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Evidence for a Matriptase-Prostasin Proteolytic Cascade Regulating Terminal Epidermal Differentiation*

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Recent gene ablation studies in mice have shown that matriptase, a type II transmembrane serine protease, and prostasin, a glycosylphosphatidylinositol-anchored membrane serine protease, are both required for processing of the epidermis-specific polyprotein, profilaggrin, stratum corneum formation, and acquisition of epidermal barrier function. Here we present evidence that matriptase acts upstream of prostasin in a zymogen activation cascade that regulates terminal epidermal differentiation and is required for prostasin zymogen activation. Enzymatic gene trapping of matriptase combined with prostasin immunohistochemistry revealed that matriptase was co-localized with prostasin in transitional layer cells of the epidermis and that the developmental onset of expression of the two membrane proteases was coordinated and correlated with acquisition of epidermal barrier function. Purified soluble matriptase efficiently converted soluble prostasin zymogen to an active two-chain form that formed SDS-stable complexes with the serpin protease nexin-1. Whereas two forms of prostasin with molecular weights corresponding to the prostasin zymogen and active prostasin were present in wild type epidermis, prostasin was exclusively found in the zymogen form in matriptase-deficient epidermis. These data suggest that matriptase, an autoactivating protease, acts upstream from prostasin to initiate a zymogen cascade that is essential for epidermal differentiation.

The serine proteases constitute one of the largest classes of proteolytic enzymes and have evolved to perform specialized functions. Trypsin-like serine proteases typically are synthesized as inactive zymogens that are activated by a single endoproteolytic cleavage. This group of enzymes often acts in either single or complex, highly regulated zymogen cascades to control important biological processes such as coagulation, fibrinolysis, blood pressure, and digestion (1–4).

The stratum corneum is the outermost, terminally differentiated layer of the epidermis that provides a physical barrier protecting the body from fluid loss, as well as from mechanical, chemical, and microbial insults. The stratum corneum is a two-compartment structure consisting of a lipid-enriched extracellular matrix in which an interlocking meshwork of flattened dead keratinocytes (corneocytes) are embedded (5–7). Our previous studies have shown that the targeted deletion of the type II transmembrane trypsin-like serine protease, matriptase, leads to loss of inwards and outwards epidermal barrier function due to incomplete corneocyte differentiation and abnormal intercorneocyte lipid extrusion correlating at the molecular level with defective proteolytic processing of profilaggrin (8–11). Interestingly, mice with the targeted deletion of the glycosylphosphatidylinositol (GPI)[3]-anchored trypsin-like serine protease, prostasin (PRSS8), in keratinized tissues recently were reported to display the identical spectrum of deficiencies in stratum corneum formation (12) to those described for matriptase-deficient mice (summarized in Table 1). Moreover, both protease-deficient transgenic mouse strains displayed identical hair follicle defects and thymic abnormalities (Table 1).

The identical phenotypes of matriptase- and prostasin-deficient mice suggested that the two membrane serine proteases either could be components of two distinct zymogen cascades that each are critical to terminal epidermal differentiation or, alternatively, could be components of the same proteolytic cascade. Here we present histological, biochemical, and genetic evidence that matriptase and prostasin define a single zymogen activation cascade in the epidermis, that matriptase acts upstream of prostasin, and that matriptase is an essential epidermal activator of the prostasin zymogen.

EXPERIMENTAL PROCEDURES

Mice—Experiments followed institutional guidelines. Matriptase knock-out and β-galactosidase-tagged matriptase knock-in mice were described in (8, 11).

Histological Stains—X-gal and immunohistochemical stains were performed as described (11). The mouse prostasin antibody has been described (13).

Generation of Soluble Recombinant Prostasin—HEK-293T cells were transfected with pCMV-SPORT6 expression vector containing full-length mouse prostasin (I.M.A.G.E clone

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We dedicate this paper to the memory of our friend Robert B. Dickson who passed away June 24, 2006.

