[Frontiers in Bioscience 16, 539-552, January 1, 2011]

Type II Transmembrane Serine Protease (TTSP) deregulation in cancer

Siobhan L Webb[1], Andrew J Sanders[1], Malcolm D Mason[2], Wen G Jiang[1]

[1]Department of Surgery, [2]Department of Clinical Oncology, Cardiff University School of Medicine, Cardiff, UK, CF14 4XN

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1. ABSTRACT

The Type II transmembrane serine proteases (TTSP) are a relatively newly identified family of proteolytic enzymes that have become the subject of intense scrutiny in the field of cancer research. Advances in genome screening technology have enabled the identification of putative members and the further characterization of existing members. The TTSPs are involved in a diverse range of physiological functions and new roles continue to be discovered. A large majority of these proteases appear to play crucial roles in the development of disease, especially cancer development and progression. This review presents the current knowledge of the biological role of those TTSPs that have been identified in the development and progression of human cancers.

2. INTRODUCTION

Cell surface proteolysis has become known as an important mechanism for the activation of proteins involved in managing a wide range of cellular functions. The chymotrypsin (S1) fold group, of which trypsin and chymotrypsin are prototypic members, are amongst the largest subfamilies of the serine proteases, one of the largest (1) and most conserved (3) family of proteases. Recently, a group of S1 serine proteases has been recognized that possess domains which anchor them directly to cell membranes. These are the type I and type II serine proteases. Type I serine proteases are anchored to the cell membrane with a carboxy-terminal transmembrane domain (4). The type II transmembrane serine proteases (TTSPs) are anchored to the membrane via an amino-

terminal transmembrane domain with a cytoplasmic extension (5, 6).

Members of the TTSP family include enteropeptidase (7) matriptase/MT-SP1 (8, 9), matriptase-2/TMPRSS6 (10), matriptase-3/TMPRSS7 (6, 11), TMPRSS1/Hepsin (12-14), TMPRSS2 (15), TMPRSS3 (16), TMPRSS4 (17), TMPRSS5/spinesin (18), TMPRSS9/polyserase-1 (19), Corin/TMPRSS10 (20), DESC1(21) and HAT (22) (See Table 1 for summary). Based on the phylogenetic analysis of the serine protease domains and the domain structure of the extracellular stem region, the TTSPs have been divided into four subfamilies (23). The largest of these is the HAT/DESC subfamily which consists of HAT, DESC1-4 and HATL3, 4 and 5. The second subfamily is the Hepsin/TMPRSS family which is comprised of TMPRSS2-5, hepsin and enteropeptidase. The next family is the matriptase subfamily which includes matriptase, matriptase-2, matriptase-3 and polyserase-1. The final subfamily is the corin subfamily of which the only member is corin.

The TTSPs are characterized by a single pass transmembrane domain which separates the short intracellular region from the larger, more variable, extracellular section of the protease. The extracellular section is composed of a stem region of variable length and a C-terminal serine protease domain containing histidine (H), aspartate (D), and serine (S) residues essential for catalytic function (5, 23, 24). The N-terminal cytoplasmic domain of TTSPs may allow signal transduction across the plasma membrane and effect changes within the cell. The stem region of TTSPs is believed to regulate diverse processes and contain as many as 11 structural domains that may serve as regulatory and/or binding domains (5, 24). These include a low density lipoprotein receptor domain class A (LDLA), Cls/Clr urchin embryonic growth factor (CUB), a sea urchin sperm protein, enterokinase, agrin (SEA) domain, a group A scavenger receptor domain (SR), frizzled (FRZ) and meprin, A5 antigen and receptor protein phosphatise μ domain (MAM) in various combinations in each of the TTSPs (2, 5, 6). The catalytic activity of the serine protease domain is dependent on the presence of the previously mentioned residues histidine, aspartate and serine (2). This domain activates or degrades protease activated receptors (PARs) (24), cytokines, growth factors and components of the extracellular matrix (25, 26). Soluble forms of several TTSPs have been detected. This suggests that the extracellular domains of these proteases may be shed from the cell surface (22, 27-29). The mechanisms involved in the regulated release of these extracellular domains and whether release may occur in response to specific cellular signals or environments have yet to be fully characterized.

