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"The key role of lipid metabolism in the epidermis"

10) The roles of ABCA12 in the keratinocyte differentiation and lipid barrier formation in the epidermis

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Abbreviations: ABC, ATP-binding cassette; ABCA12, ATP-binding cassette transporter A 12; CIE, congenital ichthyosiform erythroderma; HDL, high-density lipoprotein; HI, harlequin ichthyosis; LG, lamellar granule; LI, lamellar ichthyosis; PPAR, peroxisome proliferator-activated receptor

Keywords: ABCA12; congenital ichthyosiform erythroderma; harlequin ichthyosis; lamellar granules; lamellar ichthyosis; prenatal diagnosis

ABSTRACT

ABCA12 is a member of the large superfamily of the ATP-binding cassette (ABC) transporters, which bind and hydrolyze ATP to transport various molecules across a limiting membrane or into a vesicle. The ABCA subfamily members are thought to be lipid transporters. ABCA12 is a keratinocyte transmembrane lipid transporter protein associated with lipid transport in lamellar granules to the apical surface of granular layer keratinocytes. Extracellular lipid including ceramide is thought to be essential for skin barrier function. *ABCA12* mutations are known to underlie major three types of autosomal recessive congenital ichthyoses, harlequin ichthyosis, lamellar ichthyosis and congenital ichthyosiform erythroderma. *ABCA12* mutations lead to defective lipid transport via lamellar granules in the keratinocytes, resulting in malformation of epidermal lipid barrier and ichthyosis phenotypes. ABCA12 deficient model mouse studies indicated that lipid transport by ABCA12 is also indispensable for intact differentiation of keratinocytes.

Introduction

ABCA12 is a member of the large superfamily of the ATP-binding cassette (ABC) transporters,[1] which bind and hydrolyze ATP to transport various molecules across a limiting membrane or into a vesicle.[2] The ABCA subfamily members are thought to be lipid transporters.[3] ABC transporter A12 (ABCA12) was recognized as a key molecule in keratinocyte lipid transport (Figure 1).[4-6] ABCA12 is a keratinocyte transmembrane lipid transporter protein associated with lipid transport in lamellar granules to the apical surface of granular layer keratinocytes.[4] In this article, the importance of *ABCA12* as a keratinocyte lipid transporter is reviewed in the context of keratinocyte differentiation and skin lipid barrier formation.

ABCA12 and other ABCA transporters

Several genetic diseases have been shown to be caused by mutations in ABCA subfamily genes. The ABCA subfamily, of which the *ABCA12* gene is a member, comprises 12 full transporters and one pseudogene (ABCA11) and are essential for lipid transport and secretion.[7] Three ABCA genes of the same subfamily as ABCA12 have been also implicated in the development of genetic diseases affecting cellular lipid transport. ABCA3 is a very close molecule in a phylogenetic tree of ABCA subfamily proteins.[1] ABCA3 is known to aid lipid secretion from alveolar type II cells via lamellar granules[8] and, recently, an ABCA3 deficiency was reported to underlie a fatal lung surfactant deficiency in newborns,[9] an often lethal condition that leads to death shortly after birth.

Another important member of ABCA subfamily is ABCA1. Mutations in the human ABCA1 gene are the underlying familial high-density lipoprotein (HDL)-deficiency syndrome (Tangier disease) which suggested that ABCA1 is a major regulator of HDL metabolism.[10-12]

ABCA2, ABCA3, and ABCA7 mRNA levels were reported to be upregulated after sustained cholesterol influx,[13, 14] suggesting that ABCA transporters are involved in transmembrane transport of endogenous lipids.[15] From these facts, transporters in the ABCA subfamily were thought to be involved in transmembrane transport of cholesterol.[16-18] Interestingly, ABCA3, a member of the same protein superfamily as ABCA12, functions in pulmonary surfactant lipid secretion again via the production of similar lamellar-type granules within lung alveolar type II cells.[8, 9]

