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Membrane-anchored serine proteases as regulators of epithelial function

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Abstract

Cleavage of proteins in the extracellular milieu, including hormones, growth factors and their receptors, ion channels, and various cell adhesion and extracellular matrix molecules, plays a key role in regulation of cell behavior. Among more than 500 proteolytic enzymes encoded by mammalian genomes, membrane-anchored serine proteases (MASPs), which are expressed on the surface of epithelial cells of all major organs, are excellently suited to mediate signal transduction across the epithelia and are increasingly being recognized as important regulators of epithelial development, function, and disease (1–3). In this minireview, we summarize current knowledge of the *in vivo* roles of membrane-anchored serine proteases in acquisition and maintenance of some of the defining functions of epithelial tissues, such as barrier formation, ion transport, and sensory perception.

Membrane-Anchored Serine Proteases (MASPs)

The human MASP family currently comprises twenty proteases, with orthologs identified in all vertebrate species analyzed to date (Figure 1). Based on their membrane topology, the majority of the MASPs are classified as type II transmembrane serine proteases (TTSPs) that are anchored to the membrane via a single-pass transmembrane domain located near the amino terminus. This is followed by a variable stem region and an extracellular carboxy-terminal trypsin-like serine protease domain. Based on the sequence similarities between the catalytic domains, TTSPs have been further divided into four distinct sub-families (1). Type I MASPs include three proteases that are composed of an extracellular serine protease domain attached to the membrane via a C terminal transmembrane domain (tryptase γ1) or a glycosylphosphatidylinositol (GPI) anchor (prostasin and testisin).

All MASPs belong to the S1 family of serine endoproteases that includes trypsin as the prototypic member and show strong preference for cleavage of substrates after arginine or lysine residues (4). MASPs are synthesized as single-chain zymogens that undergo proteolytic cleavage at a conserved site within the catalytic domain, thus producing a fully active double-chain form (1). While this has long been considered an essential step towards activation of an essentially inactive zymogen, recent findings suggest that at least

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some MASPs are capable of performing their biological function independent of activation cleavage (5, 6).

MASPs in development and maintenance of epithelial barrier function

Matriptase/prostasin system as general regulator of epithelial barrier function

Epithelia provide barriers that protect tissues from external physical, chemical and microbial insults and maintain fluid homeostasis. The paracellular barrier, which limits permeability between epithelial cells, is critical to maintain transepithelial ion and nutrient gradients, and is a principal defense mechanism preventing entry of pathogens and toxic substances (7). The barrier is primarily regulated at the level of tight junctions (TJs) that are expressed at the apical margin of epithelial junctional complexes and restrict paracellular diffusion (7, 8). The notion that proteolysis may be involved in the regulation of paracellular barrier function was suggested based on the observation that a mild treatment of cultured epithelial cells with endoproteases leads to rapid assembly of TJ strands and strengthening of the barrier (9, 10).

The TTSP matriptase and its proposed activator, prostasin, are expressed in the epithelial compartments of most human and mouse tissues (11). The critical role of the prostasin/ matriptase system in epithelial barrier formation was first inferred from the study of genetically-modified mice (Table 1). Mice lacking matriptase develop to term but exhibit abnormal terminal differentiation of epidermal keratinocytes, and loss of epidermal barrier function that results in fatal postnatal dehydration (12, 13). These phenotypes closely match those observed in mice lacking epidermal prostasin, consistent with a proposed functional interaction between the two proteases during skin development (14, 15).

Role of matriptase in other epithelia has been documented using tissue-specific mouse knockouts. Inactivation of the protease results in a loss of saliva production by salivary glands and a disruption of normal tissue architecture within large intestine that results in diarrhea, growth retardation and shortened life span (13, 16). In both organs, elimination of matriptase expression leads to a diminished epithelial barrier function (Table 1) (13, 16). Inactivation of matriptase also significantly increased leakiness of placental epithelia and led to embryonic lethality in mice lacking the G protein-coupled receptor PAR2 (17). Mice and rats carrying hypomorphic mutations in *Prss8*, encoding prostasin, also exhibit defects in intestinal and placental function, although it is not clear whether any of these defects are related to altered matriptase activity (18–21).

