[Frontiers in Bioscience 12, 5060-5070, September 1, 2007]

Matriptase-dependent cell surface proteolysis in epithelial development and pathogenesis

Thomas H. Bugge, Karin List, Roman Szabo

Proteases and Tissue Remodeling Unit, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD

TABLE OF CONTENTS

1. Abstract
2. Introduction: identification of matriptase as a new epithelial membrane serine protease
3. Tissue localization of matriptase
3.1. Matriptase expression during embryogenesis
3.2. Postnatal matriptase expression
4. Physiological functions of matriptase
5. Pathogenesis of dysregulated matriptase activity
6. Perspectives
7. Acknowledgements
8. References

1. ABSTRACT

Matriptase is an epithelial type II transmembrane serine protease with a complex modular structure and sophisticated activation mechanism. Reduced matriptase activity in mice or humans is associated with incomplete terminal differentiation of epidermis, epidermal appendages, oral epithelium, and, likely, other epithelial structures. Preliminary evidence indicates that matriptase is part of a serine protease zymogen activation cascade that regulates epithelial cell proliferation and fate. Matriptase activity must be tightly controlled in epithelial tissues by transcriptional and posttranslational mechanisms, as matriptase dysregulation can cause embryonic demise as well as malignant transformation.

2. INTRODUCTION. IDENTIFICATION OF MATRIPTASE AS A NEW EPITHELIAL MEMBRANE SERINE PROTEASE

Matriptase was identified in 1993 as a novel protease with prominent gelatinolytic activity that was expressed by cultured human breast cancer cells (1). The *matriptase* cDNA was cloned independently by five different groups at the end of the millennium and the protease deduced from the translation of the cDNA was published under the names matriptase, membrane-type serine protease1, (MT-SP1), tumor-associated differentially expressed gene-15 (TADG-15), epithin, and SNC19 (2-7). The *matriptase* gene was assigned the name *suppression of*

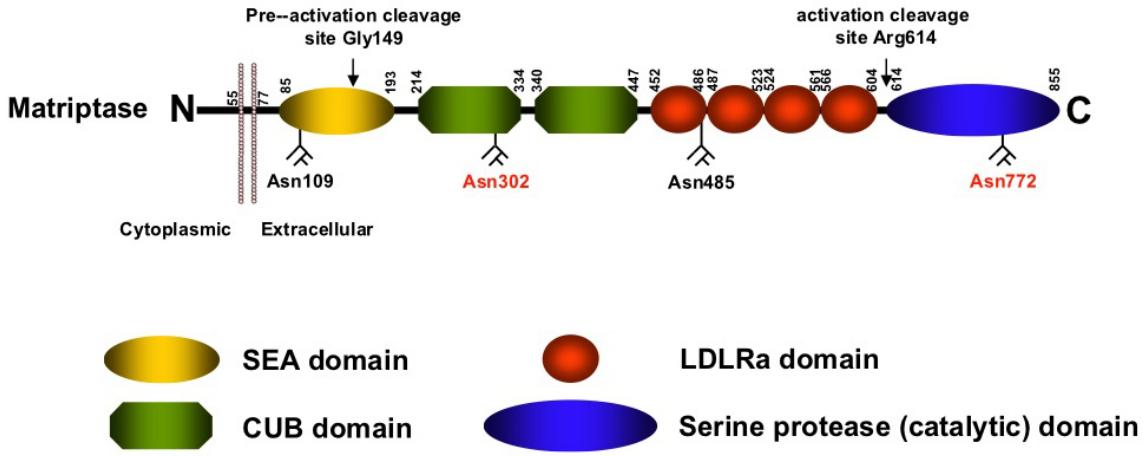

Figure 1. Structure of matriptase. Matriptase is a type II transmembrane protein consisting of a short cytoplasmic tail (amino acids 1-54), a single pass transmembrane domain (amino acids 56-77), a SEA domain (amino acids 85-193), two CUB domains (amino acids 214-334 and 340-447), four LDLRa domains (amino acids 452-486, 487-523, 524-561, and 566-604), and a C-terminal serine protease domain (amino acids 614-855). Matriptase is proteolytically-activated by an initial cleavage of the SEA domain after Gly149 (arrow), followed by autocatalytic cleavage after Arg614 within the conserved activation cleavage site (arrow). Matriptase is glycosylated at Asn109, Asn302, Asn485, and Asn772. The Asn302 and Asn772 glycans (denoted in red) are required for matriptase activation.

tumorgenecity14 (ST14). The deduced amino acid sequence of matriptase revealed it to be the sixth member of the type two transmembrane serine proteases (TTSPs), which currently comprises 20 members in human and mice (8-10, Szabo et al., unpublished data). The molecular cloning of two closely related proteases, matriptase-2 and matriptase-3 were reported thereafter (11-13). *ST14* orthologs are present in all nine vertebrate genomes analyzed, including human, chimpanzee, dog, mouse, rat, chicken, zebrafish, spotted green pufferfish, and tiger pufferfish, indicating evolutionarily conserved functions of matriptase (14).

Analysis of the matriptase cDNA revealed a complex multi-domain transmembrane serine protease (Figure 1). Like all TTSPs, matriptase lacks a classical signal peptide. Instead, an N-terminal signal anchor, which is not removed during synthesis, serves as a single pass transmembrane domain that positions the protease in the plasma membrane as a type II integral membrane protein with a cytoplasmic N-terminus and an extracellular C-terminus (15). The specific function of the short intracellular domain of matriptase (residues 1-54) is presently unknown, but the domain has been reported to interact directly with the actin-associated protein filamin, and likely serves to locate matriptase to microdomains of the plasma membrane (16). The extracellular region of matriptase contains a single SEA (sea urchin sperm protein, enteropeptidase, agrin) domain (residues 85-193), two CUB (Cls/Clr, urchin embryonic growth factor, bone morphogenetic protein-1) domains (residues 214-334 and 340-447), and four LDLRa (low density lipoprotein receptor-like protein type a repeat) domains (residues 452-486, 487-523, 524-561, and 566-604). These non-catalytic domains appear to play an essential role in the cellular localization, activation, inhibition, and, possibly, the substrate specificity of matriptase. The C-terminal serine protease domain of matriptase (residues 614-855) belongs to the S1 clan of trypsin-like serine proteases and is similar to the serine protease domains of other TTSPs and non-TTSP trypsin-like serine proteases (10, 17). Activation of the matriptase zymogen requires two sequential endoproteolytic cleavages. The single-chain proenzyme is first cleaved after Gly149 located in a conserved Gly-Ser-Val-Ile-Ala motif in the N-terminal SEA domain. This initial cleavage reaction is quite unusual inasmuch as it may occur by non-enzymatic hydrolysis of the peptide bond, as has been observed for other SEA domains (16, 18, 19). SEA-domain-cleaved matriptase remains tightly attached to the cell surface via strong non-covalent interactions within the SEA domain (19), and subsequently is converted to the catalytically active conformation by proteolytic cleavage after Arg614 within the highly conserved activation cleavage site Arg-Val-Val-Gly-Gly in the serine protease domain. The activation site cleavage appears to be at least, in part, autocatalytic, as mutations in any of the catalytic triad residues abrogates activation site cleavage (20). The autoactivation of matriptase appears to be controlled by the LDLRa domains within the stem region, and by carbohydrate-containing structural determinants within the first CUB domain and the serine protease domain (20).