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[3] The abbreviations used are: GPI, glycosylphosphatidylinositol; PN-1, protease nexin-1; X-gal, 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside; PI-PLC, phosphatidylinositol-specific phospholipase C.

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3600399) or full-length human prostasin cDNA (I.M.A.G.E clone 3138532) in pIRES2-EGFP (Clontech Laboratories, Mountain View, CA) using Polyfect reagent (Qiagen Inc., Valencia, CA). Cells were lysed 24–48 h after transfection using 50 mM Tris, pH 8.0, 150 mM NaCl, 0.1% SDS, 1% Nonidet P-40 with protease inhibitor mixture (Sigma). For phosphatidylinositol-specific phospholipase C (PI-PLC) treatment, washed cells were mechanically lifted from the plates by gentle pipetting, incubated with 1 unit/ml PI-PLC (Sigma) in phosphate-buffered saline for 4 h at 4 °C, and centrifuged for 10 min at 1000 × *g*, and the supernatant containing the PI-PLC-released proteins was collected. Protein concentrations were determined with a BCA protein assay Kit (Pierce). The concentration of PI-PLC-released prostasin was estimated by Western blot by serial dilution against a known concentration of activated prostasin obtained commercially.

Prostasin Zymogen Activation by Matriptase—Human soluble prostasin (~0.1 μM) was incubated with 1 or 10 nM recombinant active human matriptase serine protease domain (14) for 1 h at 37 °C in 50 mM Tris, pH 8.5, 100 nM NaCl. For complex formation, protease nexin-1 (PN-1), 700 mM PN-1 (R&D Systems, Minneapolis, MN) was added for 1 h at 37 °C. Proteins were analyzed by 4–12% reducing SDS-PAGE and Western blotting using a monoclonal anti-prostasin antibody (Pharmingen) and SuperSignal West Dura extended duration kit (Pierce).

Biochemical Analysis of Mouse Epidermis—Epidermis was isolated from newborn mice as described (9), ground into a fine powder in liquid nitrogen, homogenized in ice-cold lysis buffer (50 mM Tris at pH 7.4, 2 mM EDTA, 150 mM NaCl, 1% Nonidet P-40, 0.5% Triton X-100, 0.1% SDS) with protease inhibitor mixture set III (Calbiochem), cleared by centrifugation at 13,000 × *g* for 20 min at 4 °C, and protein concentration determined by the Bio-Rad protein assay (Bio-Rad). Proteins were resolved by 13% reducing SDS-PAGE and analyzed by Western blot using the monoclonal anti-prostasin antibody described above. Densitometric scanning of Western blots was performed using NIH Image software.

Real-time PCR—RNA was isolated from skin as described (8). The prostasin primers 5′-GGAGGCAAGGATGCCTGCCA-3′ and 5′-GAGAGTGGGCCCCCAGAGTCAC-3′ were used for quantitative real-time PCR. Prostasin expression levels were normalized against GAPDH mRNA levels in each sample, amplified with the primers 5′-GTGAAGCAGGCATCTGAGG-3′ and 5′-CATCGAAGGTGGAAGAGTGG-3′.