In humans and in horses, loss of function mutations in *ST14*, encoding matriptase, have been linked to autosomal recessive ichthyosis with hypotrichosis (OMIM#602400) and Naked Foal Syndrome, respectively (22, 23). Both diseases present with skin defects that include mild to moderate ichthyosis, indicative of compromised epidermal barrier function (Table 1). Finally, the matriptase and prostasin homologs, Notopleural and Tracheal-prostasin, are essential for establishment of airway barrier function and embryonic survival in *Drosophila* (see below) (24). Consistent with the *in vivo* studies, inhibition or elimination of matriptase activity results in decreased ability of cultured intestinal and kidney epithelial cells to establish and maintain fully functional barriers (25, 26).

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Despite the overwhelming evidence for the importance of matriptase for epithelial barrier development, the molecular mechanisms underlying this function remain unknown. Loss of matriptase expression leads to a decreased expression and/or recruitment of several barrier-promoting tight junction-associated proteins, including claudin-1, occludin, and ZO-1, while also increasing expression of permeability-associated protein claudin-2 both in mouse epithelia and in cultured human intestinal epithelial cells (13, 17, 25, 27). Therefore, it is plausible to hypothesize that matriptase promotes epithelial barrier function by regulating assembly and/or stability of barrier-forming junctions. However, as of now, no evidence has been presented to indicate that barrier stability is regulated by a proteolytic cleavage of any of the core components of epithelial junctional complexes.

Although the ability of matriptase to cleave and to regulate the activity of a number of biologically active molecules *in vitro* is well documented, attempts to validate the involvement of any of these substrates in matriptase-mediated regulation of epithelial development and barrier formation have been unsuccessful. Genetic inactivation of either hepatocyte growth factor (HGF) receptor, cMet, or a G-protein coupled receptor, PAR-2, prevent matriptase-driven tumorigenesis in mouse skin, indicating the ability of matriptase to stimulate HGF- and PAR-2-mediated cell signaling *in vivo* (28, 29). PAR-2 inactivation also rescued ichthyosis in mice overexpressing prostasin in skin and matriptase-induced defects in epidermal development in zebrafish embryos (30, 31). Likewise, the epithelial sodium channel (ENaC) is activated by prostasin or matriptase in *Xenopus* oocytes and in mice (see also "MASPs in regulation of transepithelial ion transport" below) (32). However, loss of PAR-2, HGF or ENaC in mice does not appear to reproduce any of the phenotypes observed in matriptase-deficient mice, indicating that activation of any of these three molecules does not critically contribute to matriptase-mediated formation of epithelial barrier function (33–36).

Recently, epithelial cell adhesion molecule (EpCAM) was proposed to be a pathogenic substrate for matriptase during intestinal development. Inactivating mutations in *EPCAM* are found in patients with congenital tufting enteropathy (CTE, OMIM #613217), an early-onset severe intestinal insufficiency characterized by epithelial dysplasia and villous atrophy leading to chronic watery diarrhea and failure to thrive (37). EpCAM is efficiently cleaved by matriptase in cell culture systems, and loss of function mutations in *SPINT2*, encoding the endogenous inhibitor of the matriptase/prostasin pathway, HAI-2, are responsible for the syndromic form of CTE (OMIM #270420) (38, 39). Furthermore, two recently generated HAI-2-deficient mouse models exhibit severe intestinal insufficiency that resembles that of CTE patients, including compromised intestinal epithelial barrier and loss of EpCAM protein expression (40, 41). In one of the models, early onset intestinal defects caused by HAI-2 deficiency were suppressed by genetic inactivation of matriptase, indicating that the intestinal failure in this model of CTE is, in part, matriptase-driven (42). It was therefore suggested that an increased matriptase-mediated cleavage and subsequent degradation of EpCAM in mice and humans lacking functional HAI-2 may be involved in the etiology of the disease. However, whether increased cleavage of EpCAM indeed drives intestinal failure CTE in HAI-2-deficient mice and humans remains to be determined. Furthermore, it is not clear if EpCAM processing has a physiological role in matriptase-mediated barrier acquisition in HAI-2-competent tissues during normal development.