3. TISSUE LOCALIZATION OF MATRIPTASE

Systematic matriptase expression studies have been performed in the human placenta and in adult human tissues by *in situ* hybridization and immunohistochemistry, and in mouse embryos and adult tissues by *in situ* hybridization and by enzymatic gene trapping using a promoterless beta-galactosidase gene trap (21-28).

3.1. Matriptase expression during embryogenesis

Embryo proper: Matriptase is expressed in the ectoderm and the epithelial lining of several developing tissues of the embryo proper, beginning at mouse embryonic day (E)9.5. These tissues include the olfactory placode, the entrance to Rathke's pouch, the mandibular component of the first branchial arch, the pharyngeal region of the foregut, the midgut/hindgut region, the otic pit/otic vesicle, and the apical ectodermal regions of the four limbs. At E14.5 and E16.5, respectively, matriptase also becomes strongly expressed in the developing hair follicles and the interfollicular epidermis (22, 24).

Extraembryonic tissues: Matriptase expression is first detected in mouse extraembryonic tissues at E8.5, with sustained expression of the membrane protease throughout the period of placental labyrinth formation. Matriptase expression in extraembryonic tissues is narrowly restricted to a single layer of chorionic trophoblast precursors known as chorionic stem cells from which the placental labyrinth develops. This pattern of expression of matriptase is also observed in the human placenta (24).

3.2. Postnatal matriptase expression

Matriptase is expressed in the epithelial component of most major organ systems (Table 1). Mesenchymally-derived organ systems, such as the central and peripheral nervous system and the circulatory system, are generally devoid of matriptase under homeostatic conditions. The specific pattern of matriptase expression is highly conserved between mice and humans, suggesting that the membrane protease has phylogenetically conserved functions in mammals (21-23).

Integumentary system and oral cavity: Matriptase is expressed in the stratum granulosum, transitional cells, and stratum corneum of the interfollicular epidermis, and stratified squamous epithelium of the cornea. Matriptase is also highly expressed in the follicular epidermis, where the membrane protease locates to hair matrix cells, companion layer, inner root sheath, sebocytes of growth phase (anagen) hair follicles, and the ductal epithelium of mammary glands. Strong matriptase expression is also observed in the oral cavity. This includes both keratinized epithelium of the tongue and hard palate, the non-keratinized epithelium of the lip and the floor of the mouth, mucus glands of the tongue, and the ductal epithelium of the submandibular and sublingual glands.

Gastrointestinal tract: Matriptase is found in both the upper and lower gastrointestinal tract, specifically locating to the bile duct epithelium and mucosal epithelial cells of the gall bladder, squamous epithelium of the esophagus, squamous mucosa of the forestomach, foveolar, and parietal cells of the glandular stomach, tall cylindrical villus and columnar absorptive cells of the jejunum/ileum colon, and columnar absorptive cells of the colon.

Respiratory system*:* High expression of matriptase is observed in ciliated and glandular epithelium of the nasal cavity, and ciliated columnar epithelium of the trachea and bronchioles, where the membrane protease locates to the apical surface.

Urogenital system: Matriptase is selectively expressed in distal and collecting tubules of both the cortex and the medulla of the kidney. Prominent matriptase expression is also observed in the transitional epithelium of the urinary bladder and ureter, and in cuboidal cells of the prostate epithelium, columnar cells of the seminal vesicle and epididymis, and in pseudo-stratified epithelium of the vas deferens. In the female reproductive tract, matriptase is prominently expressed in the luminal and glandular epithelium of the uterus and the oviduct, but undetectable in the ovary.

Other sites of matriptase expression: Within the hematopoietic/lymphatic system, matriptase expression has only been detected in ectodermally-derived epithelioreticular cells and Hassal's corpuscles of the thymus, in circulating monocytes, and in peritoneal macrophages. In the skeletal system, matriptase is highly expressed in the epithelial, enamel-forming ameloblasts of developing teeth, compatible with its epithelial expression preference.

4. PHYSIOLOGICAL FUNCTIONS OF MATRIPTASE

Insights into the physiological functions of matriptase have been gained by the generation and analysis of *ST14* null mutant mice. Collectively, these studies have revealed critical functions of matriptase in the development of multiple epithelial tissues, consistent with the wide, species-conserved epithelial expression of the membrane serine protease. Tissues that have, so far, been shown to be dependent on matriptase for proper development include epidermis, hair follicles, oral epithelium, and thymic epithelium.

Although matriptase is widely expressed during development, mice with null mutations in the *ST14* gene develop to term, showing that the membrane protease does not have critical non-redundant functions in the development of either extraembryonic or embryonic tissues. However, matriptase-deficient mice die shortly after birth, due to catastrophic dehydration caused by greatly impaired epidermal barrier function (29, 30). The compromised barrier function in *ST14* null mice is not limited to the epidermis, and includes, at least, keratinized epithelium within the oral cavity (22).

The epidermal barrier resides in the uppermost layer of the epidermis, the stratum corneum, and is composed of two interconnecting structures: a complex extracellular lipid mixture that self-assembles into an ordered multilayer structure known as the lipid lamellae (31, 32), and a water-impermeable insoluble cornified envelope that is deposited on the inner surface of the plasma membrane of terminally differentiated keratinocytes termed corneocytes (Figure 2A). Both of these structures are generated in the transitional cell layer of the epidermis, which is the first cell layer in the interfollicular epidermis that expresses matriptase (Figure 2A) (22, 33, 34). The corneocytes within the stratum corneum are connected by cell-cell junctions, termed corneodesmosomes, and the