Although the functional purpose of these proteases is largely unknown, the TTSPs have gained intense attention from the field of cancer research. This interest in TTSPs stems from the observation that many of them are aberrantly expressed in tumors compared to normal tissue. Increasing evidence demonstrates that this aberrant expression of TTSPs is a hallmark of several cancers and recent studies have attempted to define the molecular mechanisms underlying TTSP-promoted carcinogenesis. Loss of the basement membrane is a mandatory step that occurs during local invasion early in the metastatic process (30, 31). To accomplish local invasion, tumor cells use extracellular and cell surface proteolytic enzymes to degrade the basement membrane proteins (25, 32). The TTSP family is ideally located to perform this crucial task. Many recent studies have focused on the expression of specific TTSPs during tumorigenesis and their potential to influence tumor cell proliferation, motility and invasion (2, 25).

3. MATRIPTASE SUBFAMILY

3.1. Matriptase/MT-SP1

Matriptase, also known as MT-SP1, has been identified in the epithelial components of the prostate, stomach, small intestine, colon, lung, kidney, placenta and peripheral blood leukocytes (33, 34). Matriptase protein is 95kDa in length and is composed of a short cytoplasmic extension with unknown function, a transmembrane domain, a SEA domain, two CUB domains, four tandem repeats of a LDLA domain and a C-terminal active serine protease (6, 23, 35) (Figure 1). Matriptase is expressed as a zymogen that has to be activated by proteolytic cleavage to gain its biological function. The activation site is located directly N-terminal to the catalytic domain. Once processed, the active catalytic domain stays attached to the membrane by a disulfide bond linking the pro-domain to the catalytic domain (8, 34) unless it is shed at either of the shedding sites at residues 190 or 205 (33, 36). Shed matriptase has been found in a complex with hepatocyte growth factor activator inhibitor (HAI-1) in human milk, indicating that HAI-1 might be a cognate inhibitor of the protease. Paradoxically, HAI-1 has not only inhibitory function, but is also required for matriptase activation (36). This is thought to ensure that matriptase can be quickly inactivated once it is set free from the membrane to protect the cells from uncontrolled matriptase activity (35). However, a recent study by Miyake *et al* using stably transfected canine kidney cells, proposes that matriptase activation does not require HAI-1 (37).

Due to its notably consistent expression in tumors of epithelial origin, matriptase has received significant attention in the field of cancer biology. This protease was first described as a matrix degrading enzyme with major gelatinolytic activity in breast carcinoma (9, 38), and was later found to be expressed in a wide variety of other benign and malignant tumors of epithelial, but not mesenchymal, origin. In most carcinomas, tumor progression is associated with a significant increase in matriptase mRNA and protein expression. Matriptase has been found to be up-regulated in many epithelial tumors, including breast, colon, kidney, liver, lung, mesothelioma, ovarian and prostate cancers, and is a potential diagnostic and prognostic biomarker (2, 35, 39-42).

It is suggested that matriptase is able to promote cancer development and progression by processing the pro-forms of urokinase-type plasminogen activator (pro-uPA)