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Epidermal barrier formation – Tmprss13 and Tmprss11f

In addition to matriptase/prostasin pathway, the TTSPs TMPRSS13 and TMPRSS11F contribute to epidermal barrier formation in mouse skin. Both proteases are expressed in a wide array of mouse and human tissues, with high levels detected in keratinized epithelia of skin, oral cavity and upper digestive system (43–46). Both *Tmprss13*- and *Tmprss11f*-deficient newborn mice present with significantly increased transepidermal fluid loss, indicative of compromised epidermal barrier function (44, 47, 48). The rate of fluid loss is relatively small compared to that observed in mice lacking either matriptase or prostasin, and it does not affect postnatal development or long-term survival of *Tmprss13*- or *Tmprss11f*-deficient mice, suggesting that at least in the absence of additional challenge, the individual contribution of the two proteases to the establishment of epidermal barrier is relatively minor. Loss of TMPRSS11F did not alter the histological appearance of the epidermis, including stratum corneum, or the expression of any of the major components of cornified envelope, whereas newborn *Tmprss13*-deficient mice exhibit reduced stratum corneum thickness, but no obvious defects in TJ function or profilaggrin processing analogous to the ones observed in matriptase- and prostasin-deficient epidermis (44, 48). It is therefore unclear whether the two proteases contribute to the formation of epidermal barrier function either in parallel or as one of several functionally relevant targets acting downstream of the matriptase/prostasin system.

MASPs in regulation of transepithelial ion transport

Activation of the epithelial sodium channel - prostasin, matriptase, TMPRSS4

Directional transport of ions and water across epithelial barriers is essential for maintaining tissue homeostasis and is a critical function of all polarized epithelia. The epithelial sodium channel (ENaC) is a key component of sodium (Na^+) transport across high resistance epithelia and is crucial for salt tasting in tongue epithelium and sodium reabsorption in kidney, lungs and intestines, thus regulating blood pressure, blood potassium levels, and airway and alveolar surface liquid volumes (32). A number of extracellular proteases of serine, cysteine, and metalloproteinase families, including membrane-tethered serine proteases prostasin, matriptase, TMPRSS4, and TMPRSS3, have been shown to activate ENaC in a variety of *in vitro* and *in vivo* systems by proteolytic cleavage and removal of an inhibitory tract from its γ subunit (32, 49).

The importance of prostasin-dependent activation of ENaC has been demonstrated using a series of tissue-specific prostasin-deficient mice. In lungs, the level of airway surface liquid (ASL) that covers the apical surface of the airway epithelium is critical for alveolar function and is maintained by moving ASL across the epithelium in a process that is facilitated by ENaC-mediated sodium absorption (50). Mice lacking prostasin in alveolar epithelial cells show 40 % decrease in ENaC-mediated sodium currents and a reduced sodium-driven alveolar clearance, leading to a fluid accumulation in an experimental model of hydrostatic pulmonary edema (51). Aberrant activity of channel-activating proteases may also be involved in the etiology of pulmonary fibrosis. TMPRSS4 and matriptase are upregulated during bleomycin-induced lung fibrosis in mice, and genetic ablation of either of the two proteases or treatment with the serine protease inhibitor, camostat mesilate,

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attenuates development of the disease (52, 53). Similarly, intratracheal administration of camostat mesilate inhibits ENaC activity in guinea pigs and enhances mucociliary clearance in sheep (54). Furthermore, in cultured primary airway epithelial cells from cystic fibrosis patients, who often suffer from mucus plugging and chronic bacterial infection due to reduced ASL, inhibition of ENaC-activating proteases increased ASL height and improved mucociliary function (55).