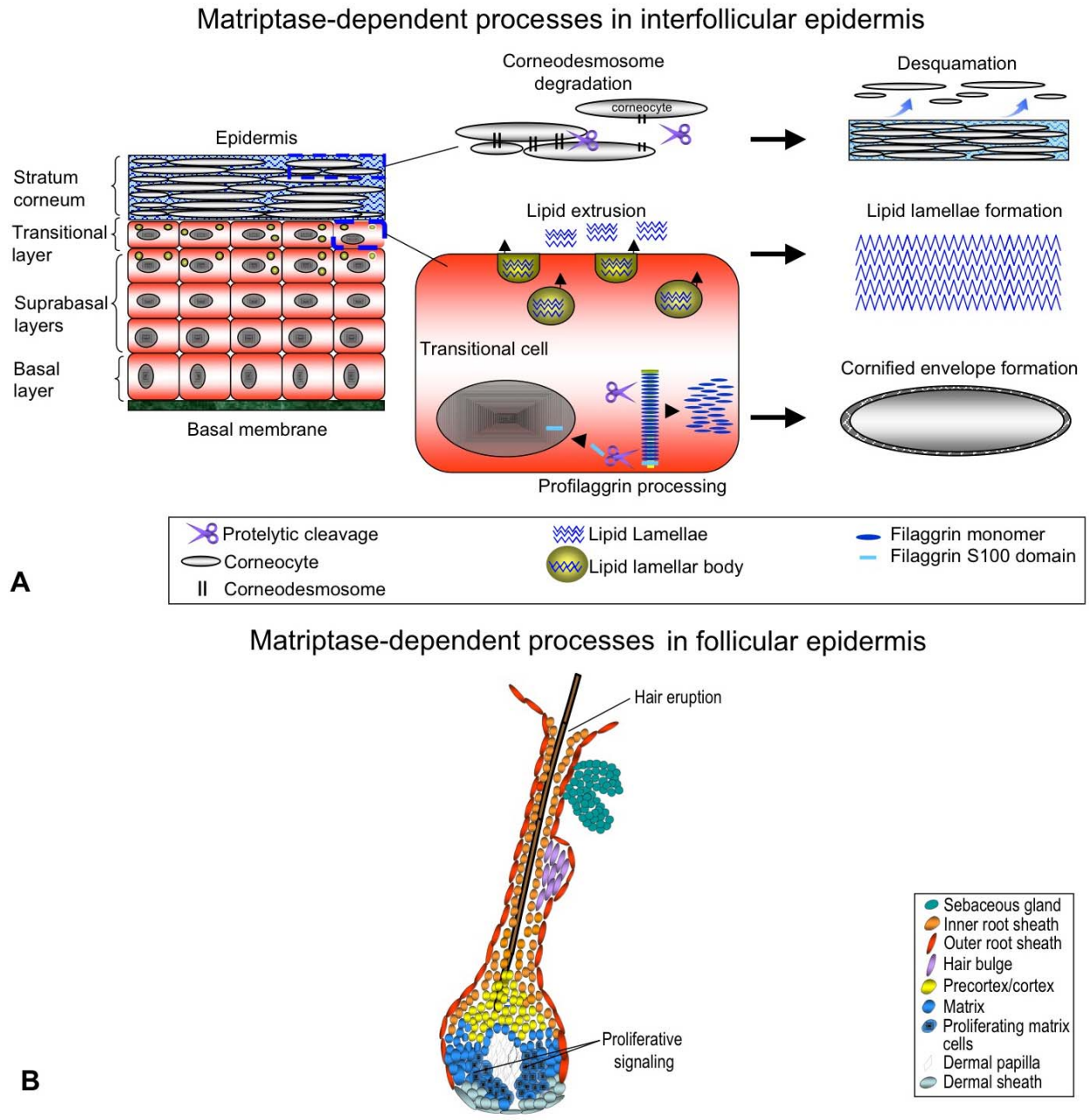

Figure 2. Functions of matriptase in the epidermis. A. The epidermal barrier function resides in the stratum corneum, the outermost layer of the interfollicular epidermis. Barrier function is conferred by a water-impermeable cornified envelope surrounding terminally differentiated keratinocytes (corneocytes) and by epidermal lipids (lipid lamellae) in which corneocytes are embedded. Stratum corneum thickness is regulated by the proteolytic degradation of cell-cell junctions between corneocytes (corneodesmosomes). Matriptase is expressed in the transitional cell layer and in the stratum corneum. In the transitional cell layer, matriptase facilitates the proteolytic processing of profilaggrin into filaggrin monomers that are structural components of the cornified envelope (arrowhead pointing right) and a regulatory S-100 protein that translocates to the nucleus and promotes terminal keratinocyte differentiation (arrowhead pointing left). In the uppermost part of the stratum corneum, matriptase is required for the proteolytic degradation of corneodesmosomes, leading to stratum corneum shedding (desquamation). B. The hair follicle is a cycling organ displaying alternating phases of hair growth and rest. Hair follicle stem cells located in the hair bulge region give rise to matrix cells that migrate to the hair follicle bulb where they undergo vigorous proliferation, move upwards and differentiate to form the various layers of the hair follicle. Matriptase is expressed in several keratinocyte populations located in the bulb region during the hair growth phase and stimulates the growth of hair matrix cells, possibly through the proteolytic activation of latent growth factors produced by dermal papilla cells. Matriptase also has a second role in the formation of the hair canal of erupting whisker hairs.

Table 1. Matriptase and prostasin expression in human and mouse tissues

Tissue/Organ	Sites of Expression	Co-localization with prostasin[1]
Skin and oral cavity		
Epidermis	Keratinocytes in stratum granulosum, transitional layer, stratum corneum (h, m[2])	Yes
Hair follicle	Inner rooth sheath (IRS), matrix, medulla, cortex, and cuticle (h [3]N.D., m)	Yes, IRS only
Oral cavity	Keratinocytes in tongue, hard palate, bucca, gingiva, and lip (h N.D., m)	Yes
Salivary gland	Ductal epithelium (h,m), serous acini in sublingual gland (m)	Yes, ductal epithelium only
Teeth	Ameloblasts (h N.D., m)	No
Respiratory system		
Nasal cavity	Ciliated and glandular epithelium (h, m)	Yes
Trachea	Epithelium (h N.D., m)	Yes
Lungs	Bronchial (h,m) and alveolar (h) epithelium	Yes
Digestive system		
Esophagus	Epithelial cells (h, m)	Yes
Stomach	Epithelium (h, m)	Yes
Small intestine	Epithelium of jejunum and ileum (h, m)	Yes
Colon	Epithelium (h, m)	Yes
Liver	Bile duct epithelium (h N.D., m)	No
Gallbladder	Epithelium (h, m)	N.D.
Pancreas	Secretory duct epithelium (h)	N.D.
Urogenital system		
Urinary bladder	Transitional epithelium (h, m)	Yes
Ureter	Transitional epithelium (h N.D., m)	Yes
Kidney	Epithelium of proximal, distal, and collecting tubules (h, m)	Yes
Prostate	Epithelium (h N.D., m)	Yes
Seminal vesicle	Epithelium (h, m)	No
Epididymis	Epithelium (h, m)	No
Vas deferens	Epithelium (h N.D., m)	Yes
Ovary	Surface epithelium (h)	N.D.
Oviduct	Epithelium (h, m)	No
Uterus	Luminal and glandular epithelium (h, m)	No
Other		
Eye	Cornea (h N.D., m)	No
Mammary gland	Ductal epithelium (h, m)	No
Thymus	Epithelial reticulum cells, Hassall's bodies (m)	No
Thyroid	Follicular epithelium (h, m N.D.)	N.D.
Adrenal medulla	Cortex zona fasciculata, Cortex zona reticularis (h, m N.D.)	N.D.
Blood	Circulating monocytes, macrophages (h, m)	N.D.

[1]Colocalization systematically studied in mouse tissues only. [2]h – human; m – mouse. [3]N.D. – Not done. Compiled from references 20-22, 26, 27.

overall thickness of the stratum corneum is controlled by shedding of the outermost layer of corneocytes by regulated proteolysis of specific desmosomal proteins. Three specific defects have been uncovered in matriptase-deficient mouse epidermis (Figure 2A) (30). 1) The proteolytic processing of the abundant epidermal polyprotein profilaggrin into filaggrin monomer units and an N-terminal filaggrin S-100 regulatory protein is abrogated. In this respect, it should be noted that the silencing of the *ST14* gene in organotypic human skin cultures also abrogates profilaggrin processing, showing that the requirement of matriptase for the processing of the polyprotein is not mouse-specific (35). 2) The extrusion of the extracellular lipids that form the lipid lamellae is greatly reduced. 3) The shedding of the stratum corneum via proteolysis of desmosomal proteins is impaired. The impediment of profilaggrin processing and extracellular lipid extrusion both likely have a critical role in epidermal barrier disruption, because mutations in either the *profilaggrin* gene or in genes involved in epidermal lipid biogenesis compromise epidermal barrier function (33, 36-41).