The role of ABCA12 in the transport of lipid into lamellar granules

Extracellular lipid including ceramide is thought to be essential for skin barrier function.[19] Mutations in the ABCA12 gene (*ABCA12*) were reported to underlie the devastating phenotype seen in harlequin ichthyosis (HI) patients,[4, 20] the most severe keratinization disorder thus far known. ABCA12 mutations underlying HI are thought to lead to major disruptive defects in ABCA12 lipid transporter function resulting in the HI phenotype.[4] We reported previously that ABCA12 is localized in lamellar granules (LGs) in the granular layer keratinocytes and might work in the lipid transport via LGs to form the intercellular lipid layers in the stratum corneum.[4] We have analyzed the epidermal localization of ABCA12 in comparison with the localization of Golgi apparatus-markers and LG-

associated proteins together with transglutaminase 1, because LGs are thought to be a part of continuous tubular net work originated from Golgi apparatus to the cell membrane.[5] We employed antibodies to well-established marker molecules of each part of Golgi apparatus-LG-cell membrane network, i.e. GM130 antibody, anti-TGN-46 antibody and anti-transglutaminase 1 antibody (B.C1) as markers for cis-Golgi, trans-Golgi and cell membrane, respectively. Our results showed that ABCA12 localized throughout the entire Golgi apparatus to LGs at the cell periphery mainly in the granular layer keratinocytes. These results suggest that ABCA12 works in lipid transport from Golgi apparatus to LGs in the granular layer cells.[5] Double-labeling immunofluorescence staining in cultured keratinocytes clearly indicated that ABCA12 was localized from Golgi apparatus (colocalized with cis-Golgi marker GM130 and trans-Golgi marker TGN-46) to cell periphery (close to the plasma membrane stained with transglutaminase 1). ABCA12 failed to colocalize with TGase1, a cell membrane-bounding protein, both *in vivo* and in the cultured keratinocytes, and ABCA12 was thought to be distributed only very sparsely, on the cell membrane.[5]

In normal human epidermis, ABCA12 is expressed in the entire epidermis, mainly in the upper spinous and granular layers.[5] Immunofluorescent double labeling revealed that the majority of ABCA12 colocalized with glucosylceramide in the cytoplasm within the upper spinous and granular cells (Figure 2).[5] Immunofluorescence labeling on ultrathin cryosections clearly revealed a localization of ABCA12 and glucosylceramide. Using immunofluorescence labeling at the light microscopic level, ABCA12 and glucosylceramide staining almost completely overlapped within the

granular layer keratinocytes.[5] Post-embedding immunoelectron microscopy revealed that both ABCA12 and glucosylceramide were observed in the LGs of the uppermost granular layer keratinocytes.[5] By immunoelectron microscopy using ultrathin cryosections, glucosylceramide labeling was seen with the lamellar structures in the LGs. ABCA12 immunogold labeling was observed on or close to the membrane surrounding LGs in the uppermost granular layer cells.[5]

We can hypothesize that ABCA12 is likely to be a membrane lipid transporter that functions in the lipid transport from the trans-Golgi network to LGs at the keratinocyte periphery (Figure 3).[4,5] Recently, it was confirmed biochemically that ABCA12 deficiency impairs that glucosylceramide accumulation in lamellar granules and that ABCA12 transports glucosylceramide to the inner side of lamellar granules.[6] In addition, Ceramide was reported to up-regulate ABCA12 expression via the PPAR delta-mediated signaling pathway, providing a substrate-driven, feed-forward mechanisim for regulation this key lipid transporter.[21] More recently, from studies using *Abca12*$^{-/-}$ mice, it was suggested that ABCA12 plays an important role in normal differentiation of epidermal keratinocytes.[22]

ABCA12 Mutations and ichthyosis

ABCA12 mutations are known to underlie major three types of autosomal recessive congenital ichthyoses, harlequin ichthyosis (HI), lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE). Harlequin ichthyosis is the most severe subtype of ichthyosis. The patients

with harlequin ichthyosis show plate-like scales on the whole body, severe eclabium and ectropion.

In 2010, a review of the literature was performed to identify all of the known *ABCA12* mutations in patients with ARCI and 56 *ABCA12* mutations have been described (online database: http://www.derm-hokudai.jp/ABCA12/) in 66 unrelated families including 48 HI, 10 LI and 8 CIE families.[23] Mutations have been reported among autosomal recessive congenital ichthyosis patients with African, European, Pakistani/Indian and Japanese backgrounds, from almost all over the world. Of the 56 mutations, 36% (20) are nonsense, 25% (14) are missense, 20% (11) comprise small deletions, 11% (6) are splice site, 5% (3) are large deletions and 4% (2) are insertion mutations. At least, 62.5% (35) of the total reported mutations are predicted to result in truncated proteins. There is no apparent mutation hot spot in *ABCA12*, although mutations underlying LI phenotype are clustered in the region of the first ATP-binding cassette.[24]