RESULTS AND DISCUSSION

Co-localization and Coordinated Expression of Matriptase and Prostasin during Terminal Epidermal Differentiation—To analyze expression of matriptase and prostasin in mouse epidermis, we used a knock-in mouse (11) that carries one wild type *matriptase* allele and one allele where the exons encoding the serine protease domain of matriptase have been replaced by a β-galactosidase marker gene (matriptase$^{+/E16\beta\text{-gal}}$ mice). This mouse strain synthesizes a matriptase-β-galactosidase fusion protein under transcriptional control of the endogenous *matriptase* gene and can be used as a sensitive marker for matriptase expression using X-gal staining. The co-localization of matriptase with prostasin was analyzed by immunohistochemistry of serial sections or, when staining intensity permitted, by immunohistochemical staining of X-gal-stained sections with prostasin antibodies to simultaneously visualize the two proteases. As described recently (11), X-gal staining of the skin of matriptase$^{+/E16\beta\text{-gal}}$ mice showed that matriptase expression was confined to the uppermost living layer of the interfollicular epidermis of 7-day-old mouse pups (Fig. 1*A*). Interestingly, immunohistochemical staining of interfollicular epidermis revealed a similar localization of prostasin (Fig. 1*B*). Combined X-gal staining for matriptase and immunohistochemical staining for prostasin revealed overlapping expression in interfollicular epidermis at this age (Fig. 1*C*) as well as in newborn pups (Fig. 1*E*), demonstrating that the two membrane-associated proteases have the potential to physically interact *in vivo*. To determine the time of onset of expression of matriptase and prostasin in the developing epidermis, combined X-gal staining and immunohistochemistry of matriptase$^{+/E16\beta\text{-gal}}$ embryos at embryonic day (E) 14.5 to E16.5 was performed. At E14.5 and E15.5 no expression of either of the two serine proteases could be detected (Fig. 1, *F* and *G*). At E16.5, however, both matriptase and prostasin were expressed (Fig. 1*H*), temporally correlating with stratum corneum formation and the onset of acquisition of the epidermal barrier (15). X-gal staining combined with immunohistochemical staining for the marker of basal keratinocytes, cytokeratin-14, demonstrated the clear suprabasal expression of the two proteases at this developmental stage (Fig. 1*I*).

Matriptase Activates the Prostasin Zymogen in a Cell-free System—Previous studies have shown that the matriptase zymogen undergoes autoactivation during synthesis (16, 17). In contrast, the prostasin zymogen is unable to undergo autoactivation and a physiological activator of prostasin has not been identified (18). Activation of the prostasin zymogen occurs by endoproteolytic cleavage after Arg[12] within the amino acid sequence QPR[12]-ITG, a cleavage reaction that could be mediated by matriptase, based on studies of matriptase specificity (19). These observations suggested that matriptase would act upstream of prostasin if the two proteases were part of the same zymogen cascade. To test this, we expressed prostasin in HEK-293T cells. The recombinant prostasin was released from the cell surface with PI-PLC to generate a soluble form of prostasin that presented as a dominant 40-kDa species and two minor species with slightly higher and lower electrophoretic mobility when analyzed by SDS-PAGE and Western blotting under reducing conditions (Fig. 2, *lane 1*). Prostasin generated this way appeared to be predominantly in the zymogen form, as it did not form complexes with the cognate serpin PN-1, which forms SDS-stable complexes with active prostasin (13) but not with the prostasin zymogen (Fig. 2, compare *lane 2* with *lanes 4* and *6*). This suggested that the faint higher and lower molecular weight species both could represent glycosylation variants of the zymogen (13). Activation of the prostasin zymogen leads to the formation of active two-chain prostasin, which can be distinguished from the prostasin zymogen by a small increase in electrophoretic mobility in high-percentage SDS-PAGE gels after reduction of the single disulfide bridge that links the two chains (13). Exposure of soluble prostasin zymogen to either 1

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FIGURE 1. **Matriptase and prostasin co-localize and are coordinately expressed in mouse epidermis.** X-gal staining (*A*), prostasin immunohistochemistry (*B*), combined X-gal staining and prostasin immunohistochemistry (*C–H*), and combined X-gal staining and cytokeratin-14 (*K14*) immunohistochemistry (*I*) of the epidermis of matriptase$^{+/E16\beta\text{-gal}}$ mice (*A*, *C* and *E–I*) of 7-day-old (*A–D*) or newborn (*E*) pups, or E14.5 (*F*), E15.5 (*G*), and E16.5 embryos (*H* and *I*). Matriptase (*cyan*, examples with *arrows* in *A*, *C*, *E*, *H*, and *I*) and prostasin (*brown*, examples with *arrowheads* in *B*, *C*, *E*, and *H*) are co-expressed in the uppermost terminally differentiating layer of the epidermis of 7-day-old (*C*) and newborn (*E*) mice. No expression of either membrane-associated protease is observed at E14.5 (*F*) or E15.5 (*G*), but both matriptase (*cyan*, examples with *arrows*) and prostasin (*brown*, examples with *arrowheads*) are expressed in the developing epidermis at E16.5 (*H*), located in suprabasal keratinocytes (*I*), as revealed by combined X-gal staining for matriptase (*cyan* examples with *arrowheads*) and cytokeratin-14 staining (*brown*, examples with *open arrowheads*). Sections were counterstained with hematoxylin to visualize nuclei. *Size bars*: *A–D* and *F–I*, 20 μm. *E*, 10 μm.