The specific molecular mechanism by which matriptase facilitates profilaggrin processing, lipid extrusion, and stratum corneum shedding still needs to be elucidated. However, recent studies indicate that matriptase may be part of an epidermal zymogen activation cascade and acts upstream of the glycosylphosphatidylinositol-linked membrane serine protease prostasin/(CAP1/PRSS8) to facilitate terminal epidermal differentiation. This hypothesis is supported by the identical phenotypes of epidermal matriptase and prostasin ablation in mice (loss of profilaggrin processing, abnormal epidermal lipid extrusion), the temporal and spatial co-localization of matriptase and prostasin in the epidermis, the efficient activation of the prostasin zymogen by matriptase *in vitro*, and the absence of active prostasin in *ST14* null epidermis (26, 42). In this respect is noteworthy that matriptase and prostasin also colocalize in a variety of other epithelia (Table 1). These include simple, stratified, and pseudo-stratified epithelium of the integumentary system, digestive tract, respiratory tract, and urogenital tract, making matriptase a candidate activator of prostasin in other physiological settings, besides epidermal differentiation (21). A large number of trypsin-like serine proteases and serine protease inhibitors are expressed in the upper layer of the epidermis, several of which have documented roles in regulating terminal epidermal differentiation (42-52). It is tempting to speculate that matriptase could be part of a finely tuned epidermal zymogen activation cascade consisting of multiple serine proteases and serine protease inhibitors that together regulate stratum corneum formation and shedding.

Keratinized oral epithelium and Hassal's corpuscles of the thymic epithelium are stratified squamous epithelia that are closely related to the interfollicular epidermis and express a number of interfollicular epidermis differentiation markers including profilaggrin (21, 53-58). In the oral cavity, matriptase deficiency causes loss of epithelial barrier function, and in the thymus, which is not exposed to the external environment, loss of matriptase dramatically accelerates apoptosis of immature CD4+/CD8+ thymocytes, leading to thymocyte depletion. This latter finding suggests that the thymic epithelium provides a microenvironment that promotes thymocyte survival in a matriptase-dependent manner.

Whereas in interfollicular epidermis and oral epithelium matriptase is exclusively expressed in terminally differentiating cells, in hair follicles the membrane serine protease is expressed in keratinocyte populations that include rapidly proliferating hair matrix cells of anagen hair follicles (Figure 2B). Consistent with a role of matriptase in regulating hair follicle cell proliferation, *ST14* null mice display a generalized hair follicle hypoplasia. Matriptase efficiently converts pro-hepatocyte growth factor and pro-macrophage stimulating protein-1 to active two-chain forms: serving, respectively, as ligands for c-met and c-ron, two receptor tyrosine kinases that are known to be involved in hair growth regulation (28, 59, 60). Hepatocyte growth factor and macrophage stimulating protein-1 are abundantly expressed by dermal papillary cells immediately juxtaposing hair matrix cells that express matriptase, c-met, and c-ron (59-63). It is therefore a tempting, though untested, hypothesis that matriptase promotes hair growth by regulating the bioavailability of hepatocyte growth factor and macrophage stimulating protein-1.

The early lethality of *ST14* null mice has complicated the analysis of the role of matriptase in many postnatal physiological processes. Recently, however, a rare congenital human disorder, autosomal recessive ichthyosis with hypotrichosis (ARIH) was linked to homozygosity for a c.2672G→A mutation located in exon 19 of the *ST14* gene. This mutation results in a Gly → Arg substitution in residue 827 of the matriptase protein (64). This amino acid residue is phylogenetically highly conserved and it is located near the active site of the serine protease domain, as deduced from the crystal structure of matriptase (17). It is very likely that the Gly to Arg substitution substantially reduces the catalytic activity of matriptase, and that ARIH therefore is caused by homozygosity for an *ST14* hypomorphic allele. Consistent with this hypothesis, ARIH patients present with proliferative and retention ichthyosis, indicative of impaired barrier function, as well as hair follicle hypoplasia manifested by fragile, brittle, dry, lusterless, and slow growing scalp hair, resembling skin from *ST14* null mice transplanted to immunocompromized recipient mice (30, 64). Interestingly, ARIH has also been associated with tooth and eye abnormalities, in agreement with the expression of matriptase in corneal epithelium and enamel-producing ameloblasts of developing teeth.

5. PATHOGENESIS OF DYSREGULATED MATRIPTASE ACTIVITY

Embryonic development: Although matriptase does not have critical non-redundant roles in embryonic development, recent studies unexpectedly have shown that matriptase proteolytic activity, nevertheless, must be tightly regulated during development. Hepatocyte growth factor activator inhibitor(HAI)-1 is a transmembrane Kunitz-type serine protease inhibitor that displays near ubiquitous co-expression with matriptase in embryonic and adult tissues and forms inhibitor complexes with matriptase *in vivo* (24, 25, 65). Ablation of the HAI-1 gene leads to embryonic demise at mid-gestation, secondary to placental insufficiency caused by the absence of placental labyrinth formation. This abrogation of placental labyrinth formation is the consequence of the disruption of the epithelial integrity of a small population of matriptase-expressing chorionic trophoblasts that are the precursors of placental labyrinth trophoblasts. Interestingly, however, embryos with combined HAI-1 and *ST14* null mutations develop normally and are outwardly indistinguishable from *ST14* null mutant mice at birth (24). In light of the proposed role of matriptase in epithelial malignancy (see below) it should be noted that the epithelial disruption caused by increased embryonic matriptase activity recapitulates certain key features of epithelial multi-stage carcinogenesis, including basement membrane disruption, loss of E-cadherin, and loss of membrane-associated b-catenin (24).

Epithelial carcinogenesis: Matriptase is expressed with remarkable consistency in epithelial tumors of diverse origin and in cell lines derived from these tumors. In contrast, matriptase does not appear to be expressed in tumors of mesenchymal origin, suggesting a specific function of the membrane protease in epithelial carcinogenesis (5, 66-76). This high frequency of expression in tumor cells is at odds with the general expression of matriptase in the non-proliferative, terminally differentiated cells of stratified epithelia that possess limited or no oncogenic capacity (21, 22). However, recent studies have shown that matriptase undergoes a dramatic spatial redistribution during squamous cell carcinogenesis to become expressed in undifferentiated, keratin-5 positive basal cells with high self-renewal capacity (21, 22). Furthermore, low level forced expression of matriptase in basal keratinocytes has proved sufficient to drive malignant transformation of these cells, showing that matriptase possesses a strong oncogenic potential that can be unmasked by a simple spatial dysregulation. Thus, transgenic mice expressing modest levels of matriptase in basal keratinocytes displayed progressive epidermal hyperplasia with fibrosis and dermal inflammation, which spontaneously progressed to invasive squamous cell carcinoma (77). Molecular analysis revealed that the spatial dysregulation of matriptase leads to the activation of the PI3K-Akt signaling pathway, and that dysregulated matriptase synergizes strongly with activated *ras* to promote epithelial carcinogenesis. The molecular mechanism by which dysregulated matriptase potently supports epithelial transformation is not known. However, the co-expression of matriptase with HAI-1 in basal

keratinocytes of mouse epidermis negates the effects of matriptase, indicating its proteolytic activity is required (77). Prostasin, the candidate physiological substrate for matriptase in the epidermis, is not co-expressed with matriptase in basal keratinocytes at any stage of squamous cell carcinogenesis, and prostasin expression is generally extinguished during squamous cell carcinogenesis (21). Therefore, matriptase-induced carcinogenesis appears to involve the cleavage of one or more substrates within the pericellular microenvironment different from prostasin, such as extracellular matrix proteins, growth factors, or growth factor receptors.

