, drugs targeting epidermal proteins, such as a new family of KLK inhibitors, are likely to become part of our therapeutic arsenal to treat NS-like disorders and possibly other atopic conditions.¹¹⁷⁻¹²¹

Conclusion

The deciphering of the pathogenesis of NT, PSS-B, and SAM syndrome has shed new light on clinical and mechanistic links between allergic reactions and abnormal desquamation, substantiating the notion that allergic manifestations might be, under some circumstances, the sole consequence of a primary epidermal defect. These recent advances in our understanding of the pathogenesis of atopic dermatitis-like congenital disorders once again emphasize how invaluable the study of rare disorders can be because, apart from its direct impact on affected subjects, it not only broadens our understanding of human biology but also often paves the way for innovative approaches in the management of common conditions.

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