Essential functions of ENaC-mediated sodium transport in kidneys have been documented in patients with hypertension associated with inherited forms of hypokalemia (Liddle syndrome, OMIM#177200), or hypotension associated with hyperkalemia (pseudohypoaldosteronism type 1, OMIM#264350), that carry, respectively, gain-of-function and loss-of-function mutations in genes encoding ENaC subunits (56). Although kidney tubule-specific prostasin knockout has not yet been described, the administration of the non-selective serine protease inhibitors, aprotinin and camostat mesilate both led to an increased excretion of sodium in mice and reduced blood pressure and renal injury in a salt-sensitive hypertension rat model, consistent with serine protease-dependent activation of ENaC (57, 58). Reduced ENaC-mediated sodium transport has also been reported in the colon of mice that carry a partial loss-of-function mutation or intestine-specific inactivation of the prostasin gene (18, 20).

Whether regulation of sodium transport plays a role in the barrier-promoting function of the matriptase/prostasin system is not clear. However, barrier acquisition did not appear to be significantly affected in alveolar epithelial cells or colons of prostasin-deficient mice, indicating that two of the proposed physiological functions of prostasin, establishment of epithelial barrier and regulation of transepithelial ion transport, may not be directly linked (20, 51).

Regulation of blood pressure and kidney function – corin, hepsin

The TTSP corin is essential for proteolytic activation of pro-atrial natriuretic peptide (pro-ANP), a pro-form of a cardiac hormone ANP that regulates water-salt balance and blood pressure by promoting excretion of both sodium and water by the kidneys (59). Loss-of-function mutations in *CORIN* are associated with hypertension, edema and heart failure in humans, and with impaired renal sodium excretion, salt-sensitive hypertension, water retention and cardiac hypertrophy in mice (59–61). While natriuretic peptides and corin are mainly produced by the heart, both pro-ANP and corin are expressed in several non-cardiac tissues involved in blood pressure regulation, including placenta and kidney (62, 63). In the kidney, corin is expressed at the apical membrane of epithelial cells along the entire length of the nephron, where it is believed to process filtered and/or locally produced pro-ANP (63). Mature ANP decreases sodium reabsorption and urine-concentrating capacity by inhibiting several sodium transport systems, most notably the Na-K-ATPase, Na/H exchanger, and type IIa Na-Pi cotransporter in the proximal tubule, and by inhibiting Cl- transport via decreasing apical membrane expression of Na-K-2Cl cotransporter (NKCC2) in the distal tubule (Figure 2) (64). Natriuretic and diuretic effects of ANP also involve suppression of both ENaC-mediated sodium reabsorption and vasopressin-stimulated water reabsorption in collecting ducts of the kidney (65). Consistent with this, impaired sodium

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excretion and increased water retention in corin-deficient mice were suppressed by treatment with an ENaC inhibitor, amiloride (60).

Corin mutations that impair the natriuretic peptide-processing activity have also been identified in patients with pregnancy-associated hypertension (preeclampsia) (62). Corin expression was detected in decidual cells in pregnant uterus in mice and in humans, and within late secretory endometrium and in villous cytotrophoblasts from first trimester placenta, and uterine corin expression was significantly lower in individuals with pre-eclampsia, compared to normal pregnancies (62, 66, 67). Histological analysis of placentas from corin-deficient mice and patients with pre-eclampsia revealed delayed trophoblast invasion and impaired spiral artery remodeling in the uterus (62, 68, 69). Pregnant mice lacking corin or ANP develop high blood pressure and proteinuria that is not prevented by heart-specific re-expression of corin that restored pro-ANP processing in the heart and normalized blood pressure in non-pregnant mice, suggesting that decreased local uterine, rather than cardiac, corin activity is critical for development of pre-eclampsia (62, 70).

Hepsin regulates sodium transport and homeostasis in the kidney via processing of the GPI-anchored, zona pellucida-type protein, uromodulin, that is expressed on the apical surface of kidney epithelial cells within the thick ascending limb of loop of Henle (71, 72). Mutations in the uromodulin gene cause medullary cystic kidney disease 2 (OMIM #603860) and familial juvenile hyperuricemic nephropathy (OMIM#162000) and have been associated with increased risk of chronic kidney disease, calcium stones, and hypertension (73–75). Uromodulin appears to modulate ion reabsorption by regulating the surface abundance and activity of the sodium, potassium, chloride cotransporter, NKCC2, and the potassium channel, ROMK2 (76, 77). Hepsin mediates proteolytic cleavage and subsequent shedding of uromodulin from the cell surface, and loss of hepsin function leads to hyperactivation of the NKCC2 transporter and increased sodium and water reabsorption (Figure 2) (71, 72). Prolonged exposure of hepsin-deficient mice to high-salt diet resulted in severe deterioration of renal function with salt wasting and subsequent rise in plasma osmolarity, hypocalcemia and hypomagnesemia, underscoring the importance of hepsin-mediated processing of uromodulin in the regulation of salt homeostasis and kidney function (72).