Strong evidence has also accumulated that matriptase can promote later stages of carcinogenesis, from studies that manipulated matriptase expression levels or activity in xenografted human tumor cell lines by overexpression, by siRNA or antisense RNA-mediated downregulation, or by the use of active site inhibitors. In all cases, diminution of matriptase protein or activity impaired tumor dissemination, while overexpression accelerated the process (78-81). How matriptase pericellular proteolysis can accelerate tumor dissemination in these model systems remains to be determined. Plausible scenarios include the activation or inactivation of downstream effector molecules such as growth factors and receptors, chemokines and protease zymogens, and the direct modification of extracellular matrix proteins. Proposed matriptase candidate substrates whose cleavage could accelerate tumor dissemination include receptor bound pro-urokinase plasminogen activator (15, 27, 82), pro-hepatocyte growth factor activator/scatter factor (82), protease activated receptor-2 (15), pro-macrophage stimulating protein-1 (28) and the src-associated transmembrane protein SIMA135/CDCP1/TRASK (83).

6. SUMMARY AND PERSPECTIVES

In the half-decade after its molecular cloning, matriptase has emerged as an essential regulator of epithelial differentiation, underscoring the critical role played by pericellular proteolysis in regulating epithelial cell fate. Since the initial report linking matriptase to terminal epidermal differentiation in 2002, a number of other membrane-associated and secreted serine proteases and their cognate serine protease inhibitors have been implicated in this process, indicating that epithelial differentiation is governed by one or more sophisticated serine protease zymogen cascades. In this respect, matriptase could be hypothesized to play a role as a zymogen cascade initiator, similar to that of the prototypic TTSP, enteropeptidase, in the digestive tract. Compatible with its key role in regulating epithelial cell fate, matriptase proteolysis must be tightly controlled. Dysregulation of matriptase activity by overexpression, misexpression, or loss of inhibitor function, prevents embryogenesis by disrupting differentiation programs of developing epithelial structures of the placenta, can cause malignant transformation of adult epithelia, and enhances both tumor invasion and metastatic dissemination.

Future studies without doubt will uncover additional physiological and pathophysiological roles of this fascinating and complex membrane serine protease.

7. ACKNOWLEDGEMENTS

We thank Drs. Robert Angerer, Silvio Gutkind, and Mary Jo Danton for critically reviewing this manuscript. This work was supported by the NIH Intramural Program and by a grant from the Department of Defense (DAMD-17-02-1-0693) to Dr. Thomas H. Bugge.

8. REFERENCES

1. Shi, Y. E., J. Torri, L. Yieh, A. Wellstein, M. E. Lippman & R. B. Dickson: Identification and characterization of a novel matrix-degrading protease from hormone-dependent human breast cancer cells. *Cancer Res*, 53, 1409-15 (1993)

2. Cao, J., X. Cai, L. Zheng, L. Geng, Z. Shi, C. C. Pao & S. Zheng: Characterization of colorectal-cancer-related cDNA clones obtained by subtractive hybridization screening. *J Cancer Res Clin Oncol*, 123, 447-51 (1997)

3. Zhang, Y., X. Cai, B. Schlegelberger & S. Zheng: Assignment1 of human putative tumor suppressor genes ST13 (alias SNC6) and ST14 (alias SNC19) to human chromosome bands 22q13 and 11q24-->q25 by in situ hybridization. *Cytogenet Cell Genet*, 83, 56-7 (1998)

4. Kim, M. G., C. Chen, M. S. Lyu, E. G. Cho, D. Park, C. Kozak & R. H. Schwartz: Cloning and chromosomal mapping of a gene isolated from thymic stromal cells encoding a new mouse type II membrane serine protease, epithin, containing four LDL receptor modules and two CUB domains. *Immunogenetics*, 49, 420-8 (1999)

5. Tanimoto, H., L. J. Underwood, Y. Wang, K. Shigemasa, T. H. Parmley & T. J. O'Brien: Ovarian tumor cells express a transmembrane serine protease: a potential candidate for early diagnosis and therapeutic intervention. *Tumour Biol*, 22, 104-14 (2001)

6. Lin, C. Y., J. Anders, M. Johnson, Q. A. Sang & R. B. Dickson: Molecular cloning of cDNA for matriptase, a matrix-degrading serine protease with trypsin-like activity. *J Biol Chem*, 274, 18231-6 (1999)

7. Takeuchi, T., Shuman, M. A. & C. S. Craik: Reverse biochemistry: use of macromolecular protease inhibitors to dissect complex biological processes and identify a membrane-type serine protease in epithelial cancer and normal tissue. *Proc Natl Acad Sci U S A,* 96, 11054-61 (1999)

8. Hobson, J. P., S. Netzel-Arnett, R. Szabo, S. M. Rehault, F. C. Church, D. K. Strickland, D. A. Lawrence, T. M. Antalis & T. H. Bugge: Mouse DESC1 is located within a cluster of seven DESC1-like genes and encodes a type II transmembrane serine protease that forms serpin inhibitory complexes. *J Biol Chem,* 279, 46981-94 (2004)

9. Szabo, R., Q. Wu, R. B. Dickson, S. Netzel-Arnett, T. M. Antalis & T. H. Bugge: Type II transmembrane serine proteases. *Thromb Haemost*, 90, 185-93 (2003)

10. Netzel-Arnett, S., J. D. Hooper, R. Szabo, E. L. Madison, J. P. Quigley, T. H. Bugge & T. M. Antalis: Membrane anchored serine proteases: a rapidly expanding group of cell surface proteolytic enzymes with potential roles in cancer. *Cancer Metastasis Rev*, 22, 237-58 (2003)

11. Velasco, G., S. Cal, V. Quesada, L. M. Sanchez & C. Lopez-Otin: Matriptase-2, a membrane-bound mosaic serine proteinase predominantly expressed in human liver and showing degrading activity against extracellular matrix proteins. *J Biol Chem*, 277, 37637-46 (2002)

12. Szabo, R., S. Netzel-Arnett, J. P. Hobson, T. M. Antalis & T. H. Bugge: Matriptase-3 is a novel phylogenetically preserved membrane-anchored serine protease with broad serpin reactivity. *Biochem J*, 390, 231-42 (2005)

13. Hooper, J. D., L. Campagnolo, G. Goodarzi, T. N. Truong, H. Stuhlmann & J. P. Quigley: Mouse matriptase-2: identification, characterization and comparative mRNA expression analysis with mouse hepsin in adult and embryonic tissues. *Biochem J*, 373, 689-702 (2003)

