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Skin Aspartic Protease - A Key enzyme in Stratum Corneum Barrier Properties

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Abstract

Human skin is a multi-layered tissue composed of three dynamic compartments, the epidermis, the dermis and the hypodermis. The outermost of these – the epidermis terminally differentiates to form the cornified layer – the stratum corneum- that has beautifully evolved to be an effective and impermeable barrier, providing us with watertight skin and a protective shield, which allows us to tolerate and live in all sorts of climatic and environmental conditions. This short review summarizes the roles of skin aspartic protease, filaggrin and filaggrin 2 in the hydration and mechano-biophysics of the stratum corneum.

Keywords: Enzyme • Stratum corneum • Corneocytes • Photoprotection

Introduction

Human skin is a multi-layered tissue composed of three dynamic compartments, the epidermis, the dermis and the hypodermis. The outermost of these – the epidermis terminally differentiates to form the cornified layer – the stratum corneum- that has beautifully evolved to be an effective and impermeable barrier, providing us with watertight skin and a protective shield, which allows us to tolerate and live in all sorts of climatic and environmental conditions.

The stratum corneum consists of highly specialized cells known as corneocytes and intercellular arrays of organized lipids. The corneocytes, are flat polyhedral shaped, anucleated cells primarily composed of intermediate filament networks made up mostly of keratins and these are organized into bundles by another protein, a filamentous aggregating protein -called filaggrin. Each corneocyte is surrounded by a highly cross-linked protein envelope which in turn is surrounded by a continuous extracellular lipid matrix the lipid envelope [1-4].

For decades the stratum corneum had been long considered as a dead layer of cornified cells whose principal function was as a barrier against Trans Epidermal Water Loss (TEWL) and external aggressions. However, research during the last thirty years has shown that it is very much alive – a haven of biochemical activity conferring a multitude of functions to this tissue (Table 1) [5]. The stratum corneum acts as an important biological sensor for our skin endowed with a capacity to adapt rapidly to changes in the external environment thanks to a reservoir of reactive cytokines and alarmins. It also plays a key role in cutaneous anti-microbial defense with its impressive arsenal of anti-microbial peptides, toll-like receptors, chemokines and proteases that make up the first line of defense in the skin's innate immune system. The stratum corneum also has a role to play in photoprotection, particularly in darker colored skins, due to the presence of the naturally occurring skin pigment, melanin granules that exist in its upper layers. In lighter skins photoprotection is offer by urocanic acid, an endogenous UV filter, which is a component of natural moisturizing factor. The cascade of protease activity in the stratum corneum is central to the proper desquamation of corneocytes from the surface of the skin- a process key to maintaining the turnover of the stratum corneum and the homeostasis of skin.

As mentioned above, the corneocyte keratins are organized into bundles by Filaggrin. This macromolecular protein is initially expressed in the stratum granulosum of the epidermis as profilaggrin, a large histidine-rich and highly cationic phosphoprotein, greater than 400 kDa in size. Filaggrin is composed of an N-terminal domain, which includes calcium binding and nuclear localization motifs, an internal domain made up of 10 to 12 nearly identical 37 kDa filaggrin repeats – and a C terminal domain. The proform of the protein is stored in keratohyalin granules in the stratum granulosum before been dephosphorylated and processed into its functional forms by a cascade of proteolytic enzymes [6].

Table 1. Five key functions of the stratum corneum.

Functions of the Stratum Corneum
Physical and photo protection
Chemical and permeability barrier
Innate defense
Regulation of hydration
Biosensor

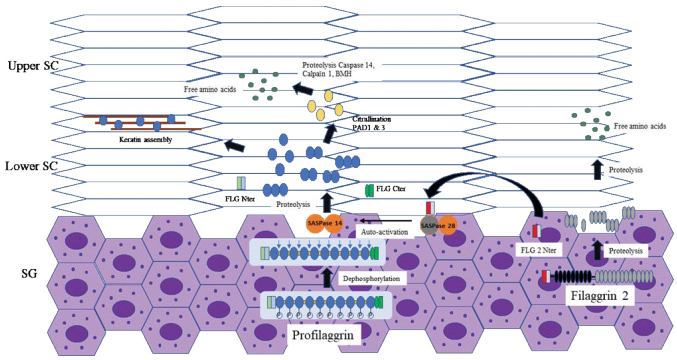

Figure 1. SASPase links the processing of filaggrin and filaggrin 2 in the stratum corneum and stratum granulosum in human skin.

Figure 1 shows the binding of the N terminal part of filaggrin 2 and SASPase 28 in the Stratum Granulosum (SG) resulting in its subsequent auto-activation to its active form SASPase 14. This catalytic form of the enzyme plays a key role in the early processing of dephosphorylated profilaggrin cleaving the linker regions between the repetitive domains and releasing monomers into the lower layers of the stratum corneum, which, are in turn proteolyzed to free amino

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acids after a process of citrullination. The monomers that are not citrullinated, partake in the organization of keratin filaments into bundles, which is an important event in modulating the shape of corneocytes.

