Keratinization and psoriasis

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SUMMARY

The modern concept of the epithelial keratinization includes at least five groups of biologic substrates and the respective molecular processes involved:

1. *Keratin*, 2. *Desmosomes*, 3. *Cornified cell envelope*, 4. *Lipids of the horny layer,* 5. *Signal reception transduction and transcription* at the cellular level are also involved in the process of keratinization.

Keratins are forming the cytoskeleton of the epidermal cells. Their structure has been extensively studied. A number of anomalies in the structure of keratins K1, K2e, K5, K6a, K9, K10 and K14 have been recognized as causes of various hereditary disorders of keratinization. Mutations in keratin genes are responsible for these events. In psoriatic lesions an increased expression of keratins K6, K16 and K17 was observed.

Desmosomes and its constituents are mainly responsible for the intercellular adhesion specially in the basal and squamous layers of the epidermis. Deficient desmosomes and their constituents are responsible for the pathology in Mb Darier, in familial benign pemphigus (Mb Hailey-Hailey) as well as in certain acquired bullous dermatoses.

Cornified cell envelope (CE) has been only lately recognized as an important structure enabling a normal barrier function. Hereditary deficiency of the enzyme transglutaminase 1 linked to chromosome 14, has been made responsible for about a half the cases of lamellar ichthyosis. The Vohwinkel syndrome has been linked to a genetic anomaly of loricrin, a constituent of CE.

Epidermal lipids play an important role in ensuring a normal barrier function of str. corneum: inhibition of penetration of foreign substances, transepidermal water loss. Ceramides and cholesterol are mainly responsible for the regeneration of the barrier function following exposition to solvents and detergents. Splitting of cholesterol esters is important for normal shedding of str. corneum.

Activation of keratinocytes. The above mentioned biologic mechanisms are regulated by the very subtle processes at the molecular level. Two physiologic pathways are open to keratinocytes, differentiation and activation. Receptors on the cell membrane are accepting signals which are then transmitted through the cytoplasm to the nucleus and to the effectors. Transducing molecules and transcription factors are active in this process.

KEY WORDS

keratinization, psoriasis keratins, desmosome, cornified cell envelope, epidermal lipids, keratinocyte differentiation and activation

Introduction

In spite of the large amount of time and energy dedicated to the research of psoriasis it was still not possible to solve the crucial problem concerning the etiology of this disorder. The aim of the present manuscript is to review the new data on the process of keratinization and to try singling out the items relevant for pathogenesis of psoriasis.

The keratinization process in a broader sense does not involve strictly keratins, but includes also desmosomes, cornified cell envelopes, epidermal lipids as well as the signaling system concerning the epidermal cells (keratinocytes). In such a context genetics are also to be at least shortly mentioned.

Keratinization

The cytoskeleton of mammalian epidermal cells is composed of a three-filament system: microfilaments, microtubules and intermediate filaments (IF). IF represent the main component of the cytoskeleton, they are composed of keratins, which are polipeptide chains predominantly in a helical configuration (1,2). They are usually subdivided into the smaller acidic *type I keratins* (K10 to K19) with a molecular weight of 40-56 kD (3). *Type II keratins* (K1 to K9) are larger, neutral to basic with a molecular weight 52-67 kD. Within a keratin molecules *a central rod domain* of helical configuration which is pretty constant in all epithelia, and two *lateral non-helical domains* are to be distinguished. A schematic presentation of a keratin molecule is given in Figure 1.

Epithelial keratins are coexpressed in specific pairings which consist of each one type I and type II molecules. In the basal cell layer K5 and K14 and in the squamous layer K1 and K10 are coexpressed, while in plantar skin K2 and K9 are also expressed.

In psoriasis the expression of K1 and K10 is decreased in the spinous layer, while these keratins are replaced by hyperproliferation associated keratins K6, K16 and K17. Other less reproducible changes include an increased expression of K7, K13 and K17 (3).

Cornified cell envelope

The cornified cell envelope (CE) is present in keratinizing, terminally differentiated keratinocytes of the stratum corneum (SC). It is a 7-15 mm thick structure on the inner side of the cell membrane, composed of many cross-linked proteins: *involucrin, cystatin, small prolin rich proteins, loricrin, trichohyaline, filaggrin, keratin intermediate filaments and elafin* (4,5) as well as *S100A11* and *10, annexin and plasminogen activator inhibitor-2* (6). Together with the lipids from the SC they are responsible for the barrier function (2). The problem has been lately discussed in this journal (7). Figure 2.