In HI affected epidermis, several morphologic abnormalities including abnormal lamellar granules in the keratinocyte granular layer and a lack of extracellular lipid lamellae within the stratum corneum had been reported.[25-28] Lack of ABCA12 function subsequently leads to disruption of lamellar granule lipid transport in the upper keratinizing epidermal cells resulting in malformation of the intercellular lipid layers of the stratum corneum in HI.[4] Cultured epidermal keratinocytes from an HI patient carrying *ABCA12* mutations demonstrated defective glucosylceramide transport and this phenotype was recoverable by *in vitro ABCA12* corrective gene transfer.[4] To date, intracytoplasmic glucosylceramide

transport has been studied using cultured keratinocytes from a total of three patients harboring *ABCA12* mutations. One patient was a homozygote for a splice site mutation c.3295-2A>G[4] and another patient was a compound heterozygote for p.Ser387Asn and p.Thr1387del.[29] Only one heterozygous mutation p.Ile1494Thr was identified in the other patient.[30] Cultured keratinocytes from all the three patients showed apparently disturbed glucosylceramide transport, although this assay is not quantitative.

In addition, defective lamellar granule formation was observed in the skin of two CIE patients with *ABCA12* mutations.[30] Electron microscopic observation revealed that, in the cytoplasm of granular layer keratinocytes, abnormal, defective lamellar granules were assembled together with some normal-appearing lamellar granules.[30]

Formation of the intercellular lipid layers is essential for epidermal barrier function. In ichthyotic skin with ABCA12 deficiency, defective formation of the lipid layers is thought to result in a serious loss of barrier function and a likely extensive compensatory hyperkeratosis.[31]

One hypothetical pathomechanism for ABCA12 deficient in autosomal recessive congenital ichthyosis is the differentiation defect theory, derived from the clinical features of HI patients. Fetuses affected with HI start developing their ichthyotic phenotype while they are in the amniotic fluid where stratum corneum barrier function is not required. Thus, barrier defects cannot be involved directly in the pathogenesis of HI phenotype, at least during the *in utero* fetal period. In this context, disturbed

keratinocyte differentiation is speculated to play an important role in the pathogenesis of HI phenotype. In fact, three dimensional culture studies revealed that HI keratinocytes differentiate poorly using morphologic criteria and show reduced expression of keratin 1 and defective conversion from profilaggrin to filaggrin.[32]

In an *ABCA12* ablated organotypic co-culture system, an *in vitro* model of HI skin, expression of keratinocyte late differentiation-specific molecules was dysregulated.[33] Expression of specific proteases associated with desquamation, kallikrein 5 and cathepsin D, was dramatically reduced in the ABCA12 ablated organotypic co-culture system.[33] In the model system, *ABCA12* ablation resulted in a premature terminal differentiation phenotype.[33] Furthermore, in the mutant mice carrying a homozygous spontaneous missense mutation, loss of Abca12 function led to premature differentiation of basal keratinocytes.[34] In contrast, in our *Abca12*$^{-/-}$ HI model mice, immunofluorescence and immunoblotting of *Abca12*$^{-/-}$ neonatal epidermis revealed defective profilaggrin/filaggrin conversion and reduced expression of the differentiation-specific molecules, loricrin, kallikrein 5 and transglutaminase 1, although their mRNA expression was up-regulated.[22] These data suggest that ABCA12 deficiency may lead to disturbed keratinocyte differentiation during fetal development, resulting in an ichthyotic phenotype at birth. From these observations, ABCA12 deficiency might have global effects on keratinocyte differentiation, resulting in both impaired terminal differentiation and premature differentiation of the epidermis.

HI patients often die in the first one or two weeks of life. However, once

they survive beyond the neonatal period, HI survivors' phenotypes improve within several weeks after birth. In order to clarify mechanisms of the phenotype recovery, we studied grafted skin and keratinocytes from *Abca12*-disrupted (*Abca12*$^{-/-}$) mouse.[22] *Abca12*$^{-/-}$ skin grafts kept in a dry environment exhibited dramatic improvements in all the abnormalities seen in the model mice. Increased transepidermal water loss, a parameter of barrier defect, was remarkably decreased in grafted *Abca12*$^{-/-}$ skin. 10 passage-sub-cultured *Abca12*$^{-/-}$ keratinocytes showed restoration of intact ceramide distribution, differentiation-specific protein expression and profilaggrin/filaggrin conversion, which were defective in the primary-culture.[22] These observations suggested that, during maturation, *Abca12*$^{-/-}$ epidermal keratinocytes regain normal differentiation processes, although the exact mechanisms of this restoration is still unknown.[22]

ABCA12 deficient animal models

Recently, bioengineered disease models were established to investigate ichthyotic pathomechanisms due to ABCA12 defective function and to aid development of innovative treatments for ichthyosis with ABCA12 deficiency.