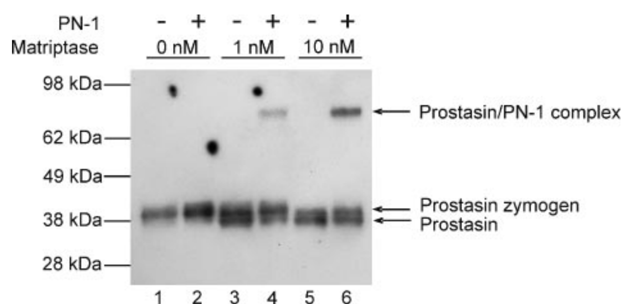

FIGURE 2. **Matriptase converts prostasin zymogen to active prostasin.** Human prostasin zymogen was expressed in HEK-293T cells and released from the surface of cells by hydrolysis of the GPI anchor with PI-PLC. Soluble prostasin zymogen (~0.1 μM) was incubated for 1 h at 37 °C with buffer (*lanes 1* and *2*), 1 nM (*lanes 3* and *4*), or 10 nM (*lanes 5* and *6*) soluble active human matriptase. At the end of the incubation, buffer (*lanes 1*, *3*, and *5*) or 700 nM PN-1 (*lanes 2*, *4*, and *6*) was added for 1 h a 37 °C. Proteins were analyzed by SDS-PAGE under reducing conditions, followed by Western blot with a monoclonal prostasin antibody. The positions of the prostasin zymogen, activated prostasin, and prostasin-PN-1 complexes are indicated. The positions of molecular mass markers (kDa) are indicated on the *left*.

or 10 nM active matriptase protease domain led to the formation of a prominent immunoreactive band with the mobility expected for active prostasin (Fig. 2, compare *lane 1* with *lanes 3* and *5*). The percentage of prostasin zymogen converted to this higher mobility species by matriptase varied between prostasin preparations and was never complete, even with very high matriptase concentrations (data not shown). This suggested that not all recombinant prostasin released from HEK-293T cells by PI-PLC was in a conformational state that permitted the activation by matriptase. To confirm that the cleavage of the prostasin zymogen by matriptase leads to the formation of active prostasin, we incubated untreated and matriptase-treated prostasin with PN-1 and detected prostasin-PN-1 complexes by Western blotting using anti-prostasin antibodies. In the absence of preincubation with matriptase, no prostasin-PN-1 complex was observed (Fig. 2, *lane 2*). However, when prostasin zymogen was first exposed to matriptase and then incubated with PN-1, a prominent 85-kDa molecular mass complex that was immunoreactive with anti-prostasin antibodies was observed (Fig. 2, compare *lane 2* with *lanes 4* and *6*). Taken together, these data show that the matriptase catalytic domain is capable of converting the zymogen of prostasin to active, serpin-reactive prostasin in a cell-free system.