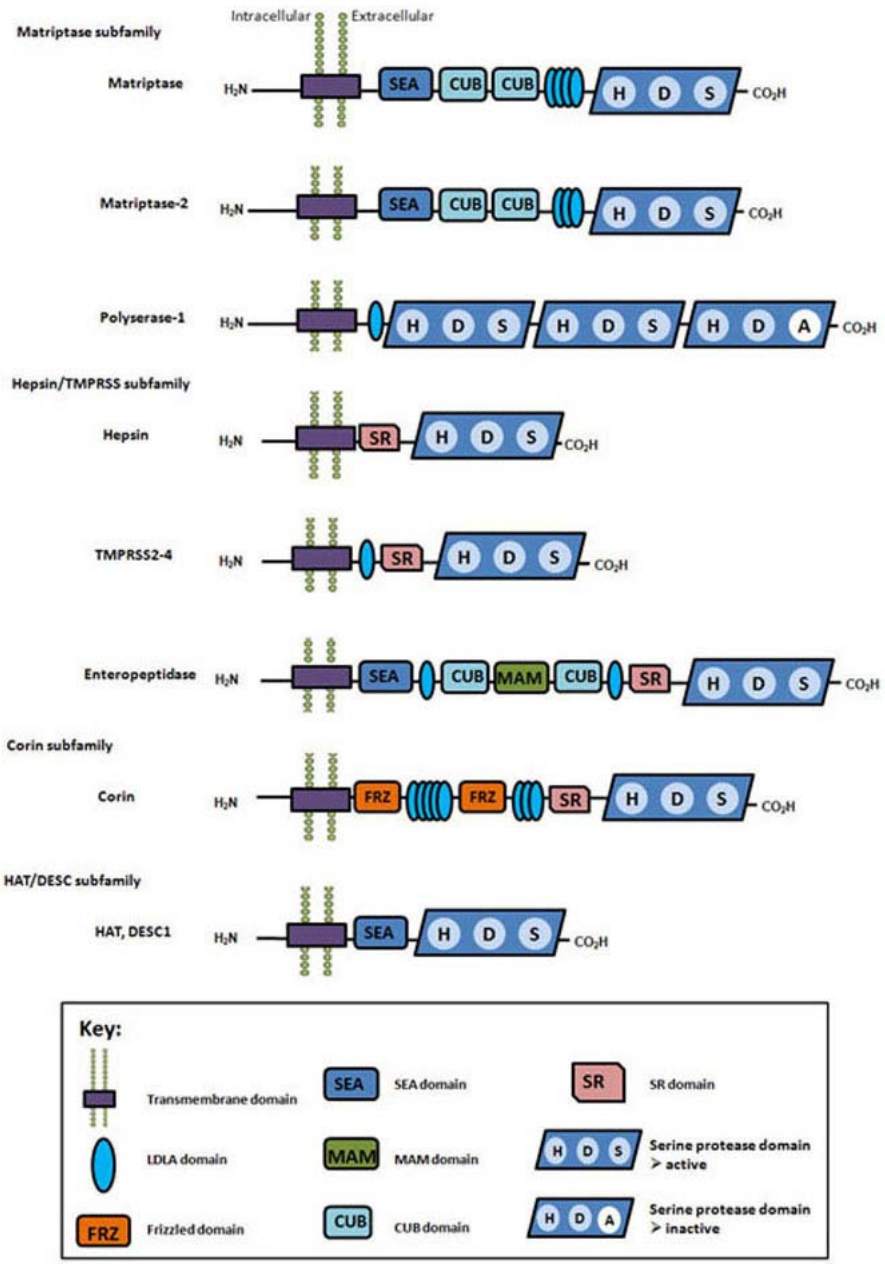

Figure 1. Multi-domain structures of human type II transmembrane serine proteases. Structures are grouped according to phylogenetic analysis (2).

and hepatocyte growth factor (pro-HGF), both of which are known to promote invasive tumor growth (34, 35, 43). In addition, matriptase might promote tissue invasion by modulating cell–cell adhesion via degradation of components of the extracellular matrix (44) or by activating PAR-2 (34, 45), a regulator of inflammation and cell–cell adhesion. However, involvement of any of these targets in matriptase-dependent tumorigenesis has yet to be tested and further investigation will be needed to validate matriptase as a novel biomarker, a predictor of patient outcome, and as a possible therapeutic target for at least some types of carcinoma.

A direct role for matriptase in tumorigenesis has been demonstrated with transgenic mice that over-express the protease in skin. This study found that increased protease expression in the epidermis induced strong proliferation of keratinocytes and squamous cell carcinoma formation (46). By contrast, double transgenic mice, which expressed both matriptase and a cognate inhibitor, HAI-1, did not develop carcinomas. Importantly, both the epidermal hyper-proliferation and the formation of matriptase-induced skin tumors was completely abolished by co-expression of the cognate inhibitor of matriptase, HAI-1, providing further evidence of matriptase proteolytic

activity being the underlying causative agent in the formation of these lesions. Interestingly stable knockdown of HAI-1 was shown to mimic the epithelial to mesenchymal transition (EMT) in both pancreatic and lung cancer cell lines. Over-expression of HAI-1 in these cell lines re-established epithelial morphology (47). There is also increasing evidence that an altered ratio of matriptase and HAI-1 might have a role in cancer development. Indeed, increased matriptase expression relative to HAI-1 expression has been demonstrated in several studies (48, 49). It appears that matriptase is involved in both the development and progression of diverse cancers and may be a viable biomarker and therapeutic target. However, further characterization of this protease will be necessary to fully elucidate its potential in the field of cancer therapy.