We transplanted cultured keratinocytes from patients with HI and succeeded in reconstituting HI skin lesions in immunodeficient mice.[35] These reconstructed HI lesions showed similar changes to those observed in HI patients' skin. In addition, we generated *Abca12* disrupted (*Abca12*$^{-/-}$) mice and our *Abca12*$^{-/-}$ mice closely reproduced the human HI phenotype, showing marked hyperkeratosis with eclabium and skin fissure.[36] Lamellar

granule abnormalities and defective ceramide distribution were remarkable in the epidermis. Skin permeability assays of *Abca12*$^{-/-}$ mouse fetuses revealed severe skin barrier dysfunction after the initiation of keratinization. Surprisingly, *Abca12*$^{-/-}$ mice also demonstrated lung alveolar collapse immediately after birth. Lamellar bodies in alveolar type II cells from *Abca12*$^{-/-}$ mice lacked normal lamellar structures.[36] The level of surfactant protein B, an essential component of alveolar surfactant, was reduced in the *Abca12*$^{-/-}$ mice.[36] Another group independently developed *Abca12*$^{-/-}$ mice and the mice also confirmed the clinical features of HI.[37]

A study in one *Abca12* disrupted HI model mouse indicated that a lack of desquamation of skin cells, rather than enhanced proliferation of basal layer keratinocytes accounts for the 5-fold thickening of the *Abca12*$^{-/-}$ stratum corneum using *in vivo* skin proliferation measurements.[37] It was suggested that this lack of desquamation was associated with a profound reduction in skin linoleic esters of long-chain omega-hydroxyceramides and a corresponding increase in their glucosylceramide precursors. Omega-hydroxyceramides are required for correct skin barrier function and these results from the HI model mice establish that ABCA12 activity is required for the generation of long-chain ceramide esters that are essential for the development of normal skin structure and function.[37]

In addition, a mouse strain carrying a homozygous spontaneous missense mutation was reported to show skin manifestations similar to ichthyosis.[34] Lipid analysis in *Abca12* mutant epidermis revealed defects in lipid homeostasis, suggesting that *Abca12* plays a crucial role in maintaining lipid balance in the skin.[34] The cells from the *Abca12* mutant mouse have

severely impaired lipid efflux and intracellular accumulation of neutral lipids.[34] Abca12 was also demonstrated as a mediator of Abca1-regulated cellular cholesterol efflux.[34] Injection of a morpholino designed to target a splice site at the exon 4/intron 4 junction to block *Abca12* pre-mRNA processing induced altered skin surface contours, disorganization of the melanophore distribution, pericardial edema and enlargement of the yolk sac at 3 days post-fertilization in the larvae of the zebrafish. It was also associated with premature death at around 6 days post-fertilization. These results suggest that *Abca12* is an essential gene for normal zebrafish skin development and provide novel insight into the function of ABCA12 (reported at the Annual Meeting of the Society for Investigative Dermatology 2010; Abstract, Frank et al., J Invest Dermatol 2010; 130 p S86).

Using our Abca12$^{-/-}$ HI model mice, we tried fetal therapy with systemic administration of retinoid or dexamethasone, which are effective treatments for neonatal HI and neonatal respiratory distress, respectively, to the pregnant mother mice. However, neither improved the skin phenotype or extended the survival period.[36] Retinoids were also ineffective in *in vivo* studies using cultured keratinocytes from the model mice.[22]

Conclusion

ABCA12 is apparently localized in the membrane of trans-Golgi network and lamellar granules in the upper epidermis, mainly in the uppermost spinous and granular layer cells. Our own studies and a review of the literature suggest that

ABCA12 works in lipid transport into trans-Golgi network and lamellar granules to accumulate lipid which is essential for skin barrier formation. Consequently, the lipid packed in lamellar granules is secreted to the extracellular space to form intercellular lipid layers in the stratum cornuem, which is important for skin barrier (Figure 4). In addition, model mouse studies indicated that lipid transport by ABCA12 is indispensable for intact differentiation of keratinocytes. Further accumulation of the data will be needed in order to elucidate the mechanisms of ABCA12 on keratinocyte differentiation/proliferation.

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ABCA12 mutation database is available at our site http://www.derm-hokudai.jp/ABCA12/

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