Development of hearing - TMPRSS3, hepsin

The ability to perceive sound depends on proper functioning of the cochlea, a spiral organ within the inner ear with a specialized epithelium that contains electro conducting hair cells for detecting vibrations from the outer and middle ear and converting them into nerve impulses (78). Loss-of-function mutations in *TMPRSS3* causes non-syndromic autosomal recessive deafness (DFNB8/10, OMIM#601072), characterized by early onset, progressive, bilateral hearing loss (79). Similarly, mice lacking a functional Tmprss3 protein exhibit severe loss of hearing associated with rapid degeneration of cochlear and vestibular hair cells (80). Prior to degeneration, loss of Tmprss3 reduced the number of Ca^{2+}-activated K^+ (BK) channels and decreased expression of several intracellular calcium-binding proteins in cultured primary hair cells, and decreased expression of the α subunit of the BK channel and a loss of BK-dependent fast K+ conductance within the cochlea of *Tmprss3*-deficient mice (81, 82). Furthermore, activation of the wildtype, but not the deafness-causing

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variants of Tmprss3 increases amiloride-sensitive sodium transport in a *Xenopus* oocyte expression system, indicating that the protease could potentially be involved in activation of inner ear-expressed ENaC (49). However, pseudohypoaldosteronism type 1 patients carrying inactivating mutations in the alpha subunit of ENaC have normal hearing, thus challenging the notion that ENaC activation is crucial for auditory system development (83). Interestingly, deficiency in hepsin also leads to loss of hearing function in mice and is associated with reduced levels of BK channels in the sensory hair cells, indicating that the two proteases may regulate development of hearing function via overlapping mechanisms, possibly even as parts of the same proteolytic cascade regulating ion transport in the inner ear (84).

MASPs in extracellular matrix remodeling – lessons from *Drosophila*

Drosophila Notopleural and *Trp*, which encode proteases homologous to, respectively, human matriptase and prostasin, have recently been shown to be essential for degradation of intraluminal chitin in the trachea of *Drosophila*, leading to a defect in barrier function, impaired tracheal liquid clearance and death before hatching (24). *Notopleural* mutant and *Trp* knockdown embryos show defects in cleavage of apical ECM zona pellucida (ZP) protein Dumpy, which plays an important role in attachment of the epithelium to the exoskeleton at later stages of *Drosophila* development (85). Interestingly, depletion of *Stubble* (*Sb-sbd*), encoding a TTSP homologous to Notopleural, impairs degradation of Dumpy in epithelial cells within imaginal discs during morphogenesis, and therefore inhibits elongation and expansion of wings and legs (86). Although Dumpy does not have a homolog in mammalian systems, the recent discovery of hepsin-mediated cleavage of another ZP protein, uromodulin, in mammalian kidney (see above) indicates that cleavage of ZP domain-containing proteins may present an evolutionary-conserved means of regulating epithelial function by cell surface-linked proteolysis.

MASPs in viral processing

Respiratory epithelium is a point of entry into the organism for a number of pathogens, including viruses. Many enveloped viruses, including influenza A and B, depend on a cleavage of hemaglutinin (HA)-type surface glycoproteins for viral entry into the target cell (87, 88). Several trypsin-like serine proteases, including airway epithelium-expressed TTSPs TMPRSS2, TMPRSS4, TMPRSS13, TMPRSS11A, TMPRSS11D/HAT, TMPRSS11E/DESC1, and matriptase, activate influenza HA and promote infectivity in cell culture systems (88, 89). Recently, TMPRSS2 was identified as a susceptibility gene for Severe 2009 Pandemic A(H1N1) and A(H7N9) Influenza, and inactivation of either TMPRSS2 or TMPRSS4 confers partial to complete resistance to the spread and pathogenesis of influenza virus in mice (90–95). Surface proteins of several other types of viruses, including Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS-CoV), parainfluenza viruses, human metapneumovirus (HMPV), and Sendai virus (SeV), undergo TTSP-mediated activation cleavage in culture, indicating a potential widespread role of membrane-anchored serine proteases in viral respiratory illnesses that makes these enzymes potential targets for new antiviral therapies (96–102).