In psoriasis the activity of the enzyme transglutaminase 1 (TGM 1) as well as the synthesis of involucrin which may be normally localized to the granular layer (stratum granulosum, SG) appear already in the lowermost portions of the spinous layer (8). The TGM 1 activity is three to seven times that of normal skin (2). It may be safely assumed that the mentioned shift in TGM 1 activity and involucrin synthesis may be responsible together with expression of the proliferating keratins (K6, K16) for the accelerated rate and incomplete keratinocyte maturation. It deserves to be mentioned that transcription of the TGM 1 gene can be activated in cultures of normal human keratinocytes by calcium ions, by protein kinase C and also by cholesterol sulfate (9). At the moment it is open to speculations if such mechanisms could be operative in psoriasis.

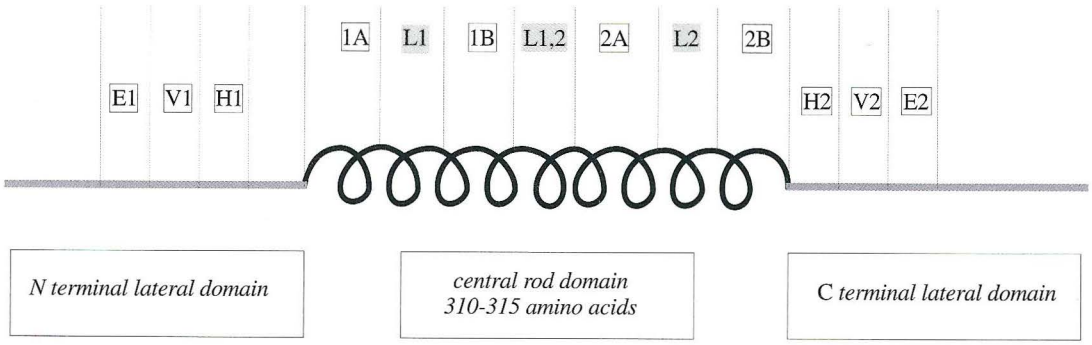

Figure 1. Simplified presentation of a keratine molecule
Central rod domains:1A, 1B, 2A, 2B: - main parts; L1,L1,2, L2: - linkers
Lateral domains: E1, V1, H1

Stratum corneum lipids

The epidermal lipids are important for a proper functioning of the epidermis. In the basal and spinous layers the lipids are mainly components of the cell membranes, in the upper SG they are contained in the lamellar bodies (LB, Odland bodies), while in SC they are present mainly as intercellular lipid bilayers. It was reported that in epidermis of atopic patients the content of phospholipids was nearly twice as high as in healthy epidermis (10). During the last few years a special attention has been paid to ceramides (11). According to Lavrijsen (12) the relative amount of ceramide fractions was different in patients with lamellar ichthyosis compared to normals; the relative amount of free fatty acids was also lower. Steinert and Marekov stressed the importance of the lipid envelope surrounding the CE of corneocytes (5). It seems that it is composed mainly of ceramides, a special role being attributed to the w-hydroxy-ceramides (13). Ceramides are supposed also to be important in the keratinocyte signaling system.

Barrier function

If the SC is exposed to solvents or injured by tape stripping the epidermal lipids and the CE become damaged, an increased permeation of substances from outside and an increased transepidermal water loss (TEWL) are observed at the injured skin site. Elias and his group have shown that a deficiency in essential, unsaturated fatty acids (linoleic and lanolenic acids) in food administered to nude mice caused symptoms similar to ichthyosis and an increased TEWL. By including essential fatty acids into the food, a good recovery was achieved (14). Additionally to acylglycerols and ceramides cholesterol also seems to play an important role in the maintenance of the proper functioning of the barrier (9).

In every-day life the skin of many people is exposed to an abuse of detergents, solvents, abrasive substances, unfavorable weather conditions and further situations exhibiting detrimental effects in respect to the SC barrier. For this reason quite a few groups of investigators are searching for solutions how to improve barrier recovery by applying adequate creams or ointments. Ghadially et al. have been able to show in aged mice after barrier disruption, that by application of an equimolar mixture of ceramides, cholesterol, linoleic acid and nonessential fatty acids, a good recovery of the barrier function was achieved after six hours (15). In another article Elias and his group showed by using a three-lipid component system that either linoleic or palmitic acids normalized the barrier function, thus proving that the structural requirement for free fatty acids in the complete lipid mixture is not restricted to essential fatty acids (16).

