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DESC1 and HAT Peptidases

DATABANKS

MEROPS name: DESC1 peptidase

MEROPS classification: clan PA, subclan PA(S), family S1, subfamily S1A, peptidase S01.021

Tertiary structure: Available

Species distribution: superclass Tetrapoda

Reference sequence from: *Mus musculus* (UniProt: Q5S248)

MEROPS name: HAT-like putative peptidase 2

MEROPS classification: clan PA, subclan PA(S), family S1A, subfamily S1A, peptidase S01.292

Species distribution: class Mammalia

Reference sequence from: *Homo sapiens* (UniProt: Q6ZMR5)

MEROPS name: HAT-like 3 peptidase

MEROPS classification: clan PA, subclan PA(S), family S1, subfamily S1A, peptidase S01.294

Species distribution: superclass Tetrapoda

Reference sequence from: *Mus musculus*

MEROPS name: HAT-like 4 peptidase

MEROPS classification: clan PA, subclan PA(S), family S1, subfamily S1A, peptidase S01.321

Species distribution: subclass Eutheria

Reference sequence from: *Mus musculus* (UniProt: Q8BHM9)

MEROPS name: HAT-like 5 peptidase

MEROPS classification: clan PA, subclan PA(S), family S1, subfamily S1A, peptidase S01.365

Species distribution: subclass Eutheria

Reference sequence from: *Homo sapiens*

MEROPS name: HAT-like 2 peptidase

MEROPS classification: clan PA, subclan PA(S), family S1, subfamily S1A, peptidase S01.436

Species distribution: class Mammalia

Reference sequence from: *Mus musculus* (UniProt: Q8BZ10)

Name and History

The HAT/DESC subfamily of trypsin-like serine proteases is comprised of five members in humans and two

HAT/DESC Subfamily

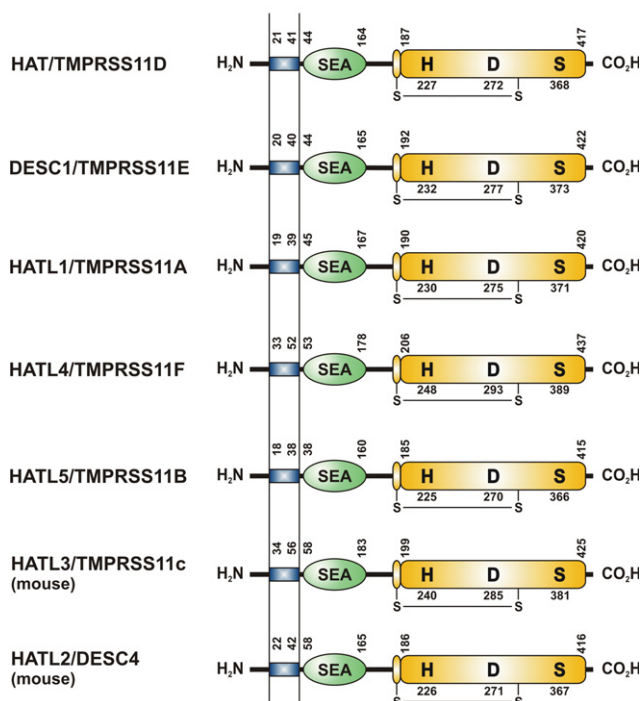


FIGURE 654.1 Domain structures of the HAT/DESC subfamily of trypsin-like serine proteases. The family is comprised of five members in humans, HAT/TMPRSS11D, DESC1/TMPRSS11E, HAT-like 4/TMPRSS11F, HAT-like 5/TMPRSS11B, and HAT-like 1/TMPRSS11A. HAT-like 2/DESC4 and HAT-like 3/TMPRSS11c are two additional members of the HAT/DESC subfamily that are expressed in rodents. The family is defined by a transmembrane domain, a structurally conserved: sea urchin sperm protein, enteropeptidase, agrin domain (SEA) domain, an activation domain, and the serine protease catalytic domain. The location of each protein domain (amino acid numbering) is indicated above the domain. Amino and carboxy termini are as indicated. Domain features and catalytic triad assignments (histidine (H), serine (S) and aspartic acid (D)) were obtained from UniProtKB and SMART.