3.2. Matriptase-2/TMPRSS6

Matriptase-2 was identified when screening for sequences common to the TTSP family. The matriptase-2 gene is found on chromosome 22 and encodes an 88,901 kDa protein. In humans matriptase-2 expression is limited to the liver (10), although expression in the kidney, uterus and nasal cavity was seen in mice (50). Matriptase-2 protein consists of a short cytoplasmic extension with unknown function, a transmembrane domain, a SEA domain, two CUB domains, three LDLA domains and a C-terminal active serine protease (2, 50) (Figure 1). Velasco *et al*. examined the enzymatic function of matriptase-2 by producing a GST-matriptase-2 fusion protein. This fusion protein was found to degrade fibronectin, fibrinogen and type 1 collagen and to have limited action against pro-uPA but was unable to process MMP-2, MMP-9 and plasminogen. It was also found to be inhibited by serine protease inhibitors such as PMSF, leupeptin, aprotinin and plasminogen activator inhibitor-1 but not by inhibitors of cysteine or metallo protease inhibitors (10, 51). Recently, membrane bound hemojuvelin (m-HJV) has also been identified as a substrate of matriptase-2 (52), giving matriptase-2 a previously unrecognized, but important, role in iron metabolism.

Altered expression of matriptase-2 in cancer has been reported in several studies. Matriptase-2 transcript was detected in mouse Leydig tumor cells (53) and elevated levels of matriptase-2 have been reported in invasive ductal cell carcinoma (54). Studies from within our laboratories showed that there were reduced levels of matriptase-2 immunostaining in cancerous breast tissue sections compared to normal tissue sections with the majority of matriptase-2 staining being confined to the epithelial sections (55). In contrast to this quantitative PCR showed that matriptase-2 levels were up-regulated in tumor compared to normal tissues, however matriptase-2 levels were significantly higher in lower NPI and TNM stages and correlated with positive patient outcome and the over-expression of matriptase-2 reduced aggressive *in vitro* and *in vivo* traits of MDA-MB-231 breast cancer cells (55). An additional study using the invasive prostate cancer cell lines PC-3 and DU-145 showed that increased expression of matriptase-2 reduced the invasiveness and motility of the cells (56). When the same cells were implanted into CD-1 athymic nude mice, the resulting tumors developed very poorly *in vivo* compared to control cells and significant reductions in tumor volume were observed between matriptase-2 over-expressing and control groups (56). There is little indication as yet to the signaling pathways through which matriptase-2 exerts its function. It has been suggested that the interaction between matriptase-2 and hemojuvelin and BMP signaling may be a potential mechanism of action through which matriptase-2 may exert its effects on cancer cells although further investigation is needed (57).

4. HEPSIN/TMPRSS SUBFAMILY

4..1 Hepsin/TMPRSS1

Hepsin is a transmembrane serine protease that was originally identified from a human hepatoma HepG2 cell library using a homology-based cloning strategy (12). Expression and characterization of recombinant hepsin show that the protein is synthesized as a single-chain zymogen with an apparent molecular mass of 51kDa (6). Hepsin expression is highest in the liver but has also been indentified in several tissues including thymus, thyroid, lung, pancreas, pituitary gland, prostate and kidney (2). Hepsin consists of a short cytoplasmic amino terminal extension, a transmembrane domain, a SR domain and an active serine protease at the carboxy terminal (2, 6, 24) (Figure 1).

Hepsin has become a high interest topic because of its marked over-expression in prostate and ovarian cancer (58-70), renal cell carcinoma (71, 72) and endometrial cancer (73). Hepsin has also been shown to be a potential biomarker for the presence of prostate cancer (74-78) and to be associated with poor patient outcome (71, 73). The physiological function of hepsin remains unknown, but within the carcinogenesis pathway it appears to play a role in cancer cell migration/invasion rather than cell proliferation (79). The effect of deregulated hepsin has been shown to promote cancer progression and metastasis in mouse models by causing disorganization of the basement membrane (80).