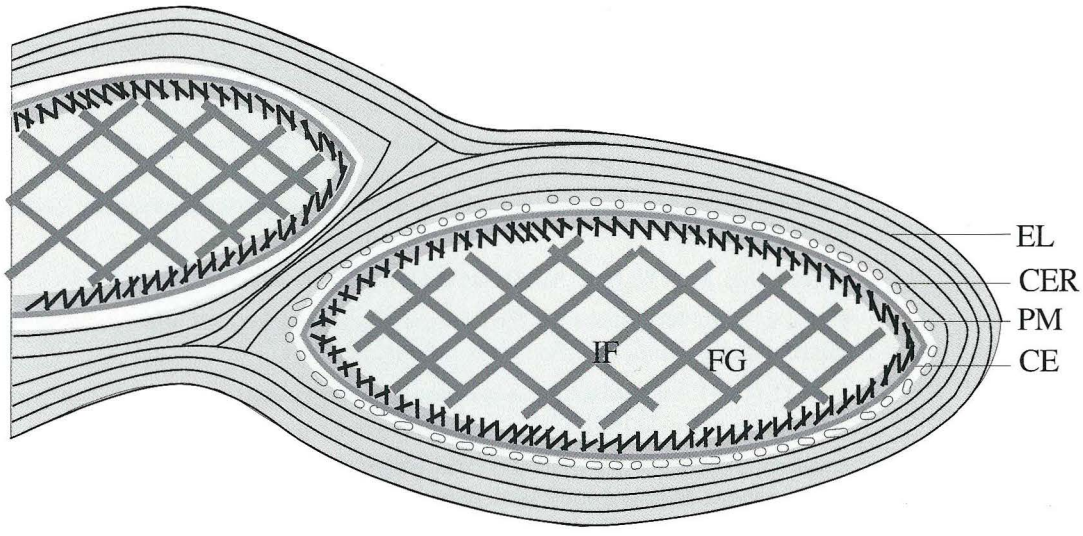

Figure 2. Simplified presentation of a human corneocyte structure
EL: epidermal lipids (bilayers)
CER: lipid envelope consisting mainly of ceramides, covalently bound to PM
CE: cornified cell envelope
PM: plasma membrane
FG: filaggrin
IF: intermediate filaments (keratins)

Activation of keratinocytes

Since the pioneer studies of the epidermal cell kinetics by Van Scott (17) it is known that the production of epidermal cells in psoriasis is increased and that the transit time from basal layer to SC is shortened about four times. Only recently it was realized however that keratinocytes not only react to, but also produce an abundance of cytokynes, chemoreactants and growth factors. Keratinocytes express receptors for many polypeptide factors and thus respond to various signals from the immune system as well as to autocrine stimulation. The signaling between keratinocytes and lymphocytes has been shown in psoriasis, delayed type hypersensitivity, atopic dermatitis and cutaneous T-cell lymphomas (18,19).

Keratinocyte differentiation is a complex process indicating the transformation of the basal cell into corneocyte. It includes various systems: different expression of keratins, transformation of keratohyline through profilaggrin to filaggrin as well as others. *Keratinocyte activation* designates primarily a response of keratinocytes to various stimuli e.g., extracellular signaling molecules, injuries, UV light, stress. The signals, which induce keratinocytes to start differentiating or become activated, are subject of intensive investigation. One well-known *signal of activation* is the *release of interleukin 1 (IL-1)* which is prestored in the cytoplasm of keratinocytes. Activated keratinocytes in the spinous layer can start to produce K6, K16 and K17 instead of the normally present K1 and K10 (20).

Signaling molecules bind to receptors on the cell membrane and activate various systems of transducing molecules (mainly kinases) in the cytoplasm which are then transmitting signals to the transcription factors in the nucleus. These in their turn activate segments of DNA and/or specific RNA molecules responsible for transcription of specific genes. At least three signaling pathways receiving signals from the extracellular environment are known to be important for keratinocyte activation: IFN-γ, the EGF family and TNF-α/IL-1 (20). It was shown that IFN-γ is a critical element in the induction of keratinocyte proliferation on psoriasis (21). A significant proportion of lesional T cells in psoriatic epidermis and dermis, represent increased numbers of both IFN-γ $CD4^+$ and IFN-γ $CD8^+$ present in appropriate anatomic location to sustain the lesional pathology (22). From these and further data it is possible to deduce that the IFN-γ signaling pathway is important for keratinocyte activation in psoriasis.

One may hope that further studies of $CD4^+$ and $CD8^+$ cells, which are a major source of IFN-γ in chronic psoriatic plaques, would provide clues for an efficient treatment.

The role of genetics in the development of psoriasis remains to be additionally clarified, it seems that a number of genes are involved in the pathogenesis (23,24): class I and II MHC loci on chromosome 6p; keratin class II cluster of genes on chromosome 12q (K2,K6); keratin class I cluster of genes on chromosome 17p (K16,K17); epidermal differentiation complex on chromosome 1q; lately the genetic defect was located to a locus on chromosome 17q.

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