Once the N terminal fragments are cleaved – they translocate to the nucleus where they are believed to function as transcription factors in the regulation of keratinocyte terminal differentiation. The C- terminal domain is also proteolytically released and to date no known function as been ascribed to this region. The internal domain is cleaved into 10 to 12 monomers and subsequently to their constituent amino acids by proteases. These monomers have several roles. First and foremost, they organize the keratins into highly ordered and condensed arrays of filaments -tight bundles - in the corneocytes of the lower stratum corneum, which is often referred to as the stratum compactum, delivering a dense filamentous network that plays a key role in collapsing the corneocytes into a flatter and compact shape - a characteristic feature that contributes to the mechanical properties of the stratum corneum. The second function of these filaggrin monomers is to provide a major source of hygroscopic amino acids. Here the arginine amino acids in the monomers are modified to citrulline through the action of peptidylarginine deiminases [7]. Once deiminated, they are released from the intermediate keratin bundles and are hydrolyzed by several proteases including caspase 14, bleomycin hydrolase and calpain 1 in the mid layers of the stratum corneum into free histidine, glutamine and arginine residues. These amino acids are subsequently modified to pyrrolidone carboxylic acid and urocanic acid, which represent a major part of the functional osmotic material in the stratum corneum -the natural moisturizing factor [6,8,9]. These amino acids and their derivatives also contribute to the maintenance of the acid mantle and pH gradient in the stratum corneum – a third notable function of the SC [10] and this is key to innate defense, the function of enzymes involved in ceramide metabolism and serine proteases required for coordinated epidermal differentiation, cornified envelope formation and desquamation. The importance of filaggrin and its processing to key functional domains and amino acids is underlined by the numerous skin conditions, such as ichthyosis vulgaris, atopic dermatitis and xerosis linked to the deficiency and/or dysfunctional processing of the protein [11].

One of the key enzymes in the early processing of filaggrin to its monomers is the skin aspartic acid protease - SASPase. The enzyme is specifically expressed, as a 28 kDa proform and an auto-activated 14 kDa form, in the stratum granulosum and stratum corneum of normal human skin where it is believed to be involved in the control of epidermal differentiation and desquamation. In psoriasis, the 28 kDa form persists in the stratum corneum whereas in normal skin only the catalytic 14 kDa form is present in the upper layers [12]. SASPase deficiency in hairless mice displayed a dry skin phenotype that was associated with a defect in filaggrin maturation [13]. In these mice, there was an accumulation of filaggrin in the stratum granulosum concomitant with a notable increase in dimeric and trimeric forms of filaggrin and a marked absence of filaggrin monomers in the stratum corneum. In addition, there was reduced SC hydration and the mice displayed a dry and flaky skin phenotype. Furthermore, SASPase cleaved the linker region between the monomer repeats in a recombinant human filaggrin. The role of SASPase in filaggrin processing was further strengthened by a study in humans describing mutations in the gene of SASPase that cause dominantly inherited lamellar ichthyosis – a condition in which there is significant scaling of the stratum corneum and hyperkeratosis with an underlying accumulation of unprocessed filaggrin in the stratum granulosum [14]. In another study of SASPase -/- mice, the corneocyte surface texture was significantly altered resulting in an increased density of villus protrusions on the surface of corneocytes. In addition, the elastic modulus, a measure of stiffness, was decreased and a small reduction in natural moisturizing factor was observed [15-17]. These discoveries indicate multi-functional roles for SASPase both in the hydration and in the mechano-biophysics of the stratum corneum linking SASPase not only to skin hydration but also potentially to the confort and sensitivity of skin.

Until recently little was known about how the expression or activity of SASPase was regulated in the epidermis. A study using yeast two hybrid and enzymatic analyses showed that the N terminal region of another member of S100 family -filaggrin 2 (FLG2) binds to and stimulates the auto-activation of SASPase28 to its active catalytic form – SASPase 14 which, in its dimeric form cleaves profilaggrin to its functional monomers. Like filaggrin – FLG2 – is expressed in the granulous layer of the epidermis where it is processed to smaller functional fragments by proteases like filaggrin, the internal domain of FLG2 contains repetitive domains that are believed to provide an additional source of natural moisturizing factor although not to the same extent as filaggrin. The sequences in the C-terminal domain of FLG 2 have been shown to act as microbial peptides while the amino terminal domain of FLG2 is a component of cornified envelopes and co-localizes with corneodesmosin indicating that FLG2 plays a role in epidermal and SC adhesion.

Conclusion

The new discovery that the N terminal domain of FLG2 regulates SASPase links, for the first time, the processing of filaggrin and filaggrin 2. Taken together, the data suggest that SASPase has major role in the processing of filaggrin to natural moisturizing factor and in the biophysical properties of the stratum corneum.

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