14. List, K., T. H. Bugge & R. Szabo: Matriptase: potent proteolysis on the cell surface. *Mol Med*, 12, 1-7 (2006)

15. Takeuchi, T., J. L. Harris, W. Huang, K. W. Yan, S. R. Coughlin & C. S. Craik: Cellular localization of membrane-type serine protease 1 and identification of protease-activated receptor-2 and single-chain urokinase-type plasminogen activator as substrates. *J Biol Chem*, 275, 26333-42 (2000)

16. Kim, C., Y. Cho, C. H. Kang, M. G. Kim, H. Lee, E. G. Cho & D. Park: Filamin is essential for shedding of the transmembrane serine protease, epithin. *EMBO Rep*, 6, 1045-51 (2005)

17. Friedrich, R., P. Fuentes-Prior, E. Ong, G. Coombs, M. Hunter, R. Oehler, D. Pierson, R. Gonzalez, R. Huber, W. Bode & E. L. Madison: Catalytic domain structures of MT-SP1/matriptase, a matrix-degrading transmembrane serine proteinase. *J Biol Chem*, 277, 2160-8 (2001)

18. Macao, B., D. G. Johansson, G. C. Hansson & T. Hard: Autoproteolysis coupled to protein folding in the SEA domain of the membrane-bound MUC1 mucin. *Nat Struct Mol Biol*, 13, 71-6 (2006)

19. Cho, E. G., M. G. Kim, C. Kim, S. R. Kim, I. S. Seong, C. Chung, R. H. Schwartz & D. Park: N-terminal processing is essential for release of epithin, a mouse type II membrane serine protease. *J Biol Chem*, 276, 44581-9 (2001)

20. Oberst, M. D., C. A. Williams, R. B. Dickson, M. D. Johnson & C. Y. Lin: The activation of matriptase requires its noncatalytic domains, serine protease domain, and its cognate inhibitor. *J Biol Chem*, 278, 26773-9 (2003)

21. List, K., J. P. Hobson, A. Molinolo & T. H. Bugge: Co-localization of the channel activating protease prostasin/(CAP1/PRSS8) with its candidate activator, matriptase. *Journal of Cellular Physiology*, *In press*, (2007)

22. List, K., R. Szabo, A. Molinolo, B. S. Nielsen & T. H. Bugge: Delineation of matriptase protein expression by enzymatic gene trapping suggests diverging roles in barrier function, hair formation, and squamous cell carcinogenesis. *Am J Pathol*, 168, 1513-25 (2006)

23. Oberst, M. D., B. Singh, M. Ozdemirli, R. B. Dickson, M. D. Johnson & C. Y. Lin: Characterization of matriptase expression in normal human tissues. *J Histochem Cytochem*, 51, 1017-25 (2003)

24. Szabo, R., A. Molinolo, K. List & T. H. Bugge: Matriptase inhibition by hepatocyte growth factor activator inhibitor-1 is essential for placental development. *Oncogene*, 26, 1546-56 (2007)

25. Fan, B., J. Brennan, D. Grant, F. Peale, L. Rangell & D. Kirchhofer: Hepatocyte growth factor activator inhibitor-1 (HAI-1) is essential for the integrity of basement membranes in the developing placental labyrinth. *Dev Biol*, 303, 222-30 (2007)

26. Netzel-Arnett, S., B. M. Currie, R. Szabo, C. Y. Lin, L. M. Chen, K. X. Chai, T. M. Antalis, T. H. Bugge & K. List: Evidence for a matriptase-prostasin proteolytic cascade regulating terminal epidermal differentiation. *J Biol Chem*, 281, 32941-5 (2006)

27. Kilpatrick, L. M., R. L. Harris, K. A. Owen, R. Bass, C. Ghorayeb, A. Bar-Or & V. Ellis: Initiation of plasminogen activation on the surface of monocytes expressing the type II transmembrane serine protease matriptase. *Blood*, 108, 2616-23 (2006)

28. Bhatt, A. S., A. Welm, C. J. Farady, M. Vasquez, K. Wilson & C. S. Craik: Coordinate expression and functional profiling identify an extracellular proteolytic signaling pathway. *Proc Natl Acad Sci U S A*,104, 5771-6 (2007)

29. List, K., C. C. Haudenschild, R. Szabo, W. Chen, S. M. Wahl, W. Swaim, L. H. Engelholm, N. Behrendt & T. H. Bugge: Matriptase/MT-SP1 is required for postnatal survival, epidermal barrier function, hair follicle development, and thymic homeostasis. *Oncogene*, 21, 3765-79 (2002)

30. List, K., R. Szabo, P. W. Wertz, J. Segre, C. C. Haudenschild, S. Y. Kim & T. H. Bugge: Loss of proteolytically processed filaggrin caused by epidermal deletion of Matriptase/MT-SP1. *J Cell Biol*, 163, 901-10 (2003)

31. Elias, P. M. & G. K. Menon: Structural and lipid biochemical correlates of the epidermal permeability barrier. *Adv Lipid Res*, 24, 1-26 (1991)

32. Wertz, P. W. & C. A. Squier: Cellular and molecular basis of barrier function in oral epithelium. *Crit Rev Ther Drug Carrier Syst*, 8, 237-69 (1991)

33. Presland, R. B., D. Boggess, S. P. Lewis, C. Hull, P. Fleckman & J. P. Sundberg: Loss of normal profilaggrin and filaggrin in flaky tail (ft/ft) mice: an animal model for the filaggrin-deficient skin disease ichthyosis vulgaris. *J Invest Dermatol*, 115, 1072-81 (2000)

34. Roop, D.: Defects in the barrier. *Science*, 267, 474-5 (1995)

35. Mildner, M., C. Ballaun, M. Stichenwirth, R. Bauer, R. Gmeiner, M. Buchberger, V. Mlitz & E. Tschachler: Gene silencing in a human organotypic skin model. *Biochem Biophys Res Commun*, 348, 76-82 (2006)

36. Segre, J. A.: Epidermal differentiation complex yields a secret: mutations in the cornification protein filaggrin underlie ichthyosis vulgaris. *J Invest Dermatol*, 126, 1202-4 (2006)

37. Smith, F. J., A. D. Irvine, A. Terron-Kwiatkowski, A. Sandilands, L. E. Campbell, Y. Zhao, H. Liao, A. T. Evans, D. R. Goudie, S. Lewis-Jones, G. Arseculeratne, C. S. Munro, A. Sergeant, G. O'Regan, S. J. Bale, J. G. Compton, J. J. DiGiovanna, R. B. Presland, P. Fleckman & W. H. McLean: Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nat Genet*, 38, 337-42 (2006)

38. Palmer, C. N., A. D. Irvine, A. Terron-Kwiatkowski, Y. Zhao, H. Liao, S. P. Lee, D. R. Goudie, A. Sandilands, L. E. Campbell, F. J. Smith, G. M. O'Regan, R. M. Watson, J. E. Cecil, S. J. Bale, J. G. Compton, J. J. DiGiovanna, P. Fleckman, S. Lewis-Jones, G. Arseculeratne, A. Sergeant, C. S. Munro, B. El Houate, K. McElreavey, L. B. Halkjaer, H. Bisgaard, S. Mukhopadhyay & W. H. McLean: Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet*, 38, 441-6 (2006)