members which are only expressed in rodents (Figure 654.1). HAT (Human Airway Trypsin-like Protease), also designated TMPRSS11D, was the first member of the HAT/DESC subfamily of trypsin-like serine proteases to be discovered, and was named based on its isolation as a novel 27 kDa trypsin-like serine protease in the sputum of patients with chronic airway diseases

[1]. DESC1 (differentially expressed in squamous cell carcinoma gene 1), or TMPRSS11E was later identified, in a representational difference analysis (RDA) performed using RNA isolated from a metastatic squamous cell carcinoma, as a novel gene downregulated in squamous cell carcinoma of the head and neck compared with matched unaffected oral tissue. Sequence analysis indicated DESC1 and HAT share 51% sequence identity in their serine protease catalytic domains [2]. Similarly, TMPRSS11A, also called HAT-like putative peptidase 2, HAT-Like 1, and ECRG-1 (esophageal cancer related gene 1), were originally identified in a screen to isolate genes differentially expressed in esophageal cancer relative to unaffected esophageal epithelium [3]. The two members not found in humans, but expressed in rodents are TMPRSS11c and DESC4. TMPRSS11c, also called neurobin or HAT-like 3, was identified from the spinal cord of postnatal mice using degenerate primers in an effort to find TTSPs expressed in the murine nervous system [4]. Rat DESC4, also called HAT-like 2, was found in a differential screen to identify genes expressed specifically in rat circumvallate papillae, but absent in taste bud free tongue epithelium [5].

Isoforms between humans and rodents exist for the members of the HAT/DESC family. The rat isoform of HAT (RAT or rat airway trypsin-like protease) was discovered in a search for a candidate serine protease responsible for cleaving the pro- γ -melanocyte-stimulating hormone (pro- γ -MSH), and identified as a novel serine protease expressed in normal adrenal glands and those undergoing compensatory growth [6]. The gene, AsP, encodes RAT2, a truncated secreted form of RAT, which lacks the SEA domain and the transmembrane domain, and is therefore a secreted protein. There is also a report of a mouse isoform of HAT called MAT (murine airway trypsin-like protease), and an associated truncated isoform called MAT2 [7]. MAT was identified in a nucleotide blast by its homology to RAT.

Activity and Specificity

The HAT/DESC1 proteases share trypsin-like specificity, with preference for cleavage of peptide substrates after Arginine or Lysine residues [8]. Recombinant and native HAT have been reported to cleave fibrinogen [9], hemagglutinin (HA) [10], pro-urokinase type plasminogen activator (uPA) [11], the uPA receptor (uPAR) [12], and protease activated receptor-2 (PAR-2) [13,14]. The proteolytic activity of HAT has been shown to be inhibited by leupeptin [1], aprotinin [1], ovomucoid trypsin inhibitor, Pefabloc SC, and soybean trypsin inhibitor [15]. Using FRET based peptides, HAT was shown to prefer a basic amino acid residue at the P1 position (Arg), and also preference for an Arg residue at P4 followed by a

hydrophobic Tyr, Val, or Phe residue. Gln was preferred in P3 and Asp at P2. P3 could also accommodate Arg, Lys, Thr, Ser, Ala, Leu, and Phe [16].

DESC1 has been shown to cleave casein, gelatin, fibronectin, pro-uPA, and possibly fibrinogen [17,18]. Mouse DESC1 prefers substrates with Arg in the P1 position. The highest catalytic activity was seen for the synthetic chromogenic peptide Suc-Ala-Ala-Pro-Arg-pNA [18]. Human DESC1 prefers substrates that have large hydrophobic P4/P3 residues, small P2 residues, Arg or Lys at P1, and hydrophobic P1' and P3' residues [19]. Reportedly, hDESC1 is relatively permissive at positions P3, P2 and P1'. In a study using internally quenched peptides, hDESC1 preferred peptides with Arg at P4, Arg/Ala/Leu at P3, Leu at P2, and Ala at P1' [20]. In a separate peptide study, hDESC1 was shown to prefer Boc-Gln-Gly-Arg-AMC over Boc-Gln-Ala-Arg-AMC [17]. Optimal DESC1 activity was found to occur at pH 8.5 [20]. The activity of hDESC1 has been found to be inhibited by BPTI [19], AEBSF [17], α -2-anti-plasmin (Serpins F2) [20], and TPCK [17]. hDESC1 was also strongly inhibited by antithrombin III (Serpins C1) in the presence of heparin. Aprotinin (0.3 μ M) and leupeptin (1 μ M) partially inhibited the cleavage of Boc-Gln-Ala-Arg-AMC [20]. mDESC1 has also been shown to form inhibitory complexes with α -2-macroglobulin, protein C inhibitor (PCI), and plasminogen activator inhibitor-1 (PAI-1) [18]. The presence of the SEA domain in a recombinant mDESC1 did not inhibit the formation of the serpin inhibitory complexes *in vitro* [18].