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Lack of Proteolytically Processed Prostasin Zymogen and Prostasin Zymogen Accumulation in Matriptase-ablated Epidermis—The striking phenotypic similarities between matriptase- and prostasin-deficient mice (Table 1), when combined with our data presented above, strongly suggested that matriptase could be a physiological activator of the prostasin zymogen during terminal epidermal differentiation and predicted the existence of a matriptase-prostasin zymogen cascade in epidermal differentiation. To definitively test this, we determined the state of activation of epidermal prostasin in the presence and absence of matriptase. Protein lysates were prepared from the epidermis of newborn wild type mice and their matriptase-deficient littermates (8), and prostasin processing was analyzed by the separation of the protein lysates by reducing SDS/PAGE on high percentage gradient gels, followed by Western blotting using prostasin antibodies (Fig. 3*A*). In wild type epidermis, prostasin was found in two forms: a 39-kDa form, compatible with the apparent molecular mass of the prostasin zymogen, and a 37-kDa form, compatible with activated prostasin (Fig. 3, *lanes 3–5*). In contrast, in matriptase-ablated epidermis, prostasin was exclusively found in the higher molecular mass 39-kDa zymogen form. Furthermore, the 39-kDa form of prostasin was frequently more abundant in matriptase-deficient epidermis (Fig. 3, *lanes 6–8*, and data not shown). This increase in prostasin zymogen did not appear to be caused by a corresponding increase in the steady state level of prostasin mRNA as judged by real-time PCR analysis (data not shown), suggesting that the accumulation was caused by loss of zymogen activation by matriptase. To quantitatively assess the formation of active prostasin in matriptase-sufficient and -deficient epidermis, protein extracts from the epidermis of five matriptase-sufficient and five matriptase-deficient littermates were analyzed by Western blot. The fraction of total prostasin presenting as active prostasin was determined by densitometric scanning of the blot (Fig. 3*B*). In matriptase-sufficient epidermis, 40–51% of prostasin was in the active two-chain form, while the amount of active prostasin in matriptase-deficient epidermis was below the level of detection. Taken together, these data provide definitive evidence that matriptase is essential for the proteolytic processing of prostasin in the epidermis.

TABLE 1
Phenotypic comparison of matriptase and prostasin-deficient mice
Data were compiled from Refs. 8, 9, and 12.

Parameter	Matriptase−/−	Prostasin−/−
Survival	Postnatal lethality	Postnatal lethality
Body weight and body length	Reduced	Reduced
External appearance of skin	Reddish and wrinkled	Reddish and wrinkled
Hair follicles	Immature	Immature
Thymus	Hypoplastic	Hypoplastic
Inwards epidermal barrier function	Impaired	Impaired
Outwards epidermal barrier function	Impaired	Impaired
Corneocytes	Enlarged	Enlarged
Epidermal lipid composition	Abnormal	Abnormal
Filaggrin	Absent	Absent
Profilaggrin processing	Impaired	Impaired
Epidermal differentiation markers besides profilaggrin/filaggrin	Normal	Normal

The coordinated expression and co-localization of matriptase and prostasin in the epidermis and the activation of prostasin zymogen by matriptase *in vitro* and *in vivo*, when combined with the identical phenotype of matriptase and prostasin-deficient mice, provides compelling evidence for the existence of a matriptase-prostasin zymogen activation cascade regulating terminal epidermal differentiation. This suggests that loss of profilaggrin processing, defective corneocyte maturation, and abnormal intercorneocyte lipid extrusion in matriptase-deficient epidermis may all be secondary to loss of prostasin zymogen activation. Increasing evidence indicates that terminal epidermal differentiation is regulated by a sophisticated cascade of serine proteases and serine protease inhibitors that all become expressed in transitional layer cells during stratum corneum formation and undergo sequential activation during stratum corneum maturation and shedding (8, 11, 20–29). The serine proteases currently proposed to be critical for stratum corneum formation include matriptase, prostasin, stratum corneum tryptic enzyme, stratum corneum chymotryptic enzyme, furin, and profilaggrin processing endopeptidase1. Additionally, serine protease inhibitors, including the Kunitz-type serine protease inhibitor, hepatocyte growth factor