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Perspectives

- *Importance of the field:* Membrane-anchored serine proteases are critical regulators of epithelial physiology. Changes in MASP expression and/or activity underlie the etiology of numerous diseases and developmental defects in both humans and in animal models.
- *Current thinking:* Localization to the cell surface makes MASPs ideal instruments of regulation of cell behavior by extracellular stimuli. Significant progress has been made in recent years to uncover some of the molecular mechanisms of MASP-mediated regulation of epithelial function, including activation of proANP in kidney and placenta, processing of zona pellucida proteins in kidney and tracheal system in *Drosophila*, or activation cleavage of viral surface proteins.
- *Future directions:* Imaging and analyzing the activity of individual proteases in living tissues using highly selective antibodies and activity probes will be crucial to provide further insight into physiological and pathological roles of MASPs, as well as into the mechanisms that govern their expression, cell localization, zymogen activation, and modulation of their proteolytic activity by auxiliary proteins. Development of selective inhibitors of matriptase and other MASPs shown to contribute to disease development may open alternative new strategies to treat conditions such as Congenital Tufting Enteropathy or viral respiratory infections.

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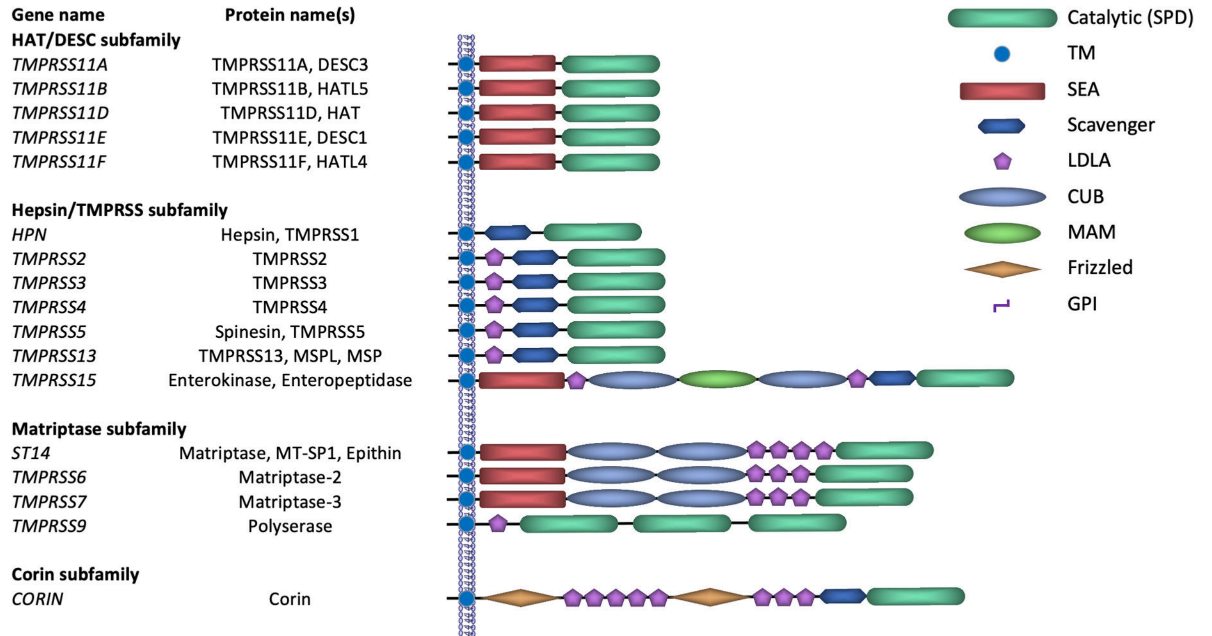

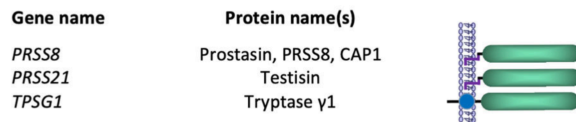

Figure 1.