Although it is clear that hepsin plays a role in cancer progression, the possible mechanisms that may be responsible for this remain largely undetermined. However, studies have begun to elucidate routes through which hepsin could exert its pro-tumorigenic effect. It has been suggested that hepatocyte growth factor (HGF) is a possible substrate for hepsin with a high degree of specificity (61, 81, 82). Herter *et al* 2005 showed that hepsin can cleave sc-HGF and that hepsin cleaved sc-HGF is biologically active in ovarian cancer cells, and may influence tumorigenesis through inappropriate activation and/or regulation of the HGF receptor c-met (61). Laminin-332 (Ln-332) is an ECM macromolecule associated with prostate cancer cell motility, and its expression is lost in cancer progression. Hepsin has been shown to cleave Ln-332, possibly aiding cancer progression by increasing the motility of cancer cells. Cleavage is specific, since it is both inhibited in a dose-dependent manner by a hepsin inhibitor (Kunitz domain-1) and does not occur when catalytically inactive hepsin is used (83, 84). Hepsin has also been shown to

efficiently activate pro-uPA, suggesting it may initiate plasmin-mediated proteolytic pathways at the tumor/stroma interface that could lead to basement membrane disruption and tumor progression (85). In light of the evidence gained, hepsin appears to be a promising therapeutic target for slowing or even preventing the development and progression of cancer.

4.2. TMPRSS2

TMPRSS2 is expressed widely in the epithelia of the gastrointestinal, urogenital and respiratory tracts, with the highest levels detected in prostate luminal epithelial cells (2). TMPRSS2 was originally cloned in 1997 and consists of a short cytoplasmic amino terminal extension, a transmembrane domain, a LDLA domain, a SR domain and an active serine protease at the carboxy terminal and forms a protein of 53.6kDa in length (15) (Figure 1). Activation of the serine protease requires its cleavage, which is autocatalytic. The active serine protease with trypsin-like specificity is then shed into the extracellular space, where it is predicted to interact with other proteins on the cell surface, as well as soluble proteins, matrix components and proteins on adjacent cells (29).

TMPRSS2 is a TTSP that has gained significant interest owing to its highly localized expression in the prostate and its over-expression in neoplastic prostate epithelium (86). The detection of chromosomal abnormalities in tumors is not a recent discovery but their significance has only recently become clear. A central aim in cancer research is to identify recurrent chromosomal rearrangements that play a vital role in cancer development. These rearrangements are of two general types. In the first, the promoter and/or enhancer elements of one gene are aberrantly juxtaposed to a proto-oncogene, thus causing altered expression of an oncogenic protein (87). In the second, the rearrangement fuses two genes, resulting in the production of a fusion protein that may have a new or altered activity (88, 89). Fusion proteins formed after chromosomal translocations are common in a range of tumor types; these are unique tumor antigens and are therefore potentially valuable targets for therapy design.

Recently a small number of fusion transcripts, specific to prostate cancer have been discovered (90), that were the result of a chromosomal rearrangement involving two genes. The first gene, TMPRSS2, is secreted by prostate epithelial cells in response to androgen exposure (29). TMPRSS2 was fused to either ERG or ETV1, two members of the ETS family of oncogenes. It had earlier been reported that the ERG gene was the most commonly over-expressed proto-oncogene in prostate cancer (present in about 72% of cases of prostate cancer) (91). It was discovered that both intra-chromosomal and inter-chromosomal genetic rearrangements led to the creation of a fusion transcript called TMPRSS2–ETS (92), it results in the translocation of an ETS (E26 transformation specific) transcription factor (ERG or ETV1) to the TMPRSS2 promoter region, which contains androgen responsive elements. ETS is a family of transcriptional activators and inhibitors and their activity is regulated by phosphorylation and protein–protein interactions (93). The TMPRSS2:ERG genetic rearrangement has been reported to occur in approximately 40% of primary prostate tumors (ETV1 genetic rearrangements occur at a much lower frequency), and it results in the aberrant androgen-regulated expression of ERG and could be a mechanism whereby the ETV1 or ERG oncogenes are over-expressed, leading to prostate cancer.