39. Herrmann, T., F. van der Hoeven, H. J. Grone, A. F. Stewart, L. Langbein, I. Kaiser, G. Liebisch, I. Gosch, F. Buchkremer, W. Drobnik, G. Schmitz & W. Stremmel: Mice with targeted disruption of the fatty acid transport protein 4 (Fatp 4, Slc27a4) gene show features of lethal restrictive dermopathy. *J Cell Biol*, 161, 1105-15 (2003)

40. McMahon, A., I. A. Butovich, N. L. Mata, M. Klein, R. Ritter, 3rd, J. Richardson, D. G. Birch, A. O. Edwards & W. Kedzierski: Retinal pathology and skin barrier defect in mice carrying a Stargardt disease-3 mutation in elongase of very long chain fatty acids-4. *Mol Vis*, 13, 258-72 (2007)

41. Owada, Y., H. Takano, H. Yamanaka, H. Kobayashi, Y. Sugitani, Y. Tomioka, I. Suzuki, R. Suzuki, T. Terui, M. Mizugaki, H. Tagami, T. Noda & H. Kondo: Altered water barrier function in epidermal-type fatty acid binding protein-deficient mice. *J Invest Dermatol*, 118, 430-5 (2002)

42. Leyvraz, C., R. P. Charles, I. Rubera, M. Guitard, S. Rotman, B. Breiden, K. Sandhoff & E. Hummler: The epidermal barrier function is dependent on the serine protease CAP1/Prss8. *J Cell Biol*, 170, 487-96 (2005)

43. Zeeuwen, P. L.: Epidermal differentiation: the role of proteases and their inhibitors. *Eur J Cell Biol*, 83, 761-73 (2004)

44. Stefansson, K., M. Brattsand, A. Ny, B. Glas & T. Egelrud: Kallikrein-related peptidase 14 may be a major contributor to trypsin-like proteolytic activity in human stratum corneum. *Biol Chem*, 387, 761-8 (2006)

45. Brattsand, M., K. Stefansson, C. Lundh, Y. Haasum & T. Egelrud: A proteolytic cascade of kallikreins in the stratum corneum. *J Invest Dermatol*, 124, 198-203 (2005)

46. Caubet, C., N. Jonca, M. Brattsand, M. Guerrin, D. Bernard, R. Schmidt, T. Egelrud, M. Simon & G. Serre: Degradation of corneodesmosome proteins by two serine proteases of the kallikrein family, SCTE/KLK5/hK5 and SCCE/KLK7/hK7. *J Invest Dermatol*, 122, 1235-44 (2004)

47. Kataoka, K., K. Nagaike, M. Kawaguchi, K. Kohama, H. Tanaka & T. Fukushima: Deletion of hepatocyte growth factor activator inhibitor type 1 (HAI-1) protein leads to ichthyosis in mice. *American Association for Cancer Research Annual Meeting* Oasis (2007)

48. Kishibe, M., Y. Bando, R. Terayama, K. Namikawa, H. Takahashi, Y. Hashimoto, A. Ishida-Yamamoto, Y. P. Jiang, B. Mitrovic, D. Perez, H. Iizuka & S. Yoshida: Kallikrein 8 is involved in skin desquamation in cooperation with other kallikreins. *J Biol Chem*, 282, 5834-41 (2007)

49. Descargues, P., C. Deraison, C. Bonnart, M. Kreft, M. Kishibe, A. Ishida-Yamamoto, P. Elias, Y. Barrandon, G. Zambruno, A. Sonnenberg & A. Hovnanian: Spink5-deficient mice mimic Netherton syndrome through degradation of desmoglein 1 by epidermal protease hyperactivity. *Nat Genet*, 37, 56-65 (2005)

50. Yang, T., D. Liang, P. J. Koch, D. Hohl, F. Kheradmand & P. A. Overbeek: Epidermal detachment, desmosomal dissociation, and destabilization of corneodesmosin in Spink5-/- mice. *Genes Dev*, 18, 2354-8 (2004)

51. Hewett, D. R., A. L. Simons, N. E. Mangan, H. E. Jolin, S. M. Green, P. G. Fallon & A. N. McKenzie: Lethal, neonatal ichthyosis with increased proteolytic processing of filaggrin in a mouse model of Netherton syndrome. *Hum Mol Genet*, 14, 335-46 (2005)

52. Borgono, C. A., I. P. Michael, N. Komatsu, A. Jayakumar, R. Kapadia, G. L. Clayman, G. Sotiropoulou & E. P. Diamandis: A potential role for multiple tissue kallikrein serine proteases in epidermal desquamation. *J Biol Chem*, 282, 3640-52 (2007)

53. Shultz, L. D.: Pleiotropic effects of deleterious alleles at the "motheaten" locus. *Curr Top Microbiol Immunol*, 137, 216-22 (1988)

54. Reske-Kunz, A. B., M. P. Scheid & E. A. Boyse: Disproportion in T-cell subpopulations in immunodeficient mutant hr/hr mice. *J Exp Med*, 149, 228-33 (1979)

55. Nakagawa, T., W. Roth, P. Wong, A. Nelson, A. Farr, J. Deussing, J. A. Villadangos, H. Ploegh, C. Peters & A. Y. Rudensky: Cathepsin L: critical role in Ii degradation and CD4 T cell selection in the thymus. *Science*, 280, 450-3 (1998)

56. Manley, N. R.: Thymus organogenesis and molecular mechanisms of thymic epithelial cell differentiation. *Semin Immunol*, 12, 421-8 (2000)

57. Flanagan, S. P.: 'Nude', a new hairless gene with pleiotropic effects in the mouse. *Genet Res*, 8, 295-309 (1966)

58. Davisson, M. T., S. A. Cook, K. R. Johnson & E. M. Eicher: Balding: a new mutation on mouse chromosome 18 causing hair loss and immunological defects. *J Hered*, 85, 134-6 (1994)

59. McElwee, K. J., A. Huth, S. Kissling & R. Hoffmann: Macrophage-stimulating protein promotes hair growth ex vivo and induces anagen from telogen stage hair follicles in vivo. *J Invest Dermatol*, 123, 34-40 (2004)

60. Lindner, G., A. Menrad, E. Gherardi, G. Merlino, P. Welker, B. Handjiski, B. Roloff & R. Paus: Involvement of hepatocyte growth factor/scatter factor and met receptor signaling in hair follicle morphogenesis and cycling. *Faseb J*, 14, 319-32 (2000)

61. Jindo, T., R. Tsuboi, K. Takamori & H. Ogawa: Local injection of hepatocyte growth factor/scatter factor (HGF/SF) alters cyclic growth of murine hair follicles. *J Invest Dermatol*, 110, 338-42 (1998)

62. Jindo, T., R. Tsuboi, R. Imai, K. Takamori, J. S. Rubin & H. Ogawa: The effect of hepatocyte growth factor/scatter factor on human hair follicle growth. *J Dermatol Sci*, 10, 229-32 (1995)

63. McCawley, L. J., P. O'Brien & L. G. Hudson: Epidermal growth factor (EGF)- and scatter factor/hepatocyte growth factor (SF/HGF)- mediated keratinocyte migration is coincident with induction of matrix metalloproteinase (MMP)-9. *J Cell Physiol*, 176, 255-65 (1998)