Classification and domain structure of human membrane-anchored serine proteases.

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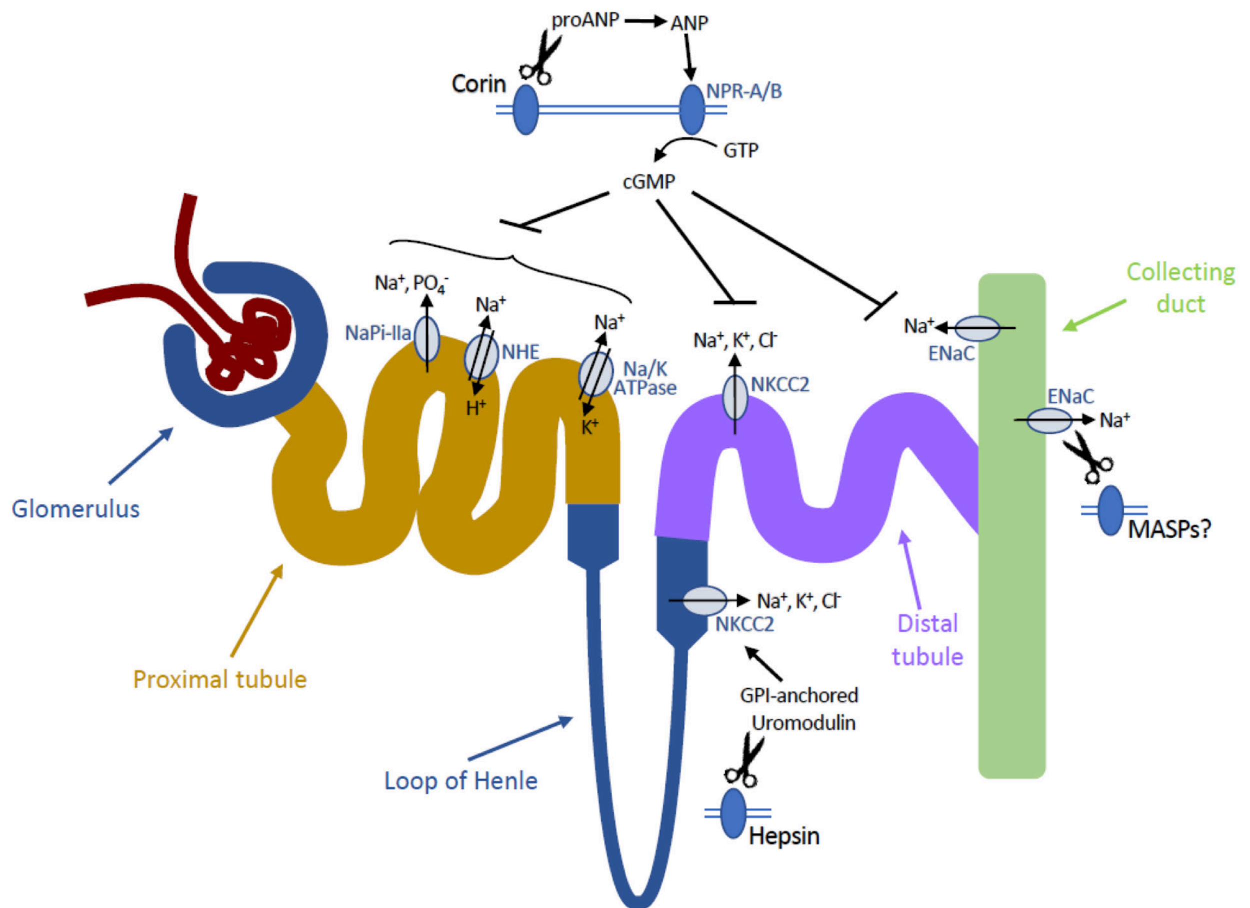

Figure 2.