An active recombinant catalytic domain of TMPRSS11c has been reported to cleave chromogenic substrates harboring Arg at P1, and uncharged amino acid residues at P2 and P3. The most effective cleavage was of Val-Gly-Arg-pNA, with an optimum pH of 8. TMPRSS11c has been shown to undergo autocatalytic activation, with cleavage of the activation domain likely occurring between Lys199 and Val200. AEBSF, leupeptin, aprotinin, and 4-aminobenzamidine were shown to inhibit TMPRSS11c activity [4]. The catalytic domain of TMPRSS11c has been reported to cleave FGF-2, which is inhibited by heparin [4].

Using a recombinant Rat DESC4 catalytic domain, it is reported that Rat DESC4 prefers Arg or Lys at P1, a hydrophobic amino acid at P1', a bulky non-charged amino acid at P3, and either a positively or negatively charged amino acid at P4, with no suggested preference for P2 [21].

Structural Chemistry

The HAT/DESC peptidases are type II transmembrane serine proteases, with a relatively short NH₂-terminal cytoplasmic tail, a single pass transmembrane domain, a

single SEA stem region domain, and a COOH-terminal catalytic domain [18]. Similar to most serine proteases, they are expressed as inactive zymogens and are believed to require proteolytic cleavage to become active enzymes.

Full length HAT is a 418 amino acid protein with a size of 48 kDa [9]. Native soluble HAT is shed from the plasma membrane as a 28 kDa protein, and recombinant activated HAT produced in insect cells is the same molecular mass [9]. Activation of the full length zymogen occurs between Arg186 and Ile187 to separate the pro- and catalytic domains [9]. HAT contains two potential *N*-linked glycosylation sites in the non-catalytic region [9], and nine cysteine residues, one of which is in the transmembrane domain. Six of these cysteine residues form disulfide bonds in the catalytic region, while two others form a disulfide bond that links the pro-domain to the catalytic domain [9].

Human DESC1 is 423 amino acids, with a size of approximately 47 kDa [2]. The DESC1 zymogen is activated by proteolytic cleavage between Arg190 and Ile191 [2]. The crystal structure of hDESC1 suggests that the SEA domain may interact with the backside of the catalytic domain to control the orientation/localization of the protease domain [19].

The mouse homolog of DESC1 is 442 amino acids, with a nominal size of 50 kDa [18], and is expressed as a 60 kDa glycoprotein [18]. mDESC1 shares 72% sequence identity with hDESC1 [18]. Activation of the mDESC1 zymogen occurs at a cleavage site located between Arg 210 and Ile 211 [18]. The N-terminal cytoplasmic domain has two potential Thr phosphorylation sites which may be involved in intracellular signaling [18].

TMPRSS11c is a 431 amino acid protein with a size of 48 kDa. TMPRSS11c has three putative *N*-linked glycosylation motifs as well as nine cysteine residues, six of which presumably form the three canonical disulfide bonds of the serine protease domain, while one of the two in the activation domain likely forms a disulfide bond with the remaining cysteine in the catalytic domain to form a link between the catalytic and activation domains [4].

There is little known about other members of the HAT/DESC subfamily. HAT-like 1/TMPRSS11A is predicted to encode a protein of 391 amino acids [22]; rat DESC4 encodes a protein of 417 amino acids [5], and MAT encodes a putative 417 amino acid protein.

Preparation

HAT has been isolated from a human trachea cDNA library [9]. The native HAT protein has been purified by gel filtration from human sputum. Recombinant HAT protein has been expressed in an insect cell system to produce a major protein of 48 kDa, and a minor protein of 28 kDa, which corresponds to the size of active HAT [9].