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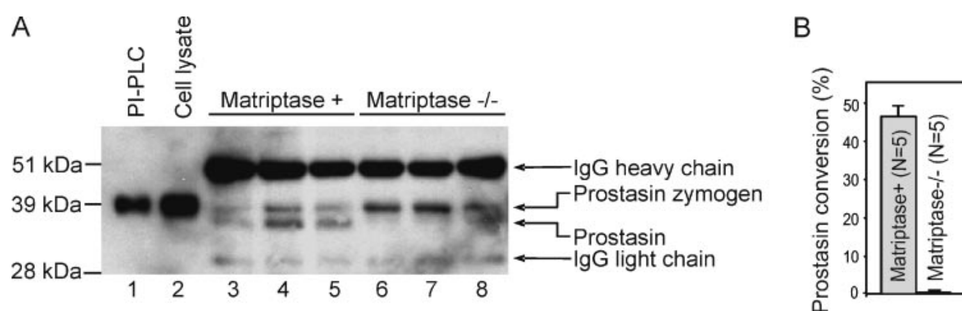

FIGURE 3. **Matriptase is required for prostasin activation in mouse epidermis.** *A*, protein lysates were prepared from the epidermis of three newborn matriptase-sufficient (*lanes 3–5*) and three matriptase-deficient littermate mice (*lanes 6–8*) and subjected to SDS-PAGE under reducing conditions followed by Western blot using a mouse monoclonal anti-prostasin antibody. *Lanes 1* and *2* are lysates of concentrated conditioned medium from PI-PLC-treated HEK-293T cells transfected with a mouse prostasin expression plasmid (*PI-PLC*) and cell lysate from mouse prostasin-transfected HEK-293T cells (*Cell lysate*), respectively. The positions of the prostasin zymogen and active prostasin are indicated. The positions of mouse IgG heavy chain and light chain, which are recognized by the secondary antibody, are also indicated. The position of the molecular mass markers (kDa) is indicated on the *left*. *B*, quantitative analysis of prostasin zymogen activation. Epidermal lysates from five newborn matriptase-sufficient and five matriptase-deficient littermate mice were subjected to SDS-PAGE and Western blotting. The fraction of active prostasin as a function of total prostasin in each epidermal lysate was estimated by densitometric scanning of the blot. Error bars indicate standard deviation. $p < 0.008$, Wilcoxon rank-sum test, two-tailed.

activator inhibitor-1, and the Kazal-type, multidomain serine protease inhibitor, SPINK5, could have key roles in regulating the activity of one or several of these proteases in both human and mouse epidermis. Pertubations causing increased or decreased serine protease activity in the upper epidermis have serious pathophysiological consequences. Thus, ablation of matriptase or prostasin prevents acquisition of the epidermal barrier by blocking terminal epidermal differentiation (9, 12), while, conversely, SPINK5 deficiency or overexpression of stratum corneum chymotryptic enzyme compromises the epidermal barrier through premature epidermal differentiation and accelerated shedding of the stratum corneum (21–23, 26). It remains to be determined whether a single proteolytic cascade or multiple independent proteolytic cascades are operational during terminal epidermal differentiation. Previously, stratum corneum tryptic enzyme has been proposed to act upstream of stratum corneum chymotryptic enzyme during the desquamation of stratum corneum (25), and our results now show that matriptase acts upstream of prostasin during terminal epidermal differentiation. In addition to loss of epidermal barrier formation, matriptase deficiency also severely impairs stratum corneum desquamation (9). These observations suggest the intriguing hypothesis that the four serine proteases and SPINK5 could be part of a single zymogen cascade with a complexity reminiscent of other serine protease zymogen cascades, such as those involved in blood coagulation or digestion.

Matriptase and prostasin both have a fairly wide expression in epithelial tissues and both are frequently dysregulated in epithelial tumors (10, 30–43). The role of matriptase as a prostasin zymogen activator and the potential function of the matriptase-prostasin cascade in other physiological processes and in pathophysiological processes, such as cancer, are clearly important areas for future study.

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