Proposed roles of MASPs in regulation of ion transport in the kidneys. Corin-generated ANP binds to its receptor NPR-A and enhances its guanylyl cyclase activity. CyclicGMP prevents sodium reabsorption by inhibiting activity of several ion transport proteins in different segments of nephron. Hepsin mediates shedding of the GPI-anchored protein uromodulin, leading to a decreased activity of Na^+, K^+, Cl^- cotransporter NKCC2 in the thick ascending limb. Finally, several MASPs, including prostasin, matriptase, and TMPRSS4, have been proposed to activate the epithelial sodium channel ENaC, suggesting their possible involvement in sodium reabsorption in the distal tubules and collecting ducts. Abbreviations: ANP, atrial natriuretic peptide; cGMP, cyclic guanosine monophosphate; ENaC, epithelial sodium channel; GPI, glycosylphosphatidylinositol, GTP, guanosine triphosphate; Na/K ATPase, sodium-potassium adenosine triphosphatase; NaPi-IIa, sodium-phosphate cotransporter IIa; NHE, sodium-proton exchanger; NKCC2, sodium-potassium-chloride cotransporter; NPR, natriuretic peptide receptor.

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Table 1.

Defects in epithelial barrier function resulting from loss of matriptase activity

Organism	Loss of matriptase function	Phenotype	Barrier defect
Human			
ARIH (OMIM#602400) (23)	Expected partial to complete; all tissues	Skin - ichthyosis, hypotrichosis, dysplastic hair Teeth - enamel notching/pitting, conical primary teeth Eye - Comeal opacity, photophobia	
Mouse			
St14$^{-/-}$(13,14)	Null, all tissues	Perinatal lethality within 48h after birth Skin - Defects in stratum corneum development, ichthyosis, hair follicle hypoplasia, lack of whiskers Thymus - increased thymocyte apoptosis	Increased transepidermal fluid loss and diffusion of topically or intradermally injected tracers, loss of TJ localization of Z01
St14$^{-/-}$ in PAR2-deficient background (17)	Null, all tissues	Embryonic lethality Placenta - underdevelopment of labyrinth layer	Increased transplacental diffusion, decreased expression of claudin 1
Vil-Cre;St14$^{fl/fl}$ (14,29)	Null, epithelium of Gl tract	Growth retardation, diarrhea, shortened lifespan Colon - Edema, loss of crypt architecture, severe inflammation	Increased transepithelial diffusion of intestinal luminal biotin into tissue stroma
MMTV-Cre;St14$^{fl/fl}$ (14,17)	Null, epithelium of salivary glands	Loss of saliva production	Increased transepithelial electrical conductance in salivary gland, loss of membrane localization of claudin 3
βAct-CreER^{TM}*;St14*$^{fl/fl}$ (14)	Inducible loss of expression, all tissues	Rapid loss of weight and viability Skin - loss of hair, ichthyosis Colon - edema, loss of crypt structure, inflammation	Skin - decreased expression of TJ proteins claudinl, Z01, and occludin Intestine - increased transepithelial diffusion of intestinal luminal dextran into bloodstream
St14$^{hypo/hypo}$ (24,27)	Reduced expression, all tissues	Skin - ichthyosis, epidermal acanthosis, impaired desquamation, delayed hair growth, sparse fur	Skin - increased transepidermal fluid loss Intestine - decreased transepithelial electrical resistance, increased diffusion intestinal luminal dextran into bloodstream, increased expression of claudin 2
Horse			
ST14:c.388G>T (25)	Null, all tissues	Skin - dry and scaly, complete alopecia Thymus - lack of cortico-medullary organization, absence of Hassal corpuscles Spleen, lymph nodes - abnormal or absent T cell zones	
Fruit fly			
Np^{P6}*/Np*^{C2} (26)	Null, all tissues	Lack of airway fluid clearance, embryonic lethality	Trachea - increased diffusion of dextran the lumen