Human DESC1 mRNA has been isolated from normal oropharyngeal mucosal epithelium [2], normal human skin [2], and human umbilical vein endothelial (HUVEC) cells [19]. Mouse DESC1 cDNA has been prepared from the skin of newborn mice [18]. Soluble mDESC1 V5-His fusion proteins containing the serine protease domain and the prodomain region (31 kDa), or the SEA stem region, catalytic domain, and prodomain region (52 kDa) have been expressed and purified from insect cells as zymogens, activated by exposure to immobilized trypsin, and purified by cobalt chelation chromatography [18]. Soluble hDESC1 has been expressed in insect cells as a C-terminal V5-His fusion protein; however, while hDESC1 was expressed as the expected 45 kDa, it was recovered following purification as a 32 kDa protein, due to autoactivation [20]. A soluble catalytic domain of hDESC1 has also been expressed with an N-terminal GST fusion tag in *E. coli*, which undergoes autocatalysis to release the GST tag [17].

A recombinant His-tagged soluble catalytic domain of TMPRSS11c has been expressed in *E. coli*. The purified recombinant protein was expressed as an inactive 30 kDa protein and an active 27 kDa protein [4]. Similarly, recombinant rat DESC4 and a mutant catalytic DESC4 domain fused to a calmodulin binding peptide affinity tag, were expressed in *E. coli* [21]. An HA-tagged HAT-like 1/TMPRSS11A has been prepared by *in-vitro* translation [3]. Endogenous RAT2 was purified from the Y1 cell line through affinity purification methods [6].

Biological Aspects

The genes encoding all members of the HAT/DESC1 subfamily are located within a single region of chromosome 4q in humans, and chromosome 5E1 in mice, suggesting that the family members originated as the result of gene duplication in a common ancestor [18].

High levels of HAT mRNA have been detected in the trachea, and lower levels have been detected in the pancreas [9]. HAT expression was also reported in tongue, lung, bladder, prostate, testes, and spinal cord [23]. Ciliated epithelial cells of the bronchi [24], and keratinocytes of the epidermal layers of the skin also express HAT [25]. HAT is thought to be synthesized as a membrane bound precursor form that traffics to the cell surface where it is activated, and retained and/or released as an active protease from the cell surface [9,26]. HAT has been implicated in host defense against pathogens [9] and also reported to influence mucus/cilia movement in an autocrine or paracrine manner [24]. The majority of the trypsin-like protease activity in mucoid sputum is attributable to HAT activity [27]. HAT has been reported to be involved in airway remodeling through activation of PAR-2, thereby stimulating human bronchial fibroblast

proliferation [27]. The activation of PAR-2 in keratinocytes leads to a release of IL-8, as well as a release of amphiregulin from bronchial epithelial cells [14,25]. It was suggested that upregulation of HAT in keratinocytes may play a role in psoriatic epidermis [25]. HAT has also been reported to regulate mucin gene expression and release in human airway epithelial cells [14,28]. HAT may also process fibrinogen in a manner that diminishes the ability of fibrin to form clots [29].

Similar to the activity of trypsin, HAT was shown to cleave the surface glycoprotein hemagglutinin of the influenza virus into two peptides HA1 and HA2, with identical mobility to those produced by trypsin cleavage [10]. HAT expressed in MDCK cells that lack proteases that cleave the monobasic cleavage site in HA, proved to be sufficient to allow infection of influenza A containing the three hemagglutinin subtypes associated with human disease (H1, H2, H3) and multi-cycle replication of virus progeny [10]. Shed HAT has been shown to be active only at a low level, while membrane bound HAT exhibits significant catalytic activity when assayed with various fluorogenic substrates [26]. Recombinant soluble HAT has been shown to cleave both soluble and cell-associated human uPAR on human bronchial epithelial cells and on monocytes, which may indicate a role in lung inflammation [12].

DESC1 is expressed in normal oral epithelium, however it is downregulated or absent in various epithelial carcinomas, suggesting a role for DESC1 as a tumor suppressor [12]. Interestingly, DESC1 is reportedly found upregulated in other cancer types, such as brain, kidney, and breast, suggesting an opposing role in tumor progression in these tissues [17]. DESC1 is expressed in specific highly differentiated epithelial tissues, including the skin, oral epithelium, salivary glands, prostate, epididymus, and the testes [2,18]. The expression of DESC1 is downregulated as some cells become more neoplastic [2,30]. PCR data suggests that when keratinocyte differentiation is induced in the presence of calcium, DESC1 expression increases significantly. Immunohistochemical data shows that DESC1 reactivity increases as keratinocytes migrate through the spinous layer, suggesting that DESC1 may play a role in regulating cell proliferation and differentiation [30].