TMPRSS2:EGR fusion gene transcripts were found to promote proliferation, motility and invasion of PNT1A cells (94) and Tomlins *et al.* concluded that ETS genetic rearrangements are sufficient to initiate prostate neoplasia. However, Carver *et al.* have shown that ETS genetic rearrangements may in fact represent progression events rather than initiation events in prostate tumorigenesis (95). The role of TMPRSS2:ERG fusion protein in clinical outcome also remains unclear, with 10 studies receiving contradictory results (96). Another study, involving mice lacking TMPRSS2, showed no effect on the development, fertility, overall survival or function of the prostate (97). Despite the disparity in these findings there is promising evidence that TMPRSS2:ERG fusion proteins may be a useful biomarker, present in urine, for early detection of prostate cancer (74, 98-103). There is also evidence to suggest that TMPRSS2 is capable of cleaving and thereby activating the PAR-2 receptor and this may be another method through which TMPRSS2 contributes to cancer progression (86). Thus, TMPRSS2 and the TMPRSS2:ERG gene fusion presents an exciting opportunity for use as a therapeutic target and drug development for the treatment of patients with TMPRSS2:ERG expressing prostate cancers.

4.3. TMPRSS3

The expression of TMPRSS3 was detected in several human tissues, including heart, lung, kidney, liver, placenta, pancreas, small intestine, colon, spleen, ovary, prostate, testis and thymus (16). TMPRSS3 is expressed as a 49kDa polypeptide and consists of a short cytoplasmic extension, a amino terminal transmembrane domain, a LDLA domain, a SR domain and an carboxy terminal active serine protease (6) (Figure 1).

There is little information to date regarding the role of TMPRSS3 in the progression of cancer. A splice variant, TADG-12 has been shown to be over-expressed in ovarian cancer (17, 104). TADG-12 was also found to be more highly expressed in advanced clinical stage ovarian cancer and this variant may be useful both as a molecular target for therapy and/or a diagnostic marker (105). A study by Bellone *et al.* identified potential immunogenic peptides derived from TADG-12 for immunotherapy of ovarian carcinoma. The TADG-12 YLPKSWTIQV peptide is an immunogenic epitope in ovarian tumors and may represent an attractive target for immunotherapy of ovarian cancer (106). This discovery may allow the development of a TADG-12 peptide-derived cell-based therapy for the vaccination of ovarian cancer patients possessing chemotherapy-resistant or residual disease.

4.4. TMPRSS4

TMPRSS4 expression has been detected on the cell surface in esophagus, stomach, small intestine, colon, kidney and bladder (2). It is also markedly up-regulated in gastric, liver, lung, ovarian, pancreatic, primary basal cell carcinomas, squamous cell carcinomas, thin melanomas and thyroid cancers (107, 108) although its oncogenic potential and mechanism of action remain unclear. TMPRSS4 is expressed as a 68kDa protein which consists of a short cytoplasmic extension, a amino terminal transmembrane domain, a LDLA domain, a SR domain and an carboxy terminal active serine protease (6) (Figure 1).

In pancreas cancer cells, TMPRSS4 is involved in the process of metastasis formation and tumor invasion, and its expression is correlated with the metastatic potential (17). TMPRSS4 has also been identified as a possible diagnostic marker in thyroid cancer and to improve the accuracy of fine needle aspiration (FNA) biopsy (109-111). Although the mechanisms of action of TMPRSS4 remain unclear several studies have proposed potential pathways by which TMPRSS4 exerts its function. Dawelbait *et al.* 2007 proposed that the interaction between the up-regulated TMPRSS4 and the down-regulated tissue factor pathway inhibitor 2 (TFPI2) in pancreas cancer cells could explain the mechanism of metastasis that makes pancreatic ductal adenocarcinoma (PDAC) a very aggressive type of cancer. TFPI2 is an extracellular protein that belongs to the small Kunitz inhibitor family. TFPI2 plays a major role in extracellular matrix degradation during tumor cell invasion and metastasis, wound healing and angiogenesis and is known to be down-regulated in PDAC (112). Dawelbait *et al.* hypothesized that TFPI2 acts as a natural inhibitor of TMPRSS4. Since TFPI2 is down-regulated, the up-regulated TMPRSS4 is no longer inhibited and might facilitate tissue invasion and metastasis.