64. Basel-Vanagaite, L., R. Attia, A. Ishida-Yamamoto, L. Rainshtein, D. Ben Amitai, R. Lurie, M. Pasmanik-Chor, M. Indelman, A. Zvulunov, S. Saban, N. Magal, E. Sprecher & M. Shohat: Autosomal Recessive Ichthyosis with Hypotrichosis Caused by a Mutation in ST14, Encoding Type II Transmembrane Serine Protease Matriptase. *Am J Hum Genet*, 80, 467-77 (2007)

65. Lin, C. Y., J. Anders, M. Johnson & R. B. Dickson: Purification and characterization of a complex containing matriptase and a Kunitz-type serine protease inhibitor from human milk. *J Biol Chem*, 274, 18237-42 (1999)

66. Zeng, L., J. Cao & X. Zhang: Expression of serine protease SNC19/matriptase and its inhibitor hepatocyte growth factor activator inhibitor type 1 in normal and malignant tissues of gastrointestinal tract. *World J Gastroenterol*, 11, 6202-7 (2005)

67. Oberst, M., J. Anders, B. Xie, B. Singh, M. Ossandon, M. Johnson, R. B. Dickson & C. Y. Lin: Matriptase and HAI-1 are expressed by normal and malignant epithelial cells in vitro and in vivo. *Am J Pathol*, 158, 1301-11 (2001)

68. Riddick, A. C., C. J. Shukla, C. J. Pennington, R. Bass, R. K. Nuttall, A. Hogan, K. K. Sethia, V. Ellis, A. T. Collins, N. J. Maitland, R. Y. Ball & D. R. Edwards: Identification of degradome components associated with prostate cancer progression by expression analysis of human prostatic tissues. *Br J Cancer*, 92, 2171-80 (2005)

69. Hoang, C. D., J. D'Cunha, M. G. Kratzke, C. E. Casmey, S. P. Frizelle, M. A. Maddaus & R. A. Kratzke: Gene expression profiling identifies matriptase overexpression in malignant mesothelioma. *Chest*, 125, 1843-52 (2004)

70. Lee, J. W., S. Yong Song, J. J. Choi, S. J. Lee, B. G. Kim, C. S. Park, J. H. Lee, C. Y. Lin, R. B. Dickson & D. S. Bae: Increased expression of matriptase is associated with histopathologic grades of cervical neoplasia. *Hum Pathol*, 36, 626-33 (2005)

71. Tanimoto, H., K. Shigemasa, X. Tian, L. Gu, J. B. Beard, T. Sawasaki & T. J. O'Brien: Transmembrane serine protease TADG-15 (ST14/Matriptase/MT-SP1): expression and prognostic value in ovarian cancer. *Br J Cancer*, 92, 278-83 (2005)

72. Santin, A. D., S. Cane, S. Bellone, E. Bignotti, M. Palmieri, L. E. De Las Casas, S. Anfossi, J. J. Roman, T. O'Brien & S. Pecorelli: The novel serine protease tumor-associated differentially expressed gene-15 (matriptase/MT-SP1) is highly overexpressed in cervical carcinoma. *Cancer*, 98, 1898-904 (2003)

73. Santin, A. D., F. Zhan, S. Bellone, M. Palmieri, S. Cane, E. Bignotti, S. Anfossi, M. Gokden, D. Dunn, J. J. Roman, T. J. O'Brien, E. Tian, M. J. Cannon, J. Shaughnessy, Jr. & S. Pecorelli: Gene expression profiles in primary ovarian serous papillary tumors and normal ovarian epithelium: Identification of candidate molecular markers for ovarian cancer diagnosis and therapy. *Int J Cancer*, 112, 14-25 (2004)

74. Kang, J. Y., M. Dolled-Filhart, I. T. Ocal, B. Singh, C.-Y. Lin, R. B. Dickson, D. L. Rimm & R. L. Camp: Tissue microarray analysis of HGF/met pathway components reveals a role for Met, matriptase, and HAI-1 in the progression of node-negative breast cancer. *Cancer Research*, 63, 1101-5 (2003)

75. Parr, C., G. Watkins, R. E. Mansel & W. G. Jiang: The hepatocyte growth factor regulatory factors in human breast cancer. *Clin Cancer Res*, 10, 202-11 (2004)

76. Bhatt, A. S., T. Takeuchi, B. Ylstra, D. Ginzinger, D. Albertson, M. A. Shuman & C. S. Craik: Quantitation of membrane type serine protease 1 (MT-SP1) in transformed and normal cells. *Biol Chem*, 384, 257-66 (2003)

77. List, K., R. Szabo, A. Molinolo, V. Sriuranpong, V. Redeye, T. Murdock, B. Burke, B. S. Nielsen, J. S. Gutkind & T. H. Bugge: Deregulated matriptase causes ras-independent multistage carcinogenesis and promotes ras-mediated malignant transformation. *Genes Dev*, 19, 1934-50 (2005)

78. Ihara, S., E. Miyoshi, J. H. Ko, K. Murata, S. Nakahara, K. Honke, R. B. Dickson, C. Y. Lin & N. Taniguchi: Prometastatic effect of N-acetylglucosaminyltransferase V is due to modification and stabilization of active matriptase by adding beta 1-6 GlcNAc branching. *J Biol Chem*, 277, 16960-7 (2002)

79. Forbs, D., S. Thiel, M. C. Stella, A. Sturzebecher, A. Schweinitz, T. Steinmetzer, J. Sturzebecher & K. Uhland: In vitro inhibition of matriptase prevents invasive growth of cell lines of prostate and colon carcinoma. *Int J Oncol*, 27, 1061-70 (2005)

80. Galkin, A. V., L. Mullen, W. D. Fox, J. Brown, D. Duncan, O. Moreno, E. L. Madison & D. B. Agus: CVS-3983, a selective matriptase inhibitor, suppresses the growth of androgen independent prostate tumor xenografts. *Prostate*, 61, 228 (2004)

81. Suzuki, M., H. Kobayashi, N. Kanayama, Y. Saga, C. Y. Lin, R. B. Dickson & T. Terao: Inhibition of tumor invasion by genomic down-regulation of matriptase through suppression of activation of receptor-bound pro-urokinase. *J Biol Chem*, 279, 14899-908 (2004)

82. Lee, S. L., R. B. Dickson & C. Y. Lin: Activation of hepatocyte growth factor and urokinase/plasminogen activator by matriptase, an epithelial membrane serine protease. *J Biol Chem*, 275, 36720-5 (2000)

83. Bhatt, A. S., H. Erdjument-Bromage, P. Tempst, C. S. Craik & M. M. Moasser: Adhesion signaling by a novel mitotic substrate of src kinases. *Oncogene*, 24, 5333-43 (2005)

Key Words: Matriptase, Cell Surface Proteolysis, Epithelial Development, Review

Send correspondence to: Thomas H. Bugge, Ph.D., Proteases and Tissue Remodeling Unit, Oral and Pharyngeal Cancer Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, 30 Convent Drive, Room 211, Bethesda, MD 20892, Tel: 301-435-1840, Fax: 301-402-0823, E-mail: thomas.bugge@nih.gov