DESC1 may also play a role in cell migration as MDCK cells stably transfected with hDESC1 show fibroblast-like morphology and increased migratory behavior in a scratch-wound assay, and increased migration/invasion in a matrigel invasion assay [17]. The capability of recombinant DESC1 to hydrolyze extracellular matrix components suggests it may also function to remodel the extracellular matrix [17]. Human and mouse DESC1 are both expressed in similar tissue locations and are predicted to share common physiological roles in development and maintenance of oral tissues and the male reproductive tract [18].

HAT-like 1/TMPRSS11A, is expressed in the upper respiratory tract including the pharynx and trachea, esophagus, colon, liver, and lung tissue. HAT-like 1 has been shown to be capable of cleaving recombinant and native, full-length S-protein trimer (triSpike) of the coronavirus (SARS-CoV) *in vitro*, the cause of severe acute respiratory syndrome [22,31]. HAT-like 1 is downregulated in tumor samples [22], and has been shown to induce G1/M cell-cycle arrest, inhibit *in vitro* esophageal cancer cell growth, and reduce tumor formation *in vivo* [22]. HAT-like 1 is also reported to interact with ECRG-4 [32] and Miz-1 [3], with both interactions increasing its putative tumor suppressive function.

TMPRSS11c RNA is expressed in the cerebellum and spinal cord of neonatal and adult mice. Immunohistochemistry and immunofluorescence studies suggest that TMPRSS11c is localized to the plasma membrane of Purkinje neurons of the cerebellum. In HEK293T cells, TMPRSS11c seems to be expressed as a 50 kDa protein, which undergoes autocatalytic activation to leave a 23 kDa protein fragment, containing the SEA domain, to remain on the cell surface [4].

The rat DESC4 gene is found on chromosome 14 (14p21) [5]. The most prominent expression of rat DESC4 has been reported to be in the lung and tongue tissues. In the tongue, it is restricted to the epithelium along the circumvallate papillae, extending into the minor ducts of the salivary glands. It is also expressed in the brain, colon, heart, liver, nasal cavity epithelium, and tear ducts and adjacent epithelial cells of the eye [5].

RAT is expressed in the esophagus, tongue, trachea, and at low levels in the pituitary. RAT2 is expressed in the adrenal gland, tongue, heart, pituitary, esophagus, lung, and trachea [7]. In the adrenal cortex, it is suspected that RAT2 localizes to the cell surface after secretion, and cleaves pro- γ -MSH to activate its mitogenic activity [6]. MAT and MAT2 are expressed in esophagus, lung, stomach, tongue, adrenal gland, pituitary gland, trachea, blood, brain, cerebellum, gut, heart, and spinal cord; however, MAT is expressed at higher levels than MAT2 [7].

At present little is known about the biological aspects of other members of the HAT/DESC family.

Distinguishing Features

The members of the HAT/DESC subfamily are type 2 transmembrane serine proteases (TTSPs) that exhibit simple modular structure in the stem region, consisting of only a single SEA domain.

Related Peptidases

The catalytic region of HAT shares 38% identity with hepsin (Chapter 652), 32% identity with enteropeptidase

(Chapter 586), 30% identity with acrosin (Chapter 602), and 29% identity with mast cell trypsin (Chapter 591) [9]. DESC1 has significant sequence homology (38% overall, 51% in the serine protease catalytic domain) with human airway trypsin-like protease (HAT) [2]. DESC1 also shares homology with normal epithelial cell specific gene (NES1) [30].

Further Reading

The more information on DESC1 and HAT Peptidases, the reader is directed to Antalis *et al.* [8,33] and Bugge *et al.* [34].

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Toni M. Antalis

Department of Physiology, Center for Vascular and Inflammatory Diseases, University of Maryland Baltimore, 800 West Baltimore Street, Baltimore, MD 21201, USA. Email: tantalis@som.umaryland.edu

Erik W. Martin

Center for Vascular and Inflammatory Diseases, University of Maryland Baltimore, 800 West Baltimore Street, Baltimore, MD 21201, USA. Email: EMartin@som.umaryland.edu

Kathryn M. Hodge

Center for Vascular and Inflammatory Diseases, University of Maryland Baltimore, 800 West Baltimore Street, Baltimore, MD 21201, USA. Email: khodge@som.umaryland.edu