Jung *et al.* 2008 proposed that TMPRSS4 mediates the invasive and metastatic potential of human cancer cells by facilitating an epithelial–mesenchymal transition (107). Kim *et al.* 2010 further explored the mechanisms by which TMPRSS4 mediates EMT and invasiveness in tumor cells. TMPRSS4 mediated FAK signaling pathway activation and extracellular signal-regulated kinase (ERK) activation via integrin a5 up-regulation, resulting in epithelial-mesenchymal transition (EMT) and invasiveness. Furthermore, TMPRSS4 over-expression in human colorectal cancer tissues correlated with enhanced expression of integrin a5. These observations implicate integrin a5 up-regulation as a molecular mechanism by which TMPRSS4 induces invasion and contributes to cancer progression (113). To further implicate TMPRSS4 in EMT, Cheng *et al.* 2008 suggests that interactions between HAI-1/SPINT1 and TMPRSS4 contribute to transcriptional and functional changes involved in EMT in certain carcinoma cells (47). Although a specific substrate molecule of TMPRSS4 that initiates the EMT stimulatory pathway is still not defined, recent studies have contributed to discovering the pathways through which TMPRSS4 may exert its function. Regulation of EMT by proteases such as TMPRSS4 may provide novel therapeutic targets for the treatment of cancer metastasis.

5. HAT/DESC SUBFAMILY

5.1 .HAT

Human airway trypsin-like (HAT) protease was originally identified in the human trachea and bronchi (22, 114) and subsequently found in diverse tissues including brain, spinal cord, skin, tongue, testis, prostate, urinary bladder and the organs of the gastrointestinal tract (2, 115-117). HAT protein is 48kDa in length and consists of a short cytoplasmic extension, a amino terminal transmembrane domain, a SEA domain and a carboxy terminal active serine protease (22) (Figure 1) (Table 1). Proposed physiological roles of HAT include mucus production (118), deposition of fibrin in the airway lumen (119), proteolytic activation of hemagglutinin antigen of influenza virus (120), activation of protease-activated receptor 2 (PAR2) (117, 118, 121, 122) and proteolytic inactivation of the urokinase receptor (123). HAT also appears to be released as a soluble protein from the surface of tracheal serous glands of patients with chronic airway disease (22). There are currently no studies investigating the possible involvement of HAT in tumorigenesis. A previous study even presented evidence against a role in adrenal tumorigenesis (115). Further investigation is required to determine the role, if any, of HAT in cancer.

5.2. DESC1

Differentially expressed in squamous cell carcinoma gene 1 (DESC1) is expressed in a number of tissues derived from the head and neck, and in skin, prostate and testes. Cell line studies demonstrate that DESC1 expression is epithelial-specific (21). The 47kDa DESC1 protein consists of a short cytoplasmic extension, a amino terminal transmembrane domain, a SEA domain and a carboxy terminal active serine protease (2) (Figure 1) (Table 1). DESC1 was first investigated in squamous cell carcinoma of the head and neck. A study by Lang *et al* 2001 (21), compared DESC1 expression between primary squamous cell carcinoma and matched normal tissue and demonstrated that DESC1 expression was reduced or absent in 11/12 SCC tissue specimens when compared to specimens of matched normal tissue. A further study by Sedhgizadeh *et al* 2006 showed that down-regulation of DESC1 occurs during squamous cell carcinoma progression and up-regulation occurs during normal epithelial differentiation (124). It has also been reported that DESC1 hydrolyses extracellular components such as fibronectin, gelatine and fibrinogen (125). Madin-Darby canine kidney (MDCK) cells expressing exogenous human DESC1 acquire properties associated with tumor growth such as enhanced motility and an increase of tubular forms in a 3D collagen lattice following HGF treatment (125). A study investigating the substrate specificities of a number of TTSPs demonstrated that DESC1 had a preference for small non-polar amino acids (Ala) and that antithrombin III has robust inhibitory properties toward DESC1, whereas plasminogen activator inhibitor-1 and alpha(2)-antiplasmin inhibited DESC1 (51). In light of these findings it appears

Table 1. Human membrane anchored serine proteases

Protease	Alternate name	Chromosomal localization	Molecular weight (kDa)	Reference
Matriptase-1	MT-SP1/TADG-15	11q25	95	(8, 9)
Matriptase-2	TMPRSS6	22q12-13	89	(10)
Matriptase-3	TMPRSS7	3q13.11	101	(6, 11)
TMPRSS9	Polyserase-1	19p13.3	114	(19)
Hepsin	TMPRSS1	19q13.1	51	(12-14)
TMPRSS2	Epitheliasin	21q22.3	53.8	(15)
TMPRSS3	TADG-12/ECHOS1	21q22.3	49	(16)
TMPRSS4	TMPRSS3	11q23.3	68	(17)
TMPRSS5	Spinesin	11q23.3	52	(18)
Enteropeptidase	Enterokinase	21q21	156	(7)
Corin	TMPRSS10	4p12-13	116	(20)
HAT	-	4q13.2	48	(22)
DESC1	-	4q13.3	47	(21)
DESC2	-	4q13.3	46.2	(6)
DESC3	-	4q13.3	44	(6)

that DESC1 could be considered as a potential therapeutic target in some types of tumors.

6. CORIN SUBFAMILY

6.1. Corin/TMPRSS10

Human corin was first cloned in the search for novel serine protease genes in the cardiovascular system. The full-length human corin cDNA is approxiametly 5 kb in length and encodes a mosaic serine protease, which is named corin for its abundant expression in the heart (20). Independently, Hooper *et al.* (126) also cloned human corin cDNA from a cancer cell line while studying novel serine protease genes in cancer. The human corin polypeptide is 116 kDa in length and consists of a short cytoplasmic extension at the N-terminus followed by an integral transmembrane domain, two frizzled-like cysteine-rich motifs, eight LDLA repeats, a SR domain, and a serine protease domain at the C-terminus (127).

Currently there are very few mentions of corin in the field of cancer research. Corin mRNA has been found in cancer cells derived from osteosarcoma, leiomyosarcoma, endometrial carcinoma, and small cell lung cancer (126, 128). It has been proposed that the ectopic expression of corin may contribute to the pathogenesis of the syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) associated with certain cancers (128).

7. CONCLUDING NOTES

The role of members of the TTSP family of proteases appears to be a very complex matter to elucidate. Each member seems to have diverse functions in normal tissues as well as in cancer progression. With the advancement of technology in recent years it has enabled researchers to more accurately identify and characterize members of the TTSP family. Despite this advancement, the role of many of the family members in development, physiological function and cancer progression remains elusive. The continued investigation into the less well known members of the family remains worthwhile when the roles of members such as hepsin, TMPRSS2, matriptase and matriptase-2 are considered. These proteases are becoming established as playing crucial roles in the development and progression of cancer. TTSPs also need to be investigated for their potential as tumor biomarkers and prognostic and diagnostic indicators in diverse cancers. Validating their use as biomarkers and prognostic and diagnostic markers would be of great advantage in the fight against cancer. Membrane anchored serine proteases also demonstrate great potential as therapeutic targets due to their marked differing expression in normal and cancerous tissues and their enzymatic actions. Continued investigation into understanding the many roles of the TTSP family will be crucial in attempting to combat the development and progression of cancer and other diseases.

8. ACKNOWLEDGEMENTS

The authors wish to thank Cancer Research Wales for funding this work. The authors would also like to apologize to the authors of any papers not mentioned in this review.

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Key Words: Cancer, TTSP, TMPRSS, Transmembrane, Protease, Review

Send correspondence to: Siobhan L Webb, Metastasis and Angiogenesis Research Group, Cardiff University School of Medicine, Heath Park, Cardiff CF14 4XN, UK, Tel: 44-29-2074-2893, Fax: 44-29-2076-1623, E-mail: webbsl1@cf